Comprehensive ENT

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Hearing Loss in Congenital, Neonatal and Childhood Infections

Springer

Comprehensive ENT

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As technology progresses, there are continuous advances in every medical subspeciality, and otorhinolaryngology/ENT is a particularly outstanding example of this. ENT lends itself well to the development of innovative and sophisticated solutions, including those affecting the vital area of airway management. Rhinoplasty and related cosmetic procedures are now a well-established part of ENT practice, and make major contributions to patient well-being, quality of life and social function. The series also covers the key principles involved in the use of social media for advertising and sharing cosmetic outcomes, from minor procedures to full-scale surgical operations.

The series gathers ENT and related sub-specialty experts from across the globe and translates their knowledge into easily accessible, well-structured summaries of the current state of knowledge, with accompanying illustrations, diagrams and summary tables. Each volume is under the leadership of editors who are thoroughly familiar with the area covered and understands exactly which information is of most relevance and interest to those entering the field for the first time or seeking to update their existing knowledge.

The series both outlines precisely the current state of the art in each area of ENT practice and shows where the future of the field may lie. The fundamental scientific basis of various disorders is covered, including molecular and cellular aspects, as well as diagnostic practice and the appropriate use of investigations. Historical aspects will be covered where they cast light on the general direction of the specialty. The latest developments in clinical management, disease prevention and public health aspects are described. The series shows how these multiple scientific and clinical aspects can be best understood in supporting an individual, personalized approach to patient care that fits the patient-centered ethos of twenty-first century ENT healthcare.

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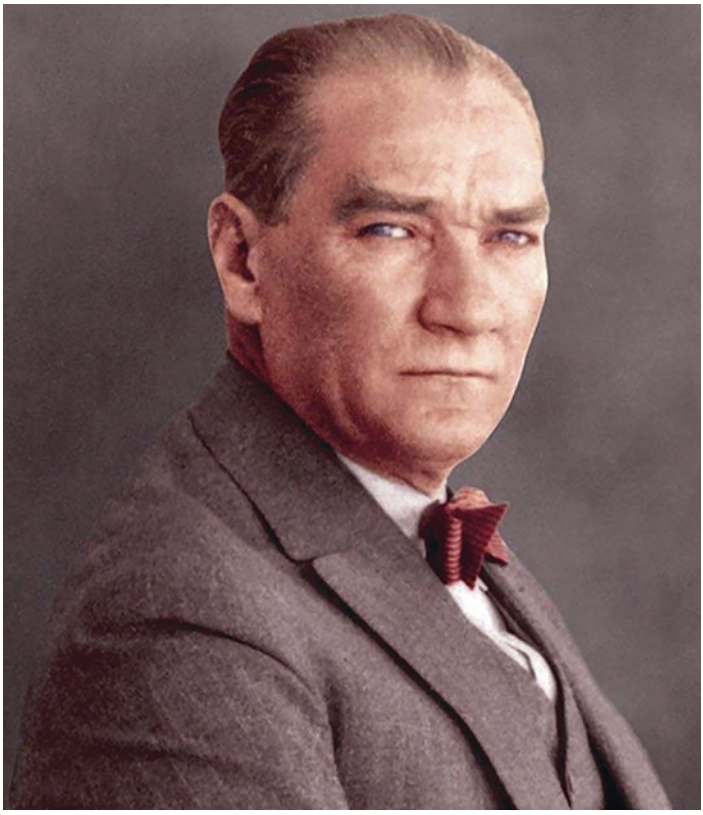

We, the editors, dedicate this book, *Hearing Loss in Congenital, Neonatal and Childhood Infections*, to Mustafa Kemal Atatürk, the founder of Türkiye, at the 100th anniversary of the Republic of Türkiye.

Preface

The *Hearing Loss in Congenital, Neonatal and Childhood Infections* is the product of the collaborative efforts of its authors, including worldwide-known experts in pediatrics, pediatric infectious diseases, and otorhinolaryngology. We, the editors, are extraordinarily honored for the opportunity to provide the *Hearing Loss in Congenital, Neonatal and Childhood Infections* textbook to physicians and other healthcare providers working in the child health field as a comprehensive, reliable, and up-to-date reference book available in printed and online.

Humankind, world history, and, more recently, globalization has sarcastically failed at equally providing health opportunities and solutions with justice for all children on behalf of a fair life in all corners of the world. In this context, during the last century, morbidity and mortality rates in children due to infectious diseases have been dramatically reduced in high-income countries. Conversely, pediatric infectious diseases in low- and middle-income countries remain among the leading causes of morbidity and mortality. Children in the low- and middle-income world also experience disproportionate rates of infectious diseases and complications such as hearing loss, often more frequently and seriously than those in high-income countries.

The experience and knowledge in child health are widening, deepening, and ever-changing. And so are the responsibilities and roles of physicians and other healthcare providers. The goal of preparing the *Hearing Loss in Congenital, Neonatal and Childhood Infections* is to provide a comprehensive, evidence-based, current reference book presenting up-to-date medical information required in the daily practice for those who care for neonates, infants, children, and adolescents with infections related to hearing loss. With the release of *Hearing Loss in Congenital, Neonatal and Childhood Infections*, we have aimed to guide the family physician, pediatrician, pediatric infectious diseases expert, and otorhinolaryngology specialists in the diagnosis and treatment of these infections and to manage children of all ages, whether they have hearing loss or not, with optimal care and outcomes, no matter what part of the world they live.

The *Hearing Loss in Congenital, Neonatal and Childhood Infections* could not have been created without our contributors' mentorship, professional expertise, co-authorship, and enthusiastic support, including world-renowned experts in pediatrics, pediatric infectious diseases, and otorhinolaryngology. One hundred forty-two author colleagues from 21 countries collaborated with their willingness,

enthusiasm, cooperation, effort, and time dedicated to preparing the *Hearing Loss in Congenital, Neonatal and Childhood Infections*. We have been exceptionally fortunate to have been able to work with them and count on their collaboration and contribution. Not enough words could be written to express our gratitude towards the authors of the *Hearing Loss in Congenital, Neonatal and Childhood Infections*.

We also would like to thank our teachers, mentors, parents, and families heartily for providing us with education, guidance, encouragement, help, patience, time, and a convenient environment supporting our intellectual aims and work.

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Part I

General Overview

Pediatric Hearing Loss

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1.1 Introduction

In adults, a majority of cases of hearing loss are sensorineural in nature, but in children, hearing loss is conductive in nature in between 90 and 95% of cases. However, sensorineural hearing losses are still commonly encountered in the clinical setting, and many cases of paediatric sensorineural hearing loss are congenital in nature. For children, an effusion of the middle ear, or otitis media accompanied by an effusion, (OME) is, by a considerable margin, the most common cause. It is still not fully known to what extent OME is responsible for persistent impairments in speech and language abilities. One reason for this uncertainty is that auditory impairment with OME can be very short-lasting and variable, the condition may be uni- or bilateral, any auditory impairment may be only mild, and there are multiple ways to treat the condition, both pharmacologically and surgically. Congenital causes of

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non-fluctuating conductive hearing loss (CHL) with a degree of severity ranging from moderate to severe are rare, but do occur in congenital aural atresia (CAA) or conditions affecting the ossicles, such as congenital stapes ankylosis. When these conditions are present, and especially if bilateral and not diagnosed and effectively managed, there is a possibility of persistent impairments in speech and language as well as academic performance [1, 2].

1.2 Sensorineural Hearing Loss

The hearing mechanism is extremely complex, and any malfunction of the inner ear, cochlea or central nervous system can lead to sensorineural auditory impairment of some degree of severity. Disorders of a biochemical, metabolic, haematological, endocrine or vascular type can all disrupt auditory function to a severe degree [3, 4].

1.2.1 Epidemiology

Auditory impairment has a global prevalence approaching 30%, with an estimated 70 million individuals suffering from deafness or bilateral profound hearing loss. There are marked differences between different international populations in terms of the number of cases due to acquired conditions and whether hearing loss is part of a syndrome or occurs in isolation. There are many reasons for this heterogeneity, including how common consanguinous unions are, the general state of health and population migration, amongst others, some of which have probably not yet been identified [4].

There are significant barriers to evaluating the true frequency of auditory impairment on a global scale. In many populations, accessing health services is challenging and health is generally poor, whilst many individuals are not aware of the possibility of auditory impairment. Furthermore, there are often elevated risks in these groups, due to a greater prevalence of neonatal distress, premature birth, extreme pyrexia, middle ear infections, meningitis, ototoxic medications and specific infections, notably rubella [5].

Both genetic and ethnic factors also influence the frequency of auditory impairment associated with syndromes, as well as, potentially, non-syndromic or acquired cases. A study in rural Nicaragua conducted by Saunders et al. ascertained that 18% of children attending school had auditory impairment, with 24% of the group having a positive family history of the same. A group of 96 children attending a clinic who presented with auditory impairment were evaluated for dysmorphological features. Anomalies were common, such as atresia, ears set low or atretic, childhood cataracts, underdeveloped cheekbones, hemifacial microsomia, undersized jaw and branchial cleft cysts. A defined syndrome was present in five individuals, although dysmorphic features were also common that appeared incidental to auditory impairment or did not fit a defined syndrome. The syndromes identified were neurofibromatosis, oculo-auriculo-vertebral, branchiootorenal, Poland and Down syndrome [5].

1.2.2 Aetiology

There are multiple ways in which sensorineural hearing loss (SNHL) may present. It may range from mild to profoundly severe and may affect high- or low-frequency sounds. Auditory impairment with a genetic cause may occur in isolation or within a syndrome. The former situation represents 70% of genetic cases, the latter 30% [4].

1.2.2.1 Autosomal Dominant Auditory Impairment as Part of a Syndrome

Autosomal dominant disorders responsible for auditory impairment occur less commonly than autosomal recessive disorders. Some of the syndromic conditions implicated are Waardenburg, neurofibromatosis, Tietze, Hermann, Leopard, Kearns-Sayre, Crouzon, Forney, achondroplasia, Duane, Marfan and branchiootorenal syndromes [4].

- Waardenburg syndrome
  - The most frequently occurring syndrome causing auditory loss with an autosomal dominant pattern of inheritance is Waardenburg syndrome (WS). This condition is responsible for 2% of cases of congenital auditory impairment in American children. The frequency is 2 in 100,000 births. According to a review undertaken by Song et al., 71% of those with WS experience auditory impairment, which mainly affects both ears and is of sensorineural type [6].
  - WS demonstrates an autosomal dominant pattern of inheritance with variable penetrance. After detailed studies of its genetic location, it has been mapped to 2q35 or 2q37.3. Mutated alleles of the PAX3 gene are responsible for WS types I and III. WS type II may sometimes be due to a mutated allele for the MITF gene. Mutated alleles coding for EDNRB, EDN3 and SOX10 are associated with type IV WS.
  - The condition results in the abnormal development of the temporal bone, with an atrophic organ of Corti and stria vascularis. There are insufficient neurons within the spiral ganglion. The resulting auditory impairment may affect one or both ears, and may be profound or moderate, in which case the ability to hear high-pitched sounds is preserved.
  - WS Type I has the following presenting features:
    The medial canthi and lacrimal puncta are always displaced laterally
    In three-quarters of cases, the nasal radix is elevated and exhibits hyperplasia
    In half of the cases, the medial section of the eyebrows is hyperplastic
    In a quarter of cases, there is complete or partial heterochromia of the iris
    The head overlying the forehead exhibits a clearly demarcated area of albinism or one of the forelocks has this appearance
    In a quarter of cases, there is sensorineural auditory impairment in one or both ears
  - Type II WS differs from type I by the absence of displaced canthi and the fact that as many as 55% of cases feature sensorineural auditory impairment. It

has been estimated that the frequency of type II WS is 20-fold that of WS type I.
  - Type III WS is associated with upper limb anomalies.
  - Type IV WS is associated with Hirschsprung disease [4].
- The next most frequently occurring type of syndromic auditory impairment exhibiting an autosomal dominant pattern of inheritance after WS is branchiootorenal syndrome. The presenting features are branchial cleft abnormalities, abnormal morphology of the kidney and abnormalities of the outer, middle and inner ear. The auditory impairment may be conductive, sensorineural or mixed in nature. There are pits located forward of the ear and the pinna is anomalous. The middle and inner ear exhibit structural anomalies. Mutated alleles for the EYA1, SIX1 and SIX5 genes are implicated in the aetiology [4].
- Neurofibromatosis 2 is the result of a mutant NF2 allele located on chromosome 22. It presents with multiple growths, which may represent schwannomas, meningiomas, gliomas or ependymomas. In some patients, these growths are seen even at the age of 8–12 years. If auditory impairment is secondary to the development of a schwannoma within the vestibule and surgery is performed at an early stage, the hearing may be recovered, although this represents an exceedingly small fraction of cases [4].

1.2.2.2 Autosomal Recessive Disorders

- **Usher syndrome** [7]
  - Usher syndrome has a stated frequency in the literature of 3 in 100,000 live births. Still, nearly 1 in 10 cases where auditory impairment is apparent from birth is due to Usher syndrome. Inheritance follows an autosomal recessive pattern. Usher syndrome is the most frequently occurring cause of deafness inherited in this fashion. Patients with the condition progressively lose sight secondary to developing retinitis pigmentosa and the auditory impairment is of sensorineural type and typically at least of moderate severity. Half of Americans who are both deaf and blind have Usher syndrome.
  - It is challenging to diagnose visual loss in infants. Examining children using a fundoscope up to the age of 10 years is challenging. Although it is possible to detect the early signs of retinal damage in a young child using electroretinographic techniques, this method is not usually easily accessible. As retinitis pigmentosa progressively develops, it may become apparent as loss of visual fields or nyctalopia. Visual ability progressively deteriorates, such that half of those affected by the condition are totally blind by the time they are 50 years old.
  - Typically, there is auditory impairment present congenitally. Progression to profound loss is eventually noted in 85% of cases. The histological appearances show the cochlear sensory epithelium is degenerated. Since there is a loss of microphonic potentials normally generated by the cochlear hair cells, it appears that the dysfunction of these cells is how auditory loss occurs. It is common to find that patients whose hearing loss is of high severity also have vestibulocerebellar syndrome.

  - Usher syndrome is found in 3 variants:
    In type I, the auditory loss is severe or profound in both ears from birth, and there are abnormalities in the vestibular system.
    In type II, congenital hearing loss is mild or moderate, and there are no vestibular abnormalities.
    In type III, hearing loss progressively worsens, and there are vestibular abnormalities.
  - The genetic mutations responsible for Usher's syndrome are complicated. Mutated alleles in at least ten different locations have been identified, in conjunction with eight actual gene mutations, notably MYO7A, USH2A, CDH23 and PCDH15 [8].
- Pendred syndrome is diagnosed by the presence of a clinical triad of hearing loss present from birth, thyromegaly with multiple nodules and abnormally rapid loss of iodine on perchlorate testing [7].
  - The thyroid enlargement is not congenital. It happens because iodine is abnormally incorporated into thyroglobulin. Between 5 and 10% of patients whose auditory impairment is inherited in an autosomal recessive fashion have Pendred syndrome. It usually affects both ears and the loss is greatest at the high frequencies. The fact that positive recruitment occurs in audiological testing points to cochlear involvement. There is frequently Mondini dysplasia present in the cochlea with enlargement of the vestibular aqueduct.
  - The SLC26A4 mutant allele is often found in such cases. This gene codes for the pendrin protein, the normal function of which is anionic exchange of chloride, iodide and bicarbonate ions through cells' outer membranes. Pendrin plays a key physiological role in the inner ear and thyroid [9]. There are genetic screens available for mutant SLC26A4 alleles. They should be used in cases where Mondini dysplasia or enlargement of the vestibular aqueduct is noted.
- The third most frequently observed syndrome causing auditory loss, inherited in an autosomal recessive fashion and responsible for 1% of such cases, is the Jervell-Lange-Nielsen syndrome. The features of this condition are abnormal elongation of the QT interval in electrocardiography, Stokes-Adams syncope, severe auditory impairment present from birth and sudden death. The Stokes-Adams episodes often commence while the child is still young. Sudden death may occur at an older age. Otoscopy findings indicate various heart-related abnormalities, such as degenerated sinoatrial nodal fibres, fibrotic tissue formation, haemorrhage and infarcted tissue [4].
  - When the temporal bone is examined, the organ of Corti and spiral ganglion are noted to be atrophic. On histological examination of periodic acid-Schiff stained sections of the membranous labyrinth, hyaline is noted to be extensively deposited in the labyrinth. The utricular and saccular sensory cells are also atrophic.
  - Although QT prolongation may be picked up on electrocardiography, this method is not very sensitive. In a child where there is a positive family history

of sudden death, sudden infant death syndrome (SIDS), fainting attacks or abnormal prolongation of the QT interval, a detailed investigation is warranted.
  - It is believed that mutant alleles for the KCNQ1 (or, more infrequently, the KCNE1) gene may be responsible for this syndrome. These genes code for proteins involved in the transportation of K^+ ions. Potassium transport is vital for both inner ear and cardiac function. The KCNE1 and KCNQ1 gene products assemble to make a transmembranous complex which can remove potassium cations out of the cytoplasm. If potassium ion transport is disrupted, the myocardium and inner ear may both malfunction, leading to the characteristic signs and symptoms [10].
- In Cockayne syndrome, patients exhibit dwarfism, atrophied retina and auditory impairment. The syndrome typically presents between the ages of 1 and 2 years. It is inherited in an autosomal recessive fashion. The clinical picture involves short stature, a kyphotic spine with fused joints, mandibular protrusion, deep-set eyes, learning disability, atrophy of the retina, thickening of the skull, dental caries and auditory impairment. Usually, the hearing loss is progressive, sensorineural and bilateral. There is also neurodegeneration in the spiral ganglion and cochlear and olivary nuclei. The Genetics Home Reference states that the aetiology is mutated alleles of the ERCC6 and CRCC8 genes. The product of these genes features in DNA repair. When repair does not occur, there is a build up of defective DNA which prevents the cell from surviving. This then explains why growth is restricted and ageing occurs prematurely [11].
- Patients with Alström syndrome have retinitis pigmentosa, diabetes mellitus and cardiomyopathy, and are abnormally short and obese and suffer from progressive auditory impairment. In some, but not all cases, hepatic and renal failure occurs, as well as lung disease. The auditory impairment is usually of sensorineural type and characteristically begins within the first decade of life. The syndrome is inherited in an autosomal recessive fashion. The mutated ALMS1 gene has been implicated in the disorder, although what role the gene product plays is not yet established [12]. Nadol et al. undertook a histopathological investigation into cases of Alström syndrome. They found that sensorineural auditory impairment was associated with degenerative features in the inner and outer hair cells of the organ of Corti, neurodegeneration within the cochlear ganglion, together with atrophic appearances of the stria vascularis and spiral ligament. These features were noted in two cases where the diagnosis had been confirmed by genetic testing [13].
- Cases of Refsum disease exhibit an autosomal recessive pattern of inheritance and present with retinitis pigmentosa, ichthyosis, polyneuropathy, cerebellar ataxia and auditory impairment. Patients with Refsum disorder generally live until the age of 10–20 years. In patients older than 20, visual impairment is characteristic. Over half of the cases feature a progressive auditory impairment of the sensorineural type. Histopathological examination shows the organ of Corti and the stria vascularis to be degenerated.

There are also a number of causes of auditory impairment where the pattern of inheritance is X-linked, variable or obscure [4].

1.2.2.3 X-Linked Disorders and Other Disorders of Variable Inheritance

- The most frequently occurring genetic cause of nephritis is Alport Syndrome. It affects 1 in 200,000 people. The features of this condition are haematuria, posterior cataract formation, a dystrophic cornea and a dislocated lens. Interestingly, Alport syndrome occurs at a higher frequency in girls than boys, but the symptoms are more severe in males, with terminal kidney failure often noted between the ages of 10 and 30 years. Without treatment, male cases are fatal before the age of 30 years. The onset of clinical features is usually before the age of 10 years [4].
  - Auditory impairment generally affects both ears to the same extent. It can also be of the sensorineural type, with the greatest loss affecting higher-pitched sounds. The condition can be inherited in various ways: autosomal dominant and recessive forms are encountered, but the majority of cases (85%) feature X-linkage. Mutated alleles for the COL4A3, COL4A4 and COL4A5 genes have been implicated in the aetiology.
  - COL4A3, COL4A4 and COL4A5 encode for collagen of type IV. This material is vital to the formation and physiological function of the basement membrane of both the renal glomerulus and the stria vascularis. Within the kidney, the defective collagen eventually causes the glomerular basement membrane to fail and thus terminal kidney failure ensues. Exactly how auditory loss occurs has not yet been established, although Merchant et al. have ascertained that, within the organ of Corti, there are dysmorphic cells and the basilar and basement membrane separate [14].
- Norrie disease is a rare disease, resulting in potential blindness, delayed motor skill acquisition, learning disability and auditory impairment. Its aetiology is a mutated allele for the NDP gene found on the X-chromosome. This gene encodes norrin, a signalling molecule involved in development, which causes cells to divide, adhere to each other or migrate [15].
- It is common for conditions causing congenital metabolic abnormalities to feature sensorineural auditory impairment amongst their presenting features. Examples include the mucopolysaccharidoses, such as Hurler and Hunter syndromes, and sphingolipidoses, such as Fabry disease [4].
  - The features of Hurler syndrome are intellectual disability, excessively short stature, a kyphotic spine, enlargement of the liver and spleen and auditory impairment. It shows a pattern of autosomal recessive inheritance. This disorder results from an excess accumulation of heparin and dermatan sulphate (both of which are glycosaminoglycans). Auditory impairment is usually of mixed type, but with a marked loss of the higher pitched sounds. Histopathological examination of the temporal bone indicates positive staining with periodic acid-Schiff of the mesenchymic material and the organ of Corti has degenerated appearances. It is unusual for patients to live beyond

the age of 13 or 14. Hunter syndrome shares many clinical features with Hurler syndrome, but exhibits X-linkage.
  - Hunter syndrome is a less severe disorder, and affected patients may live into their early twenties. Auditory impairment can follow several patterns: conductive, sensorineural or a mixture of the two.
  - Another disorder exhibiting X-linkage is Fabry disease. The aetiology involves accumulated sphingolipids within the endothelium, smooth muscle and ganglia. Auditory loss usually affects both ears and is mainly sensorineural, with the highest-pitched sounds the most affected. Histopathological examination of the temporal bone reveals an atrophic cochlear ligament with sphingolipids deposited within the endothelium of the vessels and the ganglionic cells.
- Trisomy 13 affects 1 in 6000 births. The severity of the associated anomalies present at birth is so high that the majority of such cases are fatal within the first year. Babies with the condition are microcephalic, have labiopalatal deformities, possess extra digits, rocker-bottom feet, ears which are set low and malformed, have the heart shifted to the right, the scalp is defective and there is intellectual disability. Histopathological examination of the temporal bone indicates cyst formation in the stria vascularis, an abnormally short cochlea, degeneration of the saccule and abnormality of the semi-circular canals [4].
- The incidence of trisomy 18 has been estimated at between 1 in 5000 and 1 in 10,000 live births. The majority of affected infants die within the first 3 months. However, as many as 13% of such infants may survive up to one year and beyond. The presenting features are malformation of the external ear, small jaw, prominence of the occiput, abnormality of the intestines and intellectual disability. Histopathological examination of the temporal bone shows that the stria vascularis has failed to grow to full size, the semicircular canals are abnormal and there is paucicellularity of the cochlear ganglia.
- The most frequently occurring chromosomal disorder globally is Down syndrome (Trisomy 21). Trisomy 21 occurs in 1 in 1000 of all births, but the frequency greatly increases as the age of the mother increases, with an incidence of 1 in 25 births for women over the age of 45. Some of the characteristic features are a shortened and broad trunk, epicanthal folds, low muscle tone, congenital cardiac disorders and intellectual disability. Almost 78% of patients with trisomy 21 have auditory impairment, which can be conductive, sensorineural or a mixture of the two. On histopathological examination of the temporal bone, there may be remnants of the mesenchymal tissue in the middle ear, serous accumulation within the labyrinth and the seventh cranial nerve forms a wider than usual angle at the genu [4].
- The first description of Klippel-Feil syndrome was in 1912. The features include at least two vertebrae in the neck being fused from birth, high scapula, spina bifida, an asymmetric appearance to the face, muscular spasticity and congenital cardiac disease. If Klippei-Feil syndrome occurs together with a sixth cranial nerve palsy in both eyes and deafness, the term Wildervanck syndrome is used. Auditory impairment is profound and sensorineural in kind, although some

reports also mention conductive pattern deficits or a mixed type of impairment being present. The inner ear is hypoplastic, and the osseous and membranous labyrinths both fail to develop. The condition exhibits genetic heterogeneity.

- In Wildervanck syndrome, also termed cervico-oculo-acoustic dysplasia, the vertebrae of the neck are fused, the neck is shortened and the hairline is low at the back (i.e. features of Klippel-Feil), plus the eyes are deepset, there is auditory impairment of both sensorineural and conductive type and the patient has difficulty looking to the side. More girls than boys are affected. The disorder is inherited in a dominant fashion and is X-linked [4].
- Albinism occurs when the production or distribution of melanin is abnormal. In patients with oculocutaneous albinism, the skin, hair and eyes are all unpigmented. This disorder has an autosomal recessive pattern of inheritance. The majority of patients with albinism who present with sensorineural deafness have oculocutaneous albinism. The auditory impairment ranges in how severe it is [4].
- It is believed that otopalatodigital syndrome exhibits X-linkage and has a recessive pattern of inheritance. Some of the characteristic features are cleft palate, fish mouth, clinodactyly, prominence of the forehead, wide-set eyes and antimongoloid slanting of the palpebral fissures. The ossicles are also malformed, which results in auditory impairment of the conductive type [4].
- There are a number of other syndromes inherited in an X-linked fashion which cause auditory impairment, such as oculocraniosomatic syndrome, myoclonic epilepsy with ragged red fibres, MELAS (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) and MIDD (maternally inherited diabetes and deafness) [4].

1.2.3 Signs and Symptoms

The clinical history should include the following aspects [4]:

- History of the pregnancy
- Events during birth
- Development after birth
- Family history

The following are areas of the physical examination or investigation that may reveal a syndrome underlying auditory impairment [4]:

- Otoscopy
- Ophthalmoscopy
- Dermatologic examination
- Cardiovascular examination
- Renal examination
- Oral cavity and oropharyngeal examination
- Endocrine or metabolic studies

- Chromosome examination
- Nervous system examination
- Skeletal system examination
- Craniofacial examination

The following are features of the presentation which suggest an underlying syndrome responsible for auditory impairment [4]:

- When examining the ears, the following findings are significant
  - An abnormal pinna is seen in the Treacher-Collins and Goldenhar syndromes.
  - An atretic or stenosed external auditory meatus is also seen in these two syndromes.
  - Preauricular pitting may be part of a branchiootorenal syndrome.
  - Preauricular skin tags are seen in Goldenhar syndrome.
  - Radiological evidence of an enlargement of the vestibular aqueduct may be seen in Pendred, Kabuki, Turner or Opitz-Frias syndromes.
  - Lopped ears may be part of Down syndrome or otopalatodigital syndrome.
  - Cup ears are part of Pierre-Robin syndrome.
  - Undersized ears are seen in Treacher-Collins, Goldenhar, first branchial cleft, Möbius and Duane syndromes
- When examining the eyes, the following findings are significant [4]:
  - Cataracts may indicate congenital rubella.
  - Coloboma may be part of the CHARGE syndrome: coloboma, heart abnormality, atretic choanae, growth retardation, genital and ear anomalies.
  - The canthi are displaced in Waardenburg syndrome.
  - There is also heterochromia of the iris in this condition.
  - Keratitis is observed in Cogan syndrome.
  - The eye muscles are weakened in Duane syndrome.
  - Atrophy of the retina is seen in Cockayne syndrome.
  - Usher syndrome patients have retinitis pigmentosa.
  - The retina shows a degenerative change in cases of Alström syndrome.
  - Children who have been blind since birth and present with a retinal pseudotumour may have Norrie syndrome.

1.2.4 Diagnosis

There is no consensus for a routine laboratory screening of paediatric patients with hearing loss. Some of the laboratory tests which may be of value in particular cases include [4]:

- Genetic screening, including a genetic panel of hearing loss disorders
- Full blood count including differential
- Urea and electrolytes
- Blood glucose

- Urea, nitrogen and creatinine blood level
- Thyroid function tests
- Urine analysis
- Fluorescent treponemal antibody absorption (FTA-ABS)
- IgM titres for specific antigens
- Autoimmune screening blood

The following are the imaging modalities of the most value in diagnosis [4]:

- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
- Ultrasound examination of the kidney
- CT Imaging
  - CT imaging can be set up to produce slice images at a distance of no more than 1 mm apart. The resulting scan is of high resolution and allows the osseous anatomy, the inner ear and the ossicles to be clearly seen.
  - CT is valuable in finding cases where surgery may be able to improve sensorineural hearing impairment. It also helps to evaluate the degree of dysplasia, with less dysplasia offering an improved chance of benefiting from treatment. Since CT imaging reveals an abnormality in as many as 30% of cases of auditory impairment, this imaging modality plays a key role in diagnostic assessment. As an example, patients with Pendred syndrome often show enlargement of the vestibular aqueduct and Mondini dysplasia on CT [4].
- The ability to visualise soft tissues means that MRI is especially useful when assessing the inner ear, the internal auditory canal and the cerebellopontine angle.
- Ultrasound examination of the kidney is helpful diagnostically if a renal anomaly is being considered [4].

Auditory assessment:

- This involves the use of methods designed to evaluate auditory loss, such as audiometry and tympanometry [4].
- There are tools which may be used to diagnose and qualify auditory loss in neonates even within the first 24 h after birth. These methods have a high level of reliability and validity, for example [4]:
  - Auditory evoked potential/auditory brainstem response (AEP, ABR)
  - Audiometry
  - Tympanometry
  - Acoustic reflex threshold measurement
  - Otoacoustic emissions (OAE)

1.2.5 Treatment

- Pharmacotherapy: Drug treatment is appropriate for diseases of the middle ear, such as otitis media [4].
- Amplifying hearing
  - The aim of amplifying hearing is to make use of whatever auditory function is available, so that, as a minimum, patients become accustomed to their surroundings and begin to develop at least rudimentary speech. In most cases, implantation of an amplificatory device up to the age of 6 weeks is successful.
  - There are several types of devices which may be used, including conventional analogue devices, digital hearing aids, aids which boost osseous conduction and bone-anchored hearing aids. There are a number of devices being developed which are for implantation in the middle or inner ear [4].
- Assistive listening equipment and personalised devices [4]:
  - Devices for individual use, e.g. FM (frequency modulation) trainers, are designed to reduce how noisy the signal is in environments where this presents significant difficulties, such as a classroom.
  - There are several devices to assist with telephones, such as amplifiers, coupling devices to match specific hearing aids and specially adapted telephones for deaf individuals who find an ordinary telephone too hard to use.
  - Televisual devices may offer closed captioning, which helps patients with severe auditory loss.
  - Signalling devices provide a visual warning instead of an auditory signal. For example, these devices can warn the user that the doorbell has rung, the telephone is ringing, an alarm is sounding or a child is crying.
- Surgery
- Operative interventions may be needed for some anomalies of the external or middle ear, affecting one or both ears [4].

1.2.5.1 Cochlear Implants

A cochlear device is an electronic device which can transduce a sound signal into electrical impulses to be transmitted to the cochlear nerve. Such devices are especially beneficial where an individual is not assisted in hearing by straightforward amplificatory techniques [16–18].

Prior to the procedure, an MRI scan may be helpful to confirm the integrity of the cochlear nerve. CT imaging is a routine way of assessing pathology affecting the cochlea.

There are significantly improved linguistic abilities in patients under the age of 5 years following a cochlear device being implanted. The operation may be undertaken when the child is one year; consideration is given to earlier surgery in cases of hearing loss resulting from meningitis.

Alzhrani et al. compared the outcomes from cochlear implantation in paediatric patients with auditory impairment either secondary to a syndromic condition, such as Waardenburg, Usher or Dandy-Walker syndromes or albinism or of non-syndromic cause. The outcomes in both groups were similar, with the perception of

sound, the ability to identify spoken words and the pure-tone perception not differing greatly [19].

1.3 Conductive Hearing Loss

Whilst it has been well established that sensorineural hearing loss is present from birth in between 1 in 3 children with any kind of sensorineural loss, the incidence of conductive hearing loss at birth is less clear, but likely much lower. CHL occurs secondary to obstruction, abnormal function or anomalous development of the external auditory canal/meatus, tympanic membrane or the middle ear apparatus. A trial involving 234 children under the age of one year who were referred for diagnostic evaluation following neonatal auditory screening found a rate for congenital CHL of 2.97 per 1000 infants, whilst 4.36 per 1000 of this group had middle ear disease (not always resulting in auditory impairment). The researchers comment that, "In the literature pertaining to CHL in children, the emphasis is on cause rather than severity, making prevalence data difficult to compare" [20]. Despite considerable research efforts devoted to evaluating the persistence of problems in acquired or congenital paediatric CHL, particularly in relation to otitis media with an effusion, no definite consensus on the findings has yet been reached [21–24].

1.3.1 CHL Present at Birth

CHL present from birth is rarely the result of anomalous middle ear development. The various conditions responsible for anomalous middle ear development are CAA, in cases in which the external ear canal is not present or is stenosed, coupled with underdeveloped ossicles within the middle ear and some minor anomalies of the auditory system [25]. In the latter cases, there is no abnormality of the auricle, the external auditory meatus is open and complete and the ear drum is whole, but the ossicles are deformed, immobilised or otherwise disrupted. Such minor anomalies include congenital ankylosis of the stapes, the persistence of the embryonic stapedial artery, fixation of the malleus by the formation of a bony bar and the absence of the oval window. The resulting auditory impairment may range in severity from slight effects to severe deafness and may not be apparent on neonatal auditory screening. Thus, diagnosis may not occur until a child is old enough to cooperate with auditory behavioural tests. Some of the minor anomalies may also occur in cases of CAA, in particular malleus fixation and incudo-malleolar fixation [1].

1.3.1.1 Congenital Aural Atresia

CAA occurs at a frequency of between 1 in 10,000 and 2 in 10,000. CHL associated with this condition is typically moderate or severe. The threshold for bone conduction is typically normal. In approximately 70% of cases, atresia and microtia affect only one side. The condition is more frequent in males than females and the affected side is usually the right. It is not yet known why CAA demonstrates these

characteristics. There are also ethnic factors at play, since atresia and microtia are more common in individuals of Hispanic or Asian ancestry, particularly if they originate from Ecuador. Whilst the aetiology is still obscure, one theory is that when the auditory meatus and middle ear fail to grow, the first pharyngeal arch cannot complete its transformation. There is evidence linking CAA to abnormality of chromosome 18, particularly where microtia does not occur, which is the case in a minority of patients with CAA [26]. There is also a competing hypothesis that foetal positioning in utero plays a role by restricting the vascular supply [1].

In cases where microtia is involved (the majority), recognising CAA is unproblematic. Nevertheless, in a minority of cases, there is a normal-sized ear, so this diagnostic clue is absent. Therefore, otoscopy is essential to identify the state of the auditory meatus. The diagnostic evaluation also needs to involve assessing potential abnormalities of the kidney, spine, and skull and face bones. CAA occurs in association with some syndromes, notably hemifacial microsomia in Goldenhar syndrome and Treacher Collins syndrome [1].

1.3.2 Acquired CHL

1.3.2.1 Otitis Media with Effusion

Many young patients have fluid present in the middle ear, but do not show any signs or suffer from any symptoms that imply an infection, whether acute or chronic. It has been calculated that, on average, there are always around 20% of children who have a middle ear effusion. Indeed, it has been suggested that nearly all children have at least one middle ear effusion over the course of childhood [27]. OME is frequently seen after an infection of the upper respiratory tract or may be a complication of acute otitis media. It generally resolves spontaneously. There is an elevated risk of OME compared to the general paediatric population in particular groups. For example, OME is more common when the patient has Down syndrome, as a result of relative muscular hypotonia. It is also much more common in cases of cleft palate, with a frequency approaching 100%. This is attributable to the anomalous position where the levator and tensor veli palatini muscles insert on the eustachian tube, leading to difficulty in actively opening the tube [28–30]. Boys are also at heightened risk, as are children who are immunodeficient, have dyskinetic cilia, are formula fed or where there is a smoker in the house. Other risks include having more brothers or sisters in a household and attending a childcare facility; the latter is the strongest risk factor [31]. Tympanometry reveals a type B (flat) pattern in around 85–100% of cases with OME [32]. While some treat this as a diagnostic finding, it is important to note that this abnormality is also seen even with no effusion present, such as in cases of tympanosclerosis or following tympanic membrane repair. Thus, it has been argued that the best way to diagnose OME is to make use of pneumatic otoscopy [1].

1.3.2.2 Conductive Auditory Impairment Linked to Chronic Otitis Media

The definition of chronic otitis media (COM) generally includes perforation of the eardrum, whether cholesteatoma is present or not. Most cases of tympanic membrane perforation occur in the setting of prior tympanostomy tube placement or simply as a consequence of myringotomy. Generally speaking, the tubes are placed in the anteroinferior quadrant and do not result in conductive auditory impairment. Where CHL is a result of a perforated eardrum, the loss typically affects lower frequencies. There is a correlation between the increasing size of the perforation and more severe hearing loss; however, where the perforation occurs does not seem to influence how severe the auditory impairment becomes [33]. Prior to myringoplasty, the extent of auditory loss should be quantified using audiometry to calculate the air and bone conduction thresholds. The outcome of tympanic repair in children is influenced by factors related to both the patient (i.e. intrinsic) and the clinician (i.e. extrinsic). Patient-related factors include how old the child is, whether there is drainage of liquid from the ear, if the eustachian tube continues to malfunction, whether the condition is uni- or bilateral, the general state of health and where and how large the perforation is. Factors related to the surgeon include the approach used, the method followed and how experienced the surgeon is [34, 35]. It is likely that the risk factor of greatest significance is patient age, with patients aged under 4 years generally faring less well than those above that age [36]. However, it has not yet been established at what age the outcome has the highest probability of success. Whether the condition is uni- or bilateral also plays a key part [35]. There are a large number of ways to conduct tympanic repair in children, including myringoplasty using fat with or without hyaluronic acid for grafting [37, 38], underlay and overlay or lateral graft applications. For tympanic repair to have the maximum chance of a successful outcome, the patient and surgeon factors need to be optimised and clinicians should learn from evaluating their own outcomes in practice and adjusting their practice so as to favour those techniques most associated with success [1].

1.3.2.3 Tympanosclerosis

Tympanosclerosis occurs where persistent or repeated inflammatory episodes affecting the middle ear lead to fibrotic scarring, which may result in ossicular immobilisation and therefore an auditory impairment of the conductive type. Where tympanosclerosis affects only the eardrum (i.e. myringosclerosis), it typically does not result in any measurable hearing loss, but where there is ossicular involvement, it may lead to a slowly progressive loss conductive in nature. Patients who have suffered repeated infectious episodes of the middle ear, as well as those with tympanic thickening, may have this type of progressive auditory impairment, and in such cases, the possibility of the ossicles having become fixated through fibrosis should be considered.

1.3.2.4 Cholesteatoma

Cholesteatoma is a condition wherein the stratified squamous epithelium proliferates beyond the normal level—on the external surface of the tympanic

membrane—into the region of the middle ear. It may be present from birth or acquired later. It generally causes conductive hearing loss through direct impingement on the ossicles or by eroding the ossicles. Cholesteatoma occurs as a primary condition after birth and begins with tympanic membrane retraction. This is typically the result of eustachian tube malfunction. Sinus cholesteatoma affects the posterior aspect of the pars tensa whilst the more common attic cholesteatoma affects the pars flaccida. The portion of the tympanic membrane where retraction occurs forms a pocket with a lining composed of normal stratified squamous epithelium and filled with keratin sloughed by desquamated cells. Secondary acquired cholesteatoma occurs following the perforation of the tympanic membrane if the epithelium regrows in the wrong direction (i.e. into the middle ear, rather than closing off the defect) [1].

The main objective of operative intervention is to clean and dry the ear, leaving it safe from further disease arising from recurrence or as a result of parts of the cholesteatoma remaining in situ. The condition recurs more commonly in paediatric than adult cases, which may be due to the fact the eustachian tubes are still developing in a child. The other objective is to remedy any CHL resulting from the condition. To achieve this, the reconstruction of the ossicles may be needed, either at the time of cholesteatoma removal or subsequently. A conventional hearing aid may help, as may a bone conduction device; consideration should also be given to educational accommodations, including an FM system and preferential seating [1].

1.4 Conclusion

Paediatric hearing loss may be congenital or acquired, sensorineural or conductive. While sensorineural loss is more common in pure congenital hearing loss, the most common cause of hearing loss in the general paediatric population remains otitis media with effusion. Individual patient factors dictate differences in diagnostic and therapeutic approaches.

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Newborn Hearing Screening

2

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2.1 Introduction

Congenital hearing loss (HL) is the most common congenital disability. According to the World Health Organization (WHO), the estimated prevalence of disabling HL in the neonatal period is 2 per 1000 live births [1]. Hearing loss in infancy has a marked negative impact on developing communication skills and achieving good academic and social performance. Even mild losses yield delayed speech and language development [2]. Time is crucial in managing the diagnosis and rehabilitation of HL in infancy. If early access to rehabilitation is provided, infants with hearing impairment may achieve comparable speech and language development with their normal hearing peers. Such performance is less likely in infants diagnosed with HL after the first 6 months of life due to missing the critical period for the maturation of the central auditory pathway [3, 4].

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Awareness of the positive impact of early diagnosis and prompt intervention on congenital HL dates back to the 1940s [5]. But establishing the first universal screening program took several decades because of the lack of feasible screening methods. After the introduction and widespread use of objective physiologic screening tests like automated otoacoustic emissions (A-OAEs) and automated auditory brainstem response (A-ABR), universal newborn hearing screening (NHS) programs gradually spread worldwide [6–8]. Newborn hearing screening has provided a definite advantage in detecting HL compared to previous methods, such as behavioral or risk-targeted screening [9–11].

The mean time interval for the diagnosis of congenital HL is 4.6 months, and the mean time interval for the first intervention is 6.7 months in very highly developed countries for infants enrolled in an NHS program. On the contrary, the mean time intervals for diagnosis and first intervention are 34.9 months and 36.7 months in unscreened infants [11]. As a consequence, NHS has become a routine of the national healthcare system in many countries in the new millennium, but overall global access to NHS is still limited. A recent survey showed that 38% of newborns are born in countries with less than 1% NHS coverage [12].

Screening is the initial effort for the early diagnosis and remediation of congenital HL. Further steps require strong participation of the families and interdisciplinary collaboration among medical professionals like otorhinolaryngologists, audiologists, and pediatricians. According to Holte et al. [13], only one-third of the infants who failed the initial screening receive a timely diagnosis and enroll in an early intervention program. Therefore, the NHS system should be family-centered to avoid follow-up loss and encourage the family members to maintain the diagnostic and remediation procedure. It should be emphasized that passing the screening tests does not mean that the hearing threshold of the infant is within normal limits.

Current audiologic screening tests may miss mild (thresholds under approximately 35–40 deciBel [dB]) or neural HL, and progressive or delayed-onset HLs are still cause for concern, particularly in infants who have specific risk factors [14]. As the incidence of disabling HL in school-age is twice as high as in the neonatal period, ongoing surveillance of auditory perception and communication skills should be mandatory in all children [15]. Risk factors for progressive or delayed-onset HL are listed in Table 2.1 [14, 16–18]. Infants who meet any high-risk criterion must receive a meticulous audiologic evaluation in the first 9 months of age [14].

Table 2.1 Risk factors for progressive or delayed-onset hearing loss[a]

Perinatal
1. Family history of deafness with onset in childhood
2. The neonatal intensive care unit stay longer than 5 days
3. Mechanical ventilation
4. Hyperbilirubinemia requiring exchange transfusion
5. Perinatal asphyxia and/or hypoxic–ischemic encephalopathy
6. Extracorporeal membrane oxygenation (ECMO)
7. In-utero infections: Cytomegalovirus, rubella, toxoplasmosis, syphilis, herpes, human immunodeficiency virus, Zika virus
8. Craniofacial and physical conditions related to hearing loss
9. Very low birth weight (<1500 g)
10. Maternal substance use disorder
11. Syndromes related to hearing loss
Perinatal or Postnatal
1. Ototoxic medications: aminoglycosides, diuretics
2. Meningitis or encephalitis
3. Head trauma
4. Suspicion of hearing loss and related abnormalities noticed by family or caregiver

[a] Adapted and modified from Ref. [14, 16–18]

2.2 Etiology

2.2.1 Prenatal Period

2.2.1.1 Genetic Factors

Hearing loss is genetic in origin in more than 50% of neonates [19]. Hereditary HL may accompany other disorders like visual impairment, endocrinologic and neurologic pathologies as a part of a syndrome, or present as isolated defects. More than 250 genes are associated with hereditary HL [1]. Inheritance of the genetic HL may be in autosomal recessive (AR), autosomal dominant (AD), X-linked (XL), or mitochondrial manner.

Consanguineous marriages increase the risk of congenital diseases, as well as HL [20], and linguistic homogamy (intermarriage between deaf individuals) has an essential role in the increased prevalence of recessive mutations in connexin 26 genes [21]. Genetic counseling and testing are recommended for all infants with HL [22].

Syndromic Hearing Loss

Over 400 identified syndromes exist associated with HL [23]. Of these, Pendred syndrome, related to the solute carrier family 26 member 4 (SLC26A4) gene mutations in both alleles and inherited in an AR manner, with a due of 10% seems to be the most common reason for syndromic HL [6, 24, 25]. The SLC26A4 gene provides instructions for making a protein called pendrin which transports negatively charged particles (ions), including chloride, iodide, and bicarbonate, across cell

membranes. Pendrin is produced in several organs and tissues, particularly the thyroid gland and inner ear.

Pendred syndrome is characterized by goiter, sensorineural HL (SNHL), and an enlarged vestibular aqueduct (EVA). Goiter may not be apparent until adolescence, and HL may be late-onset. Thus, the diagnosis of Pendred syndrome may be delayed. There appears to be a relationship between the most common inner ear malformation EVA and SLC26A4 mutation [24]. Apart from Pendred syndrome, 61% of nonsyndromic patients with EVA also carry a heterozygous SLC26A4 mutation [25].

Usher syndrome is characterized by retinitis pigmentosa, SNHL, and in some forms, vestibular symptoms. Usher syndrome is the most common cause of deafness and blindness combination. Impairment in hearing and visual functions yields specific limitations in communication skills, so early intervention for HL is critical to maintain auditory perception and speech and language development.

Biotinidase deficiency is one of the preventable causes of HL. Although it is a rare, about 1/60,000, metabolic disease in the Western population, the incidence may be as high as about 1/7000 in countries such as Turkey and Brazil [6, 26, 27]. When biotinidase deficiency is diagnosed in the neonatal period, it is possible to prevent HL with biotin supplements [27]. Neonatal biotinidase activity screening is routine in many countries' newborn screening programs.

Some of the most common syndromes associated with deafness are summarized in Table 2.2 [6, 22, 23].

Nonsyndromic Hearing Loss

Nonsyndromic HL constitutes the vast majority (80%) of the genetic HLs and can be caused by mutations in nuclear and mitochondrial genes. Inheritance is mostly (80%) in an AR manner. Autosomal recessive nonsyndromic HL inherited from normal-hearing parents is the most common (75–80%) scenario among congenital genetic HLs [19]. The risk is even higher in consanguineous marriages and assortative matings among the deaf population [28].

Gap junction protein beta-2 (GJB2) gene mutations are the most common cause of nonsyndromic deafness and account for about 30–50% of all cases [29]. More than 100 distinct mutations affect the GJB2 gene, but 35delG consists of about 70% of all mutations [30]. The gap junction protein beta-2 gene encodes a transmembrane protein, connexin 26, expressed widely in stria vascularis and the basement membrane of the cochlea. Connexin 26 protein is essential in potassium (K^+) ion homeostasis and maintaining the high endocochlear potential necessary for normal inner ear function [31]. The pathology in connexin 26-related deafness is limited to cochlear hair cell damage, and higher brain functions are expected to be normal, unlike in many connexin 26 unrelated etiologies. Histopathologic evaluations revealed normal neural infrastructure and spiral ganglion cell population despite the severe degeneration of sensory cells in connexin 26-related deafness [32]. These make GJB2-related deaf children excellent candidates for cochlear implantation, as cochlear implants bypass the cochlear hair cells and directly stimulate the spiral ganglion cells [33].

Table 2.2 Summary of features, type of inheritance and incidence of some of the most common syndromic hearing loss[a]

Syndrome	Characteristic features	Inheritance	Incidence (among deaf people)
Pendred syndrome	EVA and SNHL, vestibular symptoms, and goiter	AR	4–10%
Usher syndrome	SNHL, vestibular symptoms, retinal dystrophy, hematuria, and renal failure	AR	4–6%
Waardenburg syndrome	Hearing loss, hypopigmentation in the eye, skin, or hair, white forelock, heterochromia iridis, and dystopia cantorum	AD/AR	1–4%
Branchio-oto-renal syndrome	Hearing loss, branchial arch malformations (branchial fistula, external auditory canal, and auricula malformations, pre-auricular pits), and renal malformations	AD	2%
Alport's syndrome	SNHL, hematuria, progressive renal failure, and ocular abnormalities	XL/AR	1%
X-linked deafness	Characteristic with incomplete partition type 3 malformation of the cochlea (bulbous internal auditory canal, absent modiolus). Progressive hearing loss	XL	>1%
Treacher Collins syndrome	Midface hypoplasia, microtia, cleft palate, and conductive type hearing loss	AD	1%
Jervell and Lange-Nielsen syndrome	SNHL, prolonged QT interval, syncopal attacks, and sudden death	AR	0.25–0.5%
Biotinidase deficiency	Neurologic and cutaneous abnormalities: SNHL, seizures, ataxia, hypotonia, visual problems, and alopecia	AR	1/7000–1/60,000 in the general population[a]

AR autosomal recessive, *AD* autosomal dominant, *EVA* enlarged vestibular aqueduct, *SNHL* sensorineural hearing loss, *XL* X-linked

[a] Adapted and modified from Ref. [6, 22, 23]

Sensorineural HL is common in mitochondrial diseases. Mitochondrial HL may occur in isolation or as a component of a syndrome. Pathogenic mitochondrial deoxyribonucleic acid (mtDNA) is transmitted by maternal inheritance. The onset of mtDNA-related SNHL tends to be in infancy or early life, with a gradual progression. Hearing loss is exclusively symmetrical, sensorineural, and progressive and primarily affects the higher frequencies in mitochondrial disease. The penetration of the mutation may vary, and the onset and severity of the HL may differ even in family members carrying the same genetic variations. Some pathogenetic variants in mtDNA, such as A1555G, are associated with a predisposition to aminoglycoside ototoxicity [34, 35].

2.2.1.2 Intrauterine Infections

Although intrauterine infections of viral, protozoal, and bacterial pathogens can cause congenital HL, viral infections are incomparably more common and solely responsible for about 40% of nongenetic congenital HL. Hearing loss related to intrauterine infections is sensorineural, and severity and onset characteristics may vary depending on the infectious agent [36]. Common infectious causes of congenital HL are cytomegalovirus (CMV), rubella, toxoplasmosis, syphilis, herpes simplex virus type 1 and 2 (HSV-1, HSV-2), Zika virus, human immunodeficiency virus (HIV), and lymphocytic choriomeningitis virus (LCMV).

Congenital CMV infection (cCMVI) is the most common congenital infection and the most common cause of congenital infection-related HL. The prevalence of cCMVI is 0.4–2.3% in newborns and 6–7% among individuals with congenital HL [37]. About 10–15% of infants with cCMVI are diagnosed with unilateral or bilateral SNHL; of these, 3–5% have bilateral moderate to profound HL [38, 39]. Congenital CMVI may cause delayed-onset HL; up to 43% of newborns with cCMVI pass the hearing screening but develop SNHL in the following period [37]. Close follow-up and audiologic monitoring are required in all infants with cCMVI to avoid delayed diagnosis and intervention of HL.

Rubella is a common cause of congenital infections. Although rubella was eradicated in many high-income countries with large-scale immunization, it still is an important cause of intrauterine infections in low- and middle-income countries. Congenital rubella syndrome (CRS) is a devastating intrauterine infection characterized by HL, growth retardation, and neurologic, visual, and cardiac defects. Rubella infection within the first trimester results in CRS in 90% of newborns [40]. The prevalence of HL in congenital rubella infection is as high as 19% [36]. As nonimmune pregnant women constitute a significant risk for developing CRS, maternal vaccination is critical to avoid this devastating infection's consequences.

Congenital toxoplasmosis is another tragic intrauterine infection associated with HL. Fetal transmission generally occurs in primary *Toxoplasma gondii* infection during pregnancy [41]. As most infections are asymptomatic, the screening of *Toxoplasma*-specific antibodies in all pregnant women is recommended [41, 42].

Congenital syphilis was a common cause of congenital HL. It still is a cause of congenital HL in low- and middle-income countries. However, after the introduction of penicillin and prevention and treatment programs, congenital syphilis prevalence decreased gradually for decades and is a very exceptional entity today in high-income countries [43]. Hearing loss in congenital syphilis is progressive and delayed-onset in most affected children. Hearing tests are usually normal in the neonatal period, and screening tests may be ineffective [44].

Congenital Zika syndrome (CZS) is associated with numerous congenital malformations, including microcephaly. Adverse outcomes of CZS were reported as much as 46% [45]. Current literature supports a possible association between CZS and HL, and prompt audiologic evaluation of infected newborns is recommended [46].

2.2.2 Perinatal Period

2.2.2.1 Perinatal Asphyxia

Perinatal asphyxia can trigger neuronal injury that may result in hypoxic–ischemic encephalopathy (HIE). The prevalence of perinatal asphyxia is about 2%, and although most recover entirely, 0.16% of newborns develop HIE [47]. Hypoxic–ischemic injuries frequently cause sensory impairments, including HL, due to the permanent disruption of hair cells in the organ of the Corti. Hearing loss following HIE is reported as high as 17.1% in patients with accompanying neurologic impairments [48].

2.2.2.2 Hyperbilirubinemia

The prevalence of neonatal jaundice in term and late preterm newborns is 84% [49]. It is mostly transient, and long-term complications are rare. But neurologic deficits like HL may occur in some infants, particularly those with bilirubin levels over 20 mg/dL. Hearing loss is commonly caused by damage to the auditory nerve or brainstem and presents as auditory neuropathy spectrum disorder (ANSD). Hearing loss is more common in premature infants as they are more susceptible to bilirubin toxicity [50].

2.2.2.3 Low Birth Weight

As access to neonatal intensive care units (NICUs) has become widespread, survival rates of very low birth weight (VLBW, <1500 g) infants have substantially increased. The incidence of HL is significantly higher in VLBW infants. There may be no direct relationship between birth weight and HL. Still, VLBW is associated with various risk factors, such as hyperbilirubinemia, the requirement for ototoxic medications, and hypoxia that may synergistically impair hearing [16].

2.2.2.4 Perinatal Infections

The most common cause of acquired HL in infancy and early childhood is bacterial meningitis which accounts for about 6% of all SNHLs [51]. Most cases are under 2 years of age and have bilateral HL [52]. Bacterial meningitis results in SNHL in up to 30% of pediatric patients [53]. The pathogenesis of SNHL in bacterial meningitis depends on suppurative labyrinthitis due to bacterial infection spread from the subarachnoid space to the cochlea through the cochlear aqueduct. The inflammatory process in the inner ear frequently leads to fibrosis and subsequent ossification of the perilymphatic spaces, causing the destruction of the sensory hairy cells. The fibrosis and ossification may occur as early as weeks after the onset of meningitis [54]. Occlusion of the cochlear duct by fibrous tissue and subsequent ossification, and labyrinthitis ossificans, consists of an obstacle for cochlear implantation in case of severe SNHL. Therefore, severe hearing impairment after meningitis is an emergency for cochlear implantation. Patients with residual hearing compensable with conventional hearing aids should be followed up closely with audiologic and radiologic monitoring. Care must be taken to avoid missing progressive HL and cochlear ossification, which will make the salvage therapy, and cochlear implantation much more complicated [55].

2.2.2.5 Ototoxic Medications

The most common cause of ototoxicity in infants is aminoglycoside administration in NICU. Most infants in NICU receive at least 1 day of aminoglycoside medication. Johnson et al. [56] reported the rate of aminoglycoside administration for 1–24 days among infants in the NICU as 87%. The genetic susceptibility to aminoglycoside-induced HL has been revealed. Patients carrying a mutation in the A1555G substitution of mitochondrial 12S ribosomal ribonucleic acid (rRNA) were extremely sensitive to aminoglycoside ototoxicity [34]. Ealy et al. [57] reported the prevalence of mitochondrial mutations among infants administered to NICU as 1.8%. Johnson et al. [56] screened the infants in NICU who received aminoglycosides. Only 1 of the 4 infants with a mitochondrial mutation developed HL. They speculated that a possible modifier gene might exist [56]. Consequently, aminoglycoside-induced HL may not develop in every patient with a mitochondrial mutation.

The duration of the therapy is also an important predictor of HL. Administration for more than 5 days is considered a risk factor for aminoglycoside-induced HL [14]. Owing to developments in NICU and prompt monitorization of drug levels, ototoxicity-related HL is infrequent, unlike in the past. The estimated rate of aminoglycoside-related HL is lower than 4%, even in premature infants [58].

2.3 Screening

The main requirement of a global hearing screening program is a non-invasive objective hearing test that could be easily performed by nonprofessional health staff. Therefore, the implementation of NHS was only possible in the late 1980s, after the developments in audiologic testing technologies and the introduction of A-OAE and A-ABR [6]. The A-OAE and A-ABR tests are widely used as NHS tests and effectively identify neonatal HL [59].

Although both are effective in NHS and alternatives to each other, distinct differences exist between OAE and ABR measures. The OAE test detects the sound originating from the outer hair cells of the organ of Corti by a microphone placed in the external auditory canal. The vibrations of outer hair cells produce OAEs as a part of their cochlear amplifier function, indicating remarkably existing hearing [60]. The ABR test measures the sound-induced neural activity between the auditory nerve and mesencephalon. The cochlea transforms the mechanical sound into electrical signals transferred to the auditory cortex by the cochlear nerve and ascends the auditory pathway along the brainstem [61]. Acoustic stimuli are delivered into the ear with earphones, and the electricity along the auditory pathway, including the cochlear nerve and a series of nuclei, is recorded by surface electrodes. Therefore, OAE reflects cochlear status, but ABR covers both the cochlea and retrocochlear auditory pathways.

The OAE test is the most preferred neonatal hearing screening method globally. A recent global survey conducted in 158 countries worldwide reported that in a reference year, 66.5% of the infants were screened with OAE, 14.3% were assessed

with A-ABR, and 19.2% of all infants with both OAE and A-ABR were applied for hearing screening [62].

There are superiorities of OAE and ABR tests over each other in hearing screening. The A-ABR test can detect HL worse than 40–45 dB, a higher threshold when compared with the OAE test. The OAE test can identify 30–35 dB HL. Consequently, the risk of missing an HL between 25 and 40 dB is higher with the A-ABR test than with the OAE test. Levit et al. [63] reported that 24% of the infants who failed OAE and passed A-ABR tests were confirmed to have HL when evaluated with diagnostic ABR. In contrast, the ABR measure covers a more significant portion of auditory pathways, including the auditory nerve and brainstem, besides the cochlea. The coverage of the OAE test is limited to the outer hair cells of the cochlea, which means that, unlike the ABR test, the OAE test cannot detect ANSD [64]. The OAEs, in case of absent or severely abnormal ABR measurements, are one of the characteristics of ANSD. Although it is a rare entity in well-baby nurseries, ANSD is a common disorder among infants administered to NICU who had hyperbilirubinemia or received aminoglycoside antibiotic therapy [65]. Considering the higher rate of ANSD, the A-ABR test is recommended for screening and rescreening infants in the NICU [14].

Both OAE and ABR technologies are affected by external and middle ear pathologies. Obstruction in the external auditory canal or impaired middle ear functions blocks the sound transmission from the earphone, inserted into the external ear, to the inner ear resulting in a false A-ABR fail. Similarly, emissions generated in the outer hair cells cannot be recorded by the microphone in the external ear by the exact mechanism in OAE testing. Ear canal collapse and debris in the external auditory canal or amniotic fluid in the middle ear are transient obstacles for hearing screening, especially in the early post-birth period. The OAE test is claimed to be more affected by these conditions, and the failure rates are higher than the A-ABR test [8]. The A-ABR test may be considered the initial screening test in case of early discharge of the infant.

The timing of hearing screening and intervention are of great importance. Early diagnosis and prompt intervention can protect the infant from the consequences of hearing impairment in the critical auditory period. According to 1-3-6 goals of early hearing detection and intervention (EHDI) determined by the Joint Committee on Infant Hearing (JCIH) in the USA, all infants should be screened in the first month after birth, ideally before their discharge from the hospital [14]. Diagnostic tests must evaluate any infant who failed the screening and rescreening tests, and the hearing status of the infant must be confirmed within the 3 months of age. All infants with confirmed HL should receive prompt intervention no later than 6 months of age. The first screening should be as close to the discharge as possible, yet enough time must be left for rescreening failed infants. Several hours of the time interval is warranted between failed test and the second screen. The JCIH recommends upgrading the timeline to 1-2-3 months in centers that fulfill the 1-3-6 benchmark [14]. Another advantage of early testing is that younger infants have more extended sleep periods, and the tests may be conducted during their natural sleep without sedation.

Screening the infants who have received NICU care requires further attention. The rate of NICU requirement among all newborns is about 10–15%. The prevalence of HL from different etiologies, including ANSD, is significantly higher in this population than in infants without a history of NICU care [58, 65]. The A-ABR is the recommended test, and in case of failed A-ABR screening, the infant should be referred to an audiologist and evaluated with diagnostic ABR if indicated [14]. However, the A-ABR test may miss a mild HL more common in infants receiving care in the NICU.

Berg et al. [65] recommended a two-stage screening with an initial A-ABR and complementary OAE testing. The NICU graduates are at increased risk for delayed-onset HL. Suppose parental or caregiver concerns exist, or in case of the presence of risk factors for progressive or delayed-onset HL, the infant should be referred to an audiologist for a follow-up assessment even if a two-stage screening reports a pass result [14].

Besides hearing screening, genetic screening of the common mutations related to HL also contributes to early diagnosis. Screening three of the most common mutations associated with HL, GJB2, mitochondrial A1555G, and SLC26A4, together with cCMVI tests, can detect at least 40% of the congenital and 60% of delayed-onset HLs [6]. Although genetic counseling and testing are recommended for all infants with HL and their families, the current cost of genomic DNA sequencing is an obstacle to the routine genetic screening of common mutations associated with HL [22].

2.4 Conclusion

Congenital HL is one of the most common congenital disabilities. Hearing loss in infancy may cause speech and language development delays and result in lower academic and social performance. Neonatal hearing screening programs have provided a definite advantage in early detection and prompt intervention of HL. With early access to intervention within the critical period for the maturation of the central auditory pathway, infants with HL may achieve comparable speech and language development with their normal hearing peers. The most crucial goal of the early hearing detection and intervention concept is to confirm the hearing status of the infants within 3 months of age and enroll the children with HL in an early intervention program no later than 6 months. The OAE and A-ABR tests are widely used for hearing screening and effectively detect HL in newborns. But mild or neural HL may be missed with current screening strategies, and progressive or delayed-onset HLs are still cause for concern, particularly in infants with specific risk factors. As the incidence of disabling HL in school-age is twice as high as in the neonatal period, ongoing surveillance of auditory perception and communication skills is mandatory in all children.

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Pediatric Infectious Diseases and Hearing Loss

3

Hacer Aktürk, Emin Sami Arısoy, and Sheldon L. Kaplan

3.1 Introduction

Infectious diseases are still a leading cause of morbidity and mortality worldwide. Children under 5 years of age are especially the subject of infection-related morbidity and mortality. Vaccine-preventable infectious diseases were estimated to be responsible for approximately 13% of mortality in children <5 years of age in 2018 [1]. According to estimates, 6 infectious diseases, including lower respiratory tract infections, diarrheal diseases, malaria, meningitis, whooping cough, and sexually transmitted diseases, were among the most common causes of disability-adjusted life years in children younger than 10 years in 2019 [2].

Pediatric infectious diseases (PIDs) compose a unique medical subspecialty that encompasses all systems in the body and requires participation in the diagnosis and treatment of patients of other disciplines. The PIDs discipline focuses on emerging

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new infections, re-emerging old infections, and advances in diagnosing, treating, and preventing infectious diseases. In this context, hearing loss (HL) enters the boundaries of PIDs in many aspects, regarding the multiple infectious etiologies, treatment, and prevention of the infections. Childhood HL is an important health problem due to its detrimental effects on spoken language and domino effects on cognition, education, social well-being, employment, and so on. Timely diagnosis and rehabilitation, but hopefully, prevention of HL may significantly impact children's quality of life into adulthood.

3.2 Definition and Types of Hearing Loss

Hearing begins when sound waves enter the outer ear. The sound waves go through the ear canal and vibrate the tympanic membrane (TM). The TM conducts the vibrations to the ossicles of the middle ear, the movement of which amplifies and transmits vibrations to the inner ear. The cochlea, the hearing part of the inner ear, contains fluid and hair cells within the inner ear. The hair cells convert the vibrations into electrical impulses transmitted by the auditory nerve to the cortex, where they are perceived as sound and translated into specific meanings [3, 4].

A decibel (dB) is used as a unit to measure the sound pressure level, which determines the volume or loudness. The World Health Organization (WHO) defines normal hearing as hearing thresholds of 20 dB or better in both ears. Hearing loss is categorized as mild (20–30 dB hearing level), moderate (30–50 dB), moderately severe (50–70 dB), severe (75–85 dB), or profound (>85 dB) [5]. Hearing loss is considered a hearing level greater than 35 dB in the better-hearing ear [6].

Another classification can be made by locating the affected part within the hearing system as peripheral or central HL. The central or retrocochlear part begins from the proximal eighth nerve to the cerebral cortex. Any deficit in this part results in central HL, relatively rare in children. The peripheral part of the hearing system includes the outer, middle, and inner ear. The affected portion in the peripheral part can be related to transmission (conduction), perception (sensorineural), or both (mixed). Conductive HL (CHL) occurs when a problem propagates sound through the external or middle ear. Sensorineural HL (SNHL) is caused by malfunctioning inner ear structures. Hearing loss can be classified as mixed when there are both conductive and sensorineural affections [3, 5].

3.3 Epidemiology

Globally, HL is the third largest cause of years lived with disability, a measure of the impact of an illness on the quality of life. According to WHO estimates, 34 million children and 432 million adults, which make up over 5% of the world's population, have disabling HL, requiring rehabilitation [4]. This number is anticipated to rise more than 1.5-fold in the near future [4]. A recent study on the prevalence of HL reported that globally 70 million children aged 0–15 years live with HL [7]. The

Centers for Disease Control and Prevention (CDC) also reported the prevalence of HL as 1.7 per 1000 babies screened for HL in 2019 [8]. In a recent systematic review and meta-analysis, the overall prevalence rate of permanent hearing impairment of ≥40 dB was 2.21 per 1000 in neonatal populations worldwide [9].

A great majority of those people with disabling HL live in low- and middle-income countries [6]. In accordance with WHO estimates, 60% of HL in children is reported to be due to preventable causes like ear infections, vaccine-preventable diseases, birth-related problems, and ototoxic medications [7, 10]. In low- and middle-income countries, the proportion of HL due to preventable causes is 75%, higher than 49% in high-income countries [11–13]. This discrepancy may be explained by unimproved perinatal health care and higher infection rates in unindustrialized countries. According to WHO estimates, among 60% of preventable causes of HL in children, approximately 30%, 17%, and 4% are caused by infections, perinatal complications, and ototoxic medications, respectively [10].

3.4 Infectious Etiology of Hearing Loss

Congenital and neonatal infections, focal and systemic infectious diseases, systemic bacterial and viral infections, and some fungal, parasitic, and prion infections may lead to HL in children.

3.4.1 Congenital and Neonatal Infections

Congenital infections can be transmitted from the mother to her baby during pregnancy (intrauterine) or delivery (peripartum). After birth, infections acquired during the neonatal period are considered neonatal infections. Various congenital and neonatal infections may lead to HL. Newborn hearing screening programs that aim to screen all newborns within one month of birth have been introduced in many countries for early detection and timely intervention of hearing impairment in neonates.

Congenital infections may result in substantial morbidity or even mortality in neonates. Depending on the time of infection during fetal development, they may present with varying clinical spectrums with different severities. Multiple systems may be affected with early or late manifestations, including the central nervous system (CNS) abnormalities, visual defects, hematological abnormalities, hepatosplenomegaly, rash, and HL, mostly in the form of SNHL [5, 14].

3.4.1.1 Congenital Cytomegalovirus Infection and Hearing Loss

Cytomegalovirus (CMV), a member of the Herpesviridae family, can be transmitted vertically from mother to infant. It is the most common congenital viral infection and the most common infectious cause of congenital SNHL [5, 13, 15, 16]. Sensorineural HL, primarily bilateral, can accompany other organ system manifestations, or it may occur as the only finding of the congenital CMV infection [15, 17, 18].

Hearing loss associated with congenital CMV infection has some properties that warrant special attention. It may occur both in asymptomatic or symptomatic infection. Therefore, HL may present at birth in infants without any other clinical findings and may go unnoticed if not screened by hearing tests. Moreover, HL associated with congenital CMV infection may have a delayed onset and develop at any time in the first years of life. Approximately 10–15% of infants with asymptomatic congenital CMV infection will suffer from hearing deterioration at birth or later in life. This rate is higher in symptomatic disease; approximately 30–40% of infants with symptomatic congenital CMV infection will suffer from hearing deterioration [5, 18–20]. Another compelling feature of congenital CMV infection is that HL may fluctuate and be progressive in asymptomatic and symptomatic diseases, making long-term audiologic follow-up necessary [18, 20–22].

Neonatal hearing surveillance will miss the infants with asymptomatic congenital CMV infection whose hearing will deteriorate months or years later. Implementing a screening program for congenital CMV infection in newborns would identify and allow for follow-up of asymptomatically infected infants with normal hearing at birth with respect to early detection and intervention of HL and developmental delay [17]. Controversy continues regarding the treatment of asymptomatic congenital CMV infection [19]. Studies are needed to determine whom, when, and how long to treat infants with congenital CMV infection to prevent or reverse associated HL.

3.4.1.2 Congenital Toxoplasmosis and Hearing Loss

Toxoplasma gondii is an intracellular protozoan parasite infecting both humans and animals and may be transmitted by vertical route from mother to infant. Approximately 20% of infected mothers are estimated to transmit the infection to the fetus. The transmission rate is higher when the maternal infection is acquired later in pregnancy [23–25]. The prevalence of congenital toxoplasmosis is estimated to be 0.5–3/10,000 live births to 1/1000 live births in different world regions [26, 27]. Strict screening of pregnant women and national prevention programs helped reduce the incidence of congenital toxoplasmosis in European countries.

Congenital toxoplasmosis may present with a broad spectrum of clinical presentations, including asymptomatic infection (70–90%), moderate to severe neonatal disease, and sequelae of asymptomatic unnoticed infection later in childhood. Symptomatic newborns can have chorioretinitis and various neurological manifestations, including hydrocephalus, microcephaly, seizures, skin rash, jaundice, hepatosplenomegaly, hematological abnormalities, and HL, primarily as SNHL [3, 28]. The incidence of hearing disorders in infants with congenital toxoplasmosis varies greatly in different studies ranging from 0 to 30% [3, 24, 29–31]. As in congenital CMV infection, HL can manifest months to years after birth, requiring audiological follow-up of infants with congenital toxoplasmosis [5, 31]. Antiparasitic therapy of extended duration (1–2 years) is recommended for infants (<12 months old) with a confirmed or highly suspected diagnosis of congenital toxoplasmosis. Timely initiated appropriate treatment of congenital toxoplasmosis appears to reduce the occurrence of adverse neurologic outcomes, including HL [28, 31].

3.4.1.3 Congenital Rubella Infection and Hearing Loss

Rubella virus is an enveloped single-stranded RNA virus. It may cause intrauterine rubella infection when contracted during pregnancy, resulting in many clinical consequences ranging from asymptomatic infection to miscarriage or stillbirth or congenital birth anomalies, named congenital rubella syndrome. Because rubella is a vaccine-preventable illness, congenital rubella syndrome is highly sporadic in countries with an implemented routine rubella immunization program. According to WHO estimates, global rubella vaccination coverage was 69% by 2018 [32]. The lowest vaccination rates are detected in African and South-East Asian regions, where congenital rubella infection rates are high, expectedly [32, 33].

The fetus's most severe damage is caused by maternal rubella infection during the first trimester. The risk of major fetal defects is very low in maternal infections contracted after the 16th week of pregnancy. However, some clinical manifestations like SNHL may occur in late maternal infections up to the 20th week of gestation. Congenital rubella syndrome may affect almost every system of the fetus, including ophthalmologic, cardiac, neurologic, and auditory structures. Clinical manifestations may appear at birth or later in life as a late-onset sequela. Early manifestations may be transient or permanent [34, 35].

Sensorineural HL, primarily bilateral, is a common clinical manifestation in congenital rubella infection, detected in up to one-half to two-third of infants**.** The hearing may be affected permanently at birth or later in childhood. Since there is no effective specific treatment for rubella, supportive treatment and rehabilitation are warranted [3, 35].

3.4.1.4 Congenital Syphilis and Hearing Loss

Treponema pallidum, a gram-negative spirochete bacterium, is the causative agent of syphilis. It may be acquired by sexual contact leading to acquired syphilis, or by transplacental transmission from mother to fetus leading to stillbirth, prematurity, or congenital syphilis. The incidence of congenital syphilis is closely related to the rate of syphilis in women of childbearing age [36]. The incidence of syphilis is on the rise, increasing the number of congenital syphilis. According to WHO estimates, approximately 3% (1–11%) of childbearing women are found to be positive for syphilis in 78 countries [37]. A meta-analysis found that congenital syphilis can develop in 15% of infants of untreated mothers with syphilis [38].

Congenital syphilis can present with early (<2 years of age) and late (≥2 years of age) manifestations. Sensorineural HL, mostly sudden, severe, and bilateral, is associated with late congenital syphilis. The famous Hutchinson's triad of HL, notched incisors, and interstitial keratitis is historically accepted as pathognomonic for late congenital syphilis [36, 39]. The rate of SNHL in late congenital syphilis has been reported as about 10–15%. Once established, syphilitic HL is not responsive to specific antibiotic treatment. However, if congenital syphilis is diagnosed and treated appropriately in the neonatal period, SNHL can be prevented [40]. More importantly, congenital syphilis can be prevented by early and appropriate treatment of infected pregnant women detected by early screening.

Acquired syphilis can also result in HL, albeit rarer in children than adults. Otosyphilis, a congenital and acquired syphilis complication, may cause bilateral or unilateral SNHL with sudden onset or progressive HL. Tinnitus and vertigo may accompany hearing impairment, which may be the initial presentation. Therefore, syphilis should be considered in the differential diagnosis of any sexually active patient with sudden or fluctuating HL or vestibular symptoms. Hearing loss may persist despite therapy [3, 36, 39, 41].

3.4.1.5 Congenital Zika Virus Infection and Hearing Loss

Zika virus is a flavivirus transmitted by mosquitoes to humans. It may also spread among human beings through sexual and vertical transmissions and blood product transfusion. Zika virus has a geographic preference for Africa, Southeast Asia, the Pacific Islands, the Americas, and the Caribbean. Although discovered in 1947, the Zika virus was recognized globally in 2015–2016, when it caused an outbreak in the Americas, the Caribbean, and the Pacific region [42, 43]. In 2016, the devastating consequences of the Zika virus infection during pregnancy on the developing fetus causing congenital birth defects, including microcephaly, were discovered [42, 44].

Since distinctive congenital anomalies were observed in infants of mothers with Zika virus infection, a definition for congenital Zika virus syndrome (CZS) was established. Clinical manifestations of CZS may show a variable intensity and mainly include intrauterine growth retardation, microcephaly, craniofacial disproportion, neuromotor abnormalities, seizures, arthrogryposis, ocular abnormalities, cardiac anomalies, and SNHL [43, 44]. Hearing impairment has been reported in approximately 6–7% of infants with in-utero Zika virus exposure, ranging from zero to 17% [43, 45, 46]. It is prominently more frequent in infants with microcephaly reaching up to 75% with a 14-fold increased risk for SNHL [45]. However, since hearing impairment may also be observed in asymptomatic or mildly symptomatic cases, all exposed newborns should be screened for hearing [44, 45].

3.4.1.6 Herpes Simplex Virus Infection and Hearing Loss

Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are enveloped, double-stranded DNA viruses belonging to the Herpesviridae family. As in other herpes viruses, HSV develops latency after primary infection. The virus may be shed in primary infection or reactivation regardless of symptomatology. Herpes simplex virus infection is transmitted by intimate contact through inoculation of mucocutaneous sites by infected body secretions. It can be transmitted from the infected mother to the fetus or neonate in three different periods; intrauterine (congenital infection), perinatal (perinatal infection, natal infection), and postnatal (postnatal infection). Intrauterine HSV infection is rarely seen and causes a different clinical picture than perinatal (natal) and postnatal infections, which may include cutaneous scars, limb hypoplasia, diffuse brain damage, microcephaly, and ocular findings. Perinatal and postnatal HSV infections may present with disseminated infection, infection localized to the CNS, and infection localized to the skin, eye, or mouth (SEM). Asymptomatic neonatal infection is rarely seen. Although there is limited evidence for a causal relationship, HSV infections, especially those affecting the

CNS, may lead to SNHL [39, 47]. In utero HSV infections or perinatal and postnatal HSV meningitis or encephalitis are accepted as risk factors for SNHL development, and monitoring hearing is recommended for those infants [48, 49].

3.4.1.7 Neonatal Sepsis and Meningitis and Hearing Loss

Meningitis and culture-positive sepsis are risk factors for hearing impairment in the neonatal period [49, 50]. In a recent meta-analysis, the prevalence of hearing impairment in neonatal populations of middle- and high-income countries was 2.21 per 1000 [9]. Expectedly, it was much more common and more likely to be bilateral in infants managed in neonatal intensive care units (NICUs) due to risk factors like infections, hypoxia, intracranial hemorrhage, hyperbilirubinemia, and ototoxic drugs [9]. Coenraad et al. [50] determined that sepsis and meningitis are risk factors for SNHL in NICU infants. For infants hospitalized in the first month of life for a condition associated with potentially elevated hearing thresholds like culture-positive sepsis, even if they had a normal newborn hearing screening, a new hearing evaluation before discharge is recommended [49].

3.4.2 Focal and Systemic Infectious Diseases

3.4.2.1 Otitis Externa in Children and Hearing Loss

Otitis externa is defined as inflammation of the external ear canal. It is predominantly caused by bacterial infections, facilitated by a breakdown of local defense mechanisms. Risk factors include increased moisture, trauma, foreign body, dermatitis, and viral infections. Conductive HL is among the symptoms of otitis externa, together with otalgia, itching, and fullness. Hearing loss is expected to resolve after the relief of inflammation. Although erythema of the external ear canal may involve the TM, otitis externa should be differentiated from acute otitis media (AOM) since both have different treatment modalities. Treatment of external otitis mainly consists of ototopical therapy. Topical drops with ototoxic potential, like aminoglycosides and alcohol, should not be applied in patients with a suspicion of nonintact TM. Ear candles may also induce a risk of HL and should not be used in treating otitis externa [51–53].

3.4.2.2 Acute Otitis Media in Children and Hearing Loss

Otitis media is a broad term referring to inflammation of the middle ear. It covers several entities like AOM, otitis media with effusion, chronic otitis media with effusion, and chronic suppurative otitis media. Acute otitis media, also called suppurative otitis media, is defined as an acute bacterial infection of the middle ear fluid. It is a prevalent childhood disease, mainly in the first 3 years of age, causing high numbers of healthcare visits and antibiotic consumption. Symptoms may include fever, ear pain, ear drainage, and HL.

When the middle ear space is filled with fluid, whether infected or not, HL ensues. Perforation of the TM and the erosion of middle ear ossicles may also occur in AOM and interfere with the transmission of sound vibrations due to fluid

accumulation, resulting in CHL [4, 54]. On the other hand, studies have demonstrated the presence of a sensorineural component in a considerable number of patients with AOM ranging between 2.4 and 10.6% and up to 43.3% in a tertiary care hospital [55, 56]. Even during the early course of uncomplicated AOM, alteration in cochlear function has been observed [55]. It is thought that inflammatory mediators and toxins passing from the middle ear to the inner ear through the round window may lead to cochlear inflammation, leading to SNHL [55–57].

3.4.2.3 Otitis Media with Effusion in Children and Hearing Loss

Otitis media with effusion can be defined as the presence of fluid in the middle ear without any symptoms and signs of inflammation [54]. Negative pressure is built up in the middle ear when the eustachian tubes are blocked primarily due to an upper respiratory tract infection. The fluid in the middle ear can lead to a mild to moderate HL, the most common complication of otitis media with effusion [54, 58]. Hearing sensitivity and speech perception may be affected, leading to speech impairment in the growing child [58, 59]. Hearing loss is reversible if the fluid in the middle ear is resolved. Since otitis media with effusion has a chance of spontaneous resolution, watchful waiting is an option in the management. The persistence of otitis media with effusion for 3–6 months associated with HL indicates tympanostomy tube insertion [54, 60].

3.4.2.4 Recurrent Otitis Media in Children and Hearing Loss

The resurgence of all clinical findings related to AOM after successful treatment and relief of signs and symptoms is recurrent AOM. Placement of PE tubes may be considered for managing children with recurrent otitis media, defined as three or more AOM episodes in 6 months or 4 within 12 months with at least one episode during the preceding 6 months [54, 61]. Recurrent AOM in childhood is associated with adult HL [62]. Prophylactic antibiotics are not recommended in patients with recurrent AOM due to a lack of effectiveness and increased rates of antibiotic resistance [63]. Tympanostomy tubes may be helpful if there is middle ear effusion. Otherwise, they are not recommended due to increasing the risk of structural changes in the TM, which may lead to reduced hearing [61, 62].

3.4.2.5 Mastoiditis in Children and Hearing Loss

Mastoiditis can be a complication of AOM. Mastoiditis can be acute or chronic, which may lead to HL. Both CHL and SNHL may ensue due to mastoiditis. In the early phase of infection, hearing impairment may be reversible. However, chronic mastoiditis may end up with irreversible HL [64].

3.4.2.6 Bacterial Meningitis, Viral Meningitis, and Hearing Loss

As in the neonatal period, bacterial meningitis and viral meningitis may end with hearing impairment. It is thought that inflammation during meningitis may spread to inner ear structures, causing labyrinthitis and cochlear damage. Inflammation or ischemia of the auditory nerve may also be another mechanism of hearing impairment in meningitis [4]. Hearing loss is the most common significant sequela after

bacterial meningitis, followed by cognitive deficits, seizures, and motor deficits [3, 65–68]. In some patients, hearing impairment may be temporary and resolve after a while [68, 69].

Hearing impairment is the highest after pneumococcal meningitis, followed by *Haemophilus influenzae* type b (Hib) meningitis and meningococcal meningitis, both of which have comparable rates [67]. Bacterial meningitis prevalence has decreased dramatically following the introduction of conjugate vaccines, effective against the three most common bacterial etiologies. *Haemophilus influenzae* type b meningitis has been nearly eradicated in places where routine administration of the Hib conjugate vaccine has been implemented. Pneumococcal and meningococcal conjugate vaccines have also significantly reduced rates of associated bacterial meningitis [66, 69].

Patients with viral meningitis have more favorable outcomes compared with bacterial meningitis. Hearing loss can occur following viral meningitis, although it is seen far less frequently than bacterial meningitis [70].

3.4.2.7 Recurrent Meningitis, Congenital Defects, and Hearing Loss

Recurrent meningitis may result from cerebrospinal fluid (CSF) leak from the ear, namely otorrhea. A cerebrospinal fluid leak may occur posttraumatic, iatrogenic, i.e., after surgery, or spontaneously. Spontaneous CSF leak is a rare condition caused by congenital inner ear defects, creating abnormal communication between the subarachnoid space and the tympanomastoid cavity. Failure of cochlear development during fetal life may end with various inner ear malformations, like Mondini's dysplasia, associated with hearing impairment. Before recognizing inner ear defects, meningitis occurring due to these defects was thought to be the reason for HL seen in these children. In children with recurrent meningitis, a search should be undertaken for a probable inner ear deformity causing both SNHL (especially unilateral SNHL) and an abnormal CSF fistula. Temporal bone computed tomography is the preferred method for detecting inner ear deformities, and surgical closure is the choice of treatment to prevent recurrent meningitis, together with appropriate vaccination [71–73].

3.4.3 Bacterial Infections in Children and Hearing Loss

The leading bacterial infections associated with HL are AOM, its local suppurative complications, and bacterial meningitis. Besides these above-mentioned bacterial etiologies, tuberculosis is a commonly seen disease with a relatively rare connection with HL. Mostly antituberculosis drug regimens are associated with hearing impairment [74]. Acute SNHL due to tuberculous meningitis has been reported [75]. Tuberculosis of the middle ear is a rare form of the disease leading to hearing difficulties [75, 76].

Some other bacterial infections are rarely reported as the etiology of hearing impairment. Lemiere's syndrome refers to septic thrombophlebitis of the internal jugular vein that typically begins as an oropharyngeal infection and is usually

caused by *Fusobacterium* spp. There are reports describing patients with SNHL caused by otogenic Lemiere disease [77]. Epidemic typhus, a louse-borne infection, is caused by an obligate, intracellular, gram-negative coccobacillus *Rickettsia prowazekii.* Hearing loss is a CNS manifestation of epidemic typhus [78, 79]. Whipple disease, caused by *Tropheryma whipplei,* a gram-positive bacillus, is a rare systemic bacterial infection transmitted mainly by the fecal–oral route. Hearing loss is among the CNS symptoms and signs of Whipple disease [80].

3.4.4 Viral Infections in Children and Hearing Loss

Several viral infections are associated with HL, including CMV, Epstein Barr virus (EBV), HSV, varicella zoster virüs (VZV), measles virus, mumps virus, rubella virus, lymphocytic choriomeningitis virüs (LCMV), human immunodeficiency virus (HIV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. These infections are associated with SNHL, which may be congenital or acquired, unilateral or bilateral**,** mild or severe. Viruses can impair hearing by directly damaging the inner ear structures, inducing a host-mediated inflammatory response, or facilitating bacterial or fungal infections [65]. Some viral infections have appropriate antiviral treatment, which may reverse or limit HL. Some others have effective vaccines against them, preventing the disease with a potential for hearing impairment [48].

Cytomegalovirus and rubella virus infections can cause congenital HL, as mentioned above. Lymphocytic choriomeningitis virus, a rarely seen single-stranded RNA virus transmitted to humans by secretions of rodents, may also lead to congenital HL if contracted during early pregnancy, together with visual impairment and microcephaly [81]. Herpes simplex viruses may cause both congenital and acquired HL. Beyond infancy, HL is associated with HSV meningitis or encephalitis in most cases. Antiherpetic drugs and sometimes steroids are used to ameliorate HL and other findings related to HSV infections [39, 48].

Human immunodeficiency virus may lead to HL in about 30% of HIV-infected people, both in children and adults, although the risk increases with age. Infants with in-utero exposure to HIV may also develop hearing impairment. Auditory involvement may be unilateral or bilateral, progressive or sudden, conductive or sensorineural. The pathogenesis can be related to many factors, including direct effects of the virus, increased susceptibility to infections of the middle ear and CNS, and ototoxic drugs used in treatment [39, 48, 82].

Varicella zoster virus remains latent in various ganglions after primary infection. Reactivation of the VZV within the geniculate ganglion affects the seventh and eighth cranial nerves. It results in herpes zoster oticus or Ramsey Hunt syndrome with a clinical picture of herpetic vesicles, facial nerve paralysis, SNHL, and otalgia. Rarely the rash may be absent. Treatment involving antiherpetic agents and steroids may improve HL more frequently than facial nerve palsy [39, 48, 83].

Before widespread vaccination, measles was an important cause of HL, accounting for 5–10% of cases with profound HL [84]. It is still an important reason for HL

in areas with low vaccination rates. In a study conducted in Nigeria between 2009 and 2018, measles was detected as the cause of profound SNHL in 45.8% of 142 children [85].

Mumps infection generally presents as a flu-like illness and bilateral parotitis and may induce occasional and well-known complications like pancreatitis, orchitis, aseptic meningitis, encephalitis, and SNHL, mostly unilateral. Incidence of SNHL ranges from approximately 1 per 1000 to 1 per 20,000 mumps cases. Hearing impairment may develop following mumps infection with or without meningitis, encephalitis, or even after an asymptomatic infection. Although spontaneous recovery may be seen in mild to moderate cases, profound SNHL following the mumps infection seems refractory to various treatments, including steroids [3, 39, 48, 86].

Acute EBV infection has been rarely reported as a cause of sudden SNHL and is assumed to be related to cranial nerve involvement [3, 87, 88]. Finally, coronavirus disease 2019 (COVID-19) caused by SARS-CöV-2 infection has been linked to the SNHL in a number of recent reports [89, 90].

3.5 Conclusion

Hearing impairment is a common health issue in childhood; however, it may go unnoticed and result in language and social development problems since hearing is essential in communication and engagement with others. Although the exact cause is not always possible to determine, understanding and awareness of the etiology are necessary since a crucial part of the causes are preventable. Infections have an important role in hearing impairment. Some strategies may be held to prevent the occurrence of infectious causes, like strengthening the immunization programs for children and women of childbearing age, implementing antenatal screening of some infections during pregnancy, and training healthcare workers about ear diseases and their relevance to HL. If the cause of HL cannot be prevented, every effort should be made for early identification, treatment, and rehabilitation of children with HL.

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Communicating with a Child with Hearing Loss

4

Can Cemal Cingi and Dilek Turan Eroğlu

4.1 Introduction

When a child's hearing screening reveals that s/he has a hearing problem, the family is often upset. During this time, parents feel oppressed by the sadness and the decisions to be made. Besides sadness and anxiety, they feel helpless about what awaits them and what needs to be done next. Families should be told what awaits them, what steps must be taken, and the importance of early diagnosis. Language forms, the basis of future communication skills, and adequate input should be emphasized. With impartial information, parents should be offered alternative ways and free to make the right choice for the child and themselves. Language-speech and hearing professionals should tell families what needs to be done for the child to establish healthy communication, regardless of prejudices, and guide how to approach the issue in this long story [1].

Communicating with deaf and hard-of-hearing children may not be fluent as they may have language improvement delays. Some parameters of enabling the development of communication skills by supporting their speaking and language skills depend on the answers to the following questions [2]:

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How serious is the hearing problem?
What are the parents' expectations?
Is the child's first language sign language?
Is a hearing aid or cochlear implant used or not?
Does the child attend a school for the deaf?

This study emphasizes the crucial points of making children with hearing impairment able to communicate themselves as others and underlines that achievement is possible with the necessary precautions and supporting techniques. The essential tools to help them and crucial awareness details are stated in this chapter [2].

4.2 Communication Tools for Hard-of-Hearing or Deaf People

The most critical concept about hearing impairment is that they have difficulty in communicating with their environment due to their hearing impairment. As speaking is a process that develops by imitating the sounds heard from the first months of life, early diagnosis of a hearing problem is crucial. Various pieces of training are also available for individuals whose hearing impairment is subsequently detected. Throughout the way, one can learn to speak and use the voice. Most people with hearing impairment can communicate with people around them through lip-reading, writing, and sign language. Below are some of the alternatives parents can choose for their kids [1].

4.3 Listening and Speaking Skills

This methodology supports the idea that children can learn to listen and speak on the condition that timely diagnosis, treatment, and consistent use of the necessary aids are in action. It includes the "1-3-6" rule: Identification of hearing loss at one month, appropriate amplification at 3 months, and family-centered early intervention services that support the development of listening and spoken language at 6 months. The family must adopt the rules and never forget the importance of using those aids. The aids have to be used consistently no matter how hard the child tries to take them off. A regular assessment of hearing is a must to see how functional the devices are and to check the changes if there are any.

4.4 The Cued Speech

It is a technique that includes eight hand shapes in four different positions (known as cues) with mouth shapes to show all the sounds of spoken language differently. The National Cued Speech Association has defined cued speech as "a visual mode of communication." This is known as a sound-based visual communication system.

It is based on making simple hand movements around the mouth to distinguish sounds identical to the lip reader. Cued speech has been adapted to over 50 languages and facilitates language development, speech development, reading skills, and communication. Its benefits can be seen in treatment to improve speechreading and literacy [1].

4.5 Sign Language

There is no universal sign language. Different languages have different sign languages. To illustrate, there are two sign languages in Belgium: French Belgian and Dutch sign language, or Spain has two sign languages, Spanish and Catalan sign language. Even the same language has different sign languages. For example, American Sign Language (ASL) is one of the natural languages with the same linguistic features as spoken languages but grammatically different from English. Each culture and language has its own sign language features, making it hard to communicate in a different language. That is to say, if someone uses ASL, s/he will not be able to interact in the same way in British Sign Language (BSL). The critical point here is that if parents want their children to use sign language, they also need to learn how to communicate using it [1, 2].

4.6 Total Communication

Total communication (TC) includes all communication tools, such as body and sign language, gestures, symbols, fingerspelling, facial expressions, listening and speaking, lip reading, and so on, to improve language skills and to communicate what they mean in a total sense. Information is provided to the child in both audio and visual formats. This allows the child to use the information best suited to their needs. Kids with TC programs generally use amplifications like hearing devices or cochlear implants. Children have different perceptions related to TC. Some think all they need is TC, whereas, others think that they need to communicate fully with some other techniques. Families should know their kids' perception of it and ensure that their children's needs are met utterly [1, 3].

4.7 Auditory: Verbal Method

The method helps stimulate existing hearing remnants of children through appropriate hearing aids. It is to support individuals with hearing impairment to gain and develop verbal communication to integrate them into society and use their existing potential most efficiently. An important point and prerequisite in the auditory-verbal approach is the development of listening skills. The child must have listening skills in order to receive healthy inputs.

4.8 Auditory: Oral Method

This method teaches deaf children to use their residual hearing with lip reading and context clues to understand and use spoken language in a better way. In this method, kids do not use sign language. To get the best out of this method, teachers, families, and the kids need to work hard and equip the child with spoken input as much as possible.

4.9 Family Awareness for a Deaf or Hard of Hearing Child

The studies show that families with great awareness can create a big difference for their kids to communicate with the world and integrate with the society that they are living in. Other people like teachers, peers, relatives, or neighbors can also be helpful. However, it is the parent's responsibility to help their kids to develop auditory skills and use residual hearing at maximum. To achieve that, what should be done is not a sprint but a marathon. Some crucial points to bear in mind during that run are as follows:

- They need to organize a suitable environment for child–parent communication.
- They need to set short- and long-term goals.
- They must model their kids with techniques to give input and help to communicate.
- Listening, speaking, and other interaction tools must be adapted to their daily routines.
- They must monitor each change in their kids and discuss them with their professional guides. Recording and discussing the process with professionals will create a big difference.
- They must be with the child during therapy and inform the therapist about their child's abilities and interests.
- They must evaluate all the communication opportunities and respond appropriately.
- They have to adopt the most appropriate behavior management. They try hard to be patient and understanding and know how to manage their anger or sadness.
- They have to support their kid along the path.
- They should speak with their child in sentences and avoid single-word expressions bearing in mind that they need naturally spoken input.
- They also need to bear in mind that their kid might be the only student with hearing problems at the school. In such a case, they might choose a school where the other peers also have the same impairment. The teachers knowing how to use the language techniques that those kids need might be preferred [4–6].

4.10 Communicating with Hearing-Impaired or Deaf Children

The importance of the idea and studies stating that disabled individuals should be integrated with society is so positive. Deaf and hard-of-hearing individuals use visual language to communicate their emotions, thoughts, wishes, and needs. They are easy to learn, however, the public awareness rate could be higher.

This makes it difficult for the hearing impaired to communicate with the people around them. However, there are some other things one can do to communicate more effectively with them.

As stated above hearing-impaired people can use different communication methods. It is helpful to find out which way they use before contacting them. Knowing their way of communicating will make it easier for you to interact with them. Using the same codes and signs will be a real help to them [2–6].

Other times there are some other things to take into consideration:

- You need to be aware that those individuals mostly know lip reading, so while communicating with them, make sure that your lips are seen clearly and try not to eat or chew anything, and do not smoke, as those things might hide the movements of your lips. Be careful to speak directly to that person.
- You do not need to shout at someone hard of hearing. This makes communication harder for those who need to see your natural mouth movements. Instead, tell them that you can repeat what you have said if anything is unclear.
- Using gestures and body language will also help you interact more clearly. Doing that, try to be as natural as possible.
- If anything interrupts communication, such as a phone ringing or a doorbell, someone calling you, etc., before leaving, tell the person about it.
- Try to be understanding, patient, and encouraging.
- Never ask personal questions about the hearing problem.

4.11 Conclusion

Success in helping kids with hearing impairment requires hard work from the teachers, parents, and children. The first step is being prompt to have the diagnosis and start the treatment immediately. During the treatment process, the parents have to accept all the facts as they are and be supportive of the achievement. It must not be a dream to integrate the kids into society and help them be as happy and prosperous as their peers, but a goal [2–6].

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Communication in the Family of a Hearing-Impaired Child

5

Dilek Turan Eroğlu and Can Cemal Cingi

5.1 Introduction

When a family member is diagnosed with a serious illness, it affects all family members, not just the patient. The situation can be even more distressing if the diagnosis of this serious illness is chronic and will affect the patient's entire life. Diagnoses given to children upset the parents and they have difficulty in coping with them. The family, who is informed about the child's hearing loss, feels helpless about acceptance and what needs to be done next, especially at first times. This issue, unlike other diseases, includes much more sensitivity in terms of not breaking away from normal life and gaining and using communication skills, as well as treatment. For many years, people have been working to help hearing-impaired individuals be at the highest level in using their communication skills, and they have dealt this issue from all aspects [1].

The aim of this chapter is to explain what kind of action plan and behavior management the family should have in this process for the hearing-impaired children to gain the required communication skills.

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5.2 The Important Points for Families with Children Having Hearing Loss or Deafness

Family–child interaction is such an important factor in the social and emotional development of the hearing impaired. During infancy and early childhood, individuals interact with the people around them and have access to auditory inputs that will support the development of language and communication skills. These interactions help the infant develop naturally in terms of language and communication skills without the need for additional support. However, children with hearing loss do not get auditory inputs during these interactions and encounter various problems in language acquisition, which results in communication problems. In such cases, early diagnosis is vitally important for the success of the treatment and in overcoming communication barriers. Thus, it is suggested that all infants should have a hearing screening, which is an important indicator of deafness or hearing loss in a child. Early intervention, when such a diagnosis is received, is offered to children with special needs aged 0–3 years. Since it covers special education and other support services, the family should take action as soon as possible and start implementing the necessary measures. What kind of action plan and behavior management the family should take in this process is explained below.

1. When intervention is initiated early, it is possible to exploit invaluable opportunities in the early years of verbal and nonverbal language acquisition [1].
2. Before everything, people should bear in mind the fact that every child is unique, so the first thing to do for the family is discover the child's other features other than hearing impairment. Then the unique features of his/her deafness have to be known, too.
3. It would be wise to find out about all the services for the hearing impaired where you live [1]. Information about schools, specialists, and events can be obtained from people with similar problems and from city health centers.
4. There may be children who object to wearing devices. The family should understand that the child does not have a chance without a hearing aid, and the device should be worn constantly no matter what the child wants.
5. The methods to optimize existing hearing remnants of children through appropriate hearing aids should be chosen. To nurture the child to develop verbal communication skills with adequate input is a must. In order to do that, the use of existing potential in the most efficient way is essential.
6. Throughout this journey the families have to work with a team of professionals, such as a pediatrician, an otolaryngologist, and a speech-language pathologist. Those professionals need to have experiences to work with infants and children with hearing impairment. Each specialist should be informed about others' actions and thoughts and they should work coordinately [1].
7. It is important to get information about the process and activities from the school administration and teachers where your child will attend. In addition, it should be learned how to cooperate with the teacher to work effectively [1].

8. It should never be forgotten that the child needs love, care, support, and a smiley face as well as friendly language inputs. The parents and all the caregivers around the child should always treat the child with love and affection. Frequent holding, facing, smiling, and responding are such vital remedies. It is a well-known fact that what children need most is to receive love from everyone around them [1].
9. In order to teach the child to understand the sounds they hear, families have to be trained in terms of improving listening skills. Listening activities are to be included in family education so that the child can gain experiences to improve his/her comprehension.
10. Parents of children with hearing loss are constantly trying to teach their children something. Without play-supported activities, the child's growth is unthinkable. Experts have to put play-assisted learning to work by planning different types of plays for families.
11. Daily routines are important opportunities for language acquisition. Going shopping together, reading a book, preparing a meal, participating in celebrations, and other visits are facilitators that provide the child's language development in a natural environment.
12. Speaking with the child in sentences and avoiding expressing in single words are important. In the early stages of the child's language development, single-word speech leads to non-uniform melodic speech. Highlight the word you want to teach in the sentence. For example, instead of just saying "banana" say "Would you like to eat a BANANA?"
13. It is important to help the child by saying the words that the child intends to say but cannot. While doing this, approach in an encouraging way, so that the child can feel secure.
14. Sound, noise, music, crowd, and distance in the communication environments are so important in interpersonal communication for individuals with hearing impairment. Noise impairs communication and makes it difficult to understand the words that you utter. Thus, in such cases try to be close to the person and make sure that your face is visible to him.

When communicating with a hearing-impaired individual, much more care should be taken than usual. One has to be more careful and understanding not to be offensive as a hearing-impaired individual may be irritable or overly sensitive. Below are some important points to keep in mind for the families and others while communicating with those people.

5.3 Communication Facts

5.3.1 Emotions

When communicating with a hearing-impaired individual, first of all, do not neglect to be visible and use the method of showing your presence with eye contact.

Otherwise, even if you say something, the person may think that you have never contacted them because they cannot hear you, and they may be hurt.

People may need emotional support whether they have a problem/disability or not. When it comes to the emotional needs of people with a disability, this sensitivity becomes even more important. The more families, the environment, and peers communicate in a friendly way with a hearing-impaired individual, the better the person will feel and achieve accordingly.

5.3.2 Positive Parenting

When families are informed that their child is deaf, they might stop interacting or reduce their communication with the child during the psychological stages they go through and this may negatively affect the child's communication with the community and his social and emotional development is negatively affected, too. However, if the child is not in communication, and a part of the social world, s/he will not be in harmony with his/her close environment, which will result in problems in terms of self-esteem and communication abilities. If the child is left alone in early childhood and s/he is withdrawn from the environment, the child will have difficulty in communicating in all social settings and it is inevitable to experience adaptation problems.

Families should be quick about acknowledging their child's problem. Make them feel valued in every situation. Thus, the child will think that hearing loss has nothing to do with being less valuable and will not have to worry about being accepted by society [2].

When it comes to family, not only parents but also other children come to mind. All family members should be open and accepting regarding this issue. It is natural for the other children to ask questions about the topic and talking to them openly is crucial [2].

The hearing-impaired child should feel included in all activities and communication environments. Exclusionary or impatient responses are not welcome [2].

It is the families' responsibility to help such kids to eliminate the feeling of loneliness and nurture the feeling of belongingness and get the support of others to make their kids become a part of society.

It is very important to discuss the Individual Education Plan (IEP) with the school administration before your child starts school [2].

It is important to talk to the teachers about how the child's social and academic development is going on and what can be done more if there is any gap [2].

In a file belonging to the child, all things done, reports, the manual of the devices used, the warranty certificate, developmental features, and other related things should be recorded [2]. The parents will ensure nothing is neglected in this way.

Being knowledgeable about the rights of the disabled and the laws will both enable the child to act knowing their rights and enable them to be advocated appropriately where necessary [2].

Communication is not only communicating with others. It also covers inner person communication. When an individual is happy with himself, he is happy with others.

5.3.3 Support and Self-confidence

Peers and teachers of hearing-impaired children are as important as their families. Hence, families should use adequate gathering opportunities with those to teach how to communicate effectively being aware of the social rules, speech rules, and different situations.

It is of great importance in learning how to react appropriately and act properly in society for those groups, too. By establishing close relationships with those people, impaired children will be integrated into society and that will result in confidence and happiness.

Hearing-impaired children growing up in a restricted environment due to their disability are unable to communicate well as a result of lack of communication. That will result in low self-esteem and personality problems. Support of others is the most crucial thing in the development of communication skills and personality order for those children, so public awareness and consciousness should be given urgent consideration.

In order to have healthy communication with the child, it is recommended that parents cooperate with other parents [3]. No single method is perfect. It is wise to learn about other people's methods as well [3].

5.4 Impacts on Families

Having a disabled child inevitably affects the family sadly [4, 5]. In a family with hearing impairment, the way of life is affected [6]. Often a deaf child leads to a change in relationships among family members [7]. Family members often behave differently than usual to include the disabled child in communication. Usually, the mother of a deaf child tries to set healthy communication among the family members [8]. All these attempts sometimes have adverse effects that affect the psychological health of the family members and can sometimes cause problems in marriage [9]. Parenting skills can create a big difference in well-being and communication skills of parents and children. So the aim of Positive Parenting Program (Triple-P) is rendering parents–child interaction improvement [10]. Being deaf creates the illusion that people in the world are divided into hearing and deaf people [11]. Hearing impairment is associated with behavioral change and communication change [12]. Family members of the hearing-impaired individual are thought to be unhappy and in difficulty [13]. It is associated with negative things such as low self-confidence, behavioral problem, social life deprivation, and psychological disorder. [14–16]. Hearing-impaired individuals may prevent communication within the family [17],

or due to the adverse effects on the mother; she may cause poor communication within the family [9, 18].

5.5 Positive Parenting Program

Considering the impacts of having a disabled child, the issue seems so devastating. Nevertheless, with some awareness and education parents can take it more softly. Parenting is the most effective factor in the development of the child, in the formation of his personality, and in gaining the mental, physical, emotional, and social skills that he will need in his life [6]. Triple-P is based on social learning to support the development of the child in the best way, to help him gain the skills he needs in the best way, and to guide him in the formation of his personality [19]. The program is educating parents by the principles designed by Sanders which are based on Bandura's theory [10, 20]. Triple-P, which was created in Australia, covers developmental, cognitive, and behavioral elements [21]. It can be used to help with the emotional and behavioral problems of the child as well as the mother, and the child's communication and interaction via creating awareness about the different needs of both parties and the relationship between them [22]. The program contributes to family relations and their social needs [20]. The program is mostly recommended for children aged 0–16 [23, 24] to improve their social skills including developmental, cognitive, and behavioral management [10]. Triple-P was designed aiming to improve self-esteem, knowledge, and self-efficacy and to nurture parent–child relations [18, 22, 25].

5.6 Conclusion

If we want to talk about the positive effect on children with hearing problems in terms of communication skills, social relations, education, and so on, they must be given full support by their families, peers, teachers, and society. It has to be reminded once again that family–child interaction is such an important factor in the social and emotional development of the hearing impaired.

During infancy and early childhood, individuals interact with the people around them and have access to auditory inputs that will support the development of language and communication skills. Hence, each and every chance of input access should be used by the family to have a child who is happy in the society of which s/he a part and can communicate with others with great self-esteem.

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Part II

Congenital and Neonatal Infections

Congenital Infections and Hearing Loss: An Overview

6

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6.1 Introduction

Hearing loss (HL), defined as a partial or total loss of the ability to detect sound, can appear at any age and occurs when a part of the ear or auditory system has suffered a structural or functional deviation from the norm [1]. Three of the major categories of HL include (1) conductive: secondary to a mechanical concern preventing sound from traveling efficiently to the inner ear; (2) sensorineural: secondary to the inner ear or eighth cranial nerve damage); and (3) mixed: a combination of conductive and sensorineural [2]. Hearing loss can be mild to profound, may be unilateral or bilateral, and may be stable, progressive, or fluctuating.

Congenital HL is any hearing impairment identified at or shortly after birth and is typically sensorineural [3]. Congenital HL may be due to hereditary or nonhereditary causes, including congenital infections and ototoxic medications (Table 6.1) [4].

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Table 6.1 Leading causes of congenital and acquired sensorineural hearing loss

Congenital			
	Hereditary	Multiple syndromes	e.g., Alport, Pendred, Usher, and Waardenburg syndromes
	Nonhereditary		
		Congenital infections	Cytomegalovirus infection is the most common, and others include congenital toxoplasmosis, rubella, syphilis, and Zika virus infections
		Inner ear dysplasia or malformation	Ranges from mild to progressive
		Perilymph fistula	A leak of inner ear fluid through a defect in the otic capsule
Acquired			
	Prematurity	Perinatal complications, hyperbilirubinemia, noise, and ototoxic drugs increase the risk	
	Hyperbilirubinemia	The highest risk with levels above the threshold for exchange transfusion	
	Bacterial meningitis	Occurs early during the infection	
	Ototoxic drugs	e.g., aminoglycosides, high-dose loop diuretics, certain chemotherapeutic agents (cisplatin), salicylates, and antimalarial drugs	
	Noise exposure	Can occur over time with constant or repeated exposure	
	Trauma	Trauma to the temporal bone can cause sensorineural or mixed hearing loss	
	Tumor	Vestibular schwannoma occurs mostly in children with neurofibromatosis type 2	
	Heavy metals	Lead poisoning is the most common, but cadmium, mercury, and arsenic also may have toxic effects on cochlear cells	

Infections, including cytomegalovirus (CMV), rubella, Zika virus, lymphocytic choriomeningitis (LCMV), varicella-zoster virus (VZV), herpes simplex virus (HSV) infections, toxoplasmosis, and syphilis, transmitted to the fetus or newborn during pregnancy or childbirth may cause congenital HL [5]. The HL resulting from congenital infections may be identified at birth but is frequently progressive or delayed, emphasizing the need for universal newborn hearing screening (NHS) and continued close monitoring.

Congenital HL affects approximately 2–3 of every 1000 newborns in one or both ears [6]. The universal NHS in the United States of America (USA) in 2007 improved HL detection with earlier speech and language intervention [7–11]. Universal NHS programs have also been available in Canada, Europe, and most middle- and high-income countries [12]. Prevalence estimates are higher in countries where universal NHS programs are not implemented [13].

Many childhood HL cases can be detected right after birth through NHS. However, passing this test does not always lead to normal hearing. Thus, postnatal identification of HL will depend on later interactions and interventions [14].

The outcomes of HL, mainly if classified at a severe or profound degree, may include behavioral difficulties and learning and cognitive delays, and negatively affect the quality of life of children [15]. Therefore, early detection of HL and intervention are critical.

6.2 Pathophysiology

The pathophysiology leading to HL in viral infections is likely multifactorial. Inflammation may damage the cochlea, resulting in sensorineural HL (SNHL) [16]. A murine model study of HL induced in newborn mice infected with CMV found a significant inflammatory component [17]. Another study suggested that CMV infection (CMVI) associated with HL may be related to reactive oxygen species (ROS) induced inflammation [18]. Human CMVI increases ROS levels and activates inflammatory bodies of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in the cochlea [19]. A study with newborn mice infected with murine CMV reported virus-induced cochlear inflammation during auditory development instead of direct virus-cytopathic effects that might contribute to cochlea pathology and altered auditory function [20].

6.3 Infections

Congenital infections are among the primary causes of SNHL. Table 6.2 summarizes the general characteristics of leading congenital infections.

Table 6.2 The general characteristics of leading congenital infections

Infectious agent	Mode of acquisition	Transmission	Diagnosis (postnatal)	Clinical manifestations, in addition to sensorineural hearing loss
Toxoplasma gondii: Intracellular protozoan	Foodborne	Higher risk of transmission in later gestation More severe symptoms in earlier gestation	*T. gondii* specific IgG, IgM, and IgA, and PCR in blood and CSF	Intracranial calcifications, hydrocephalus, and chorioretinitis; asymptomatic >60% of cases
Rubella virus: RNA virus, Togaviridae family	Inhalation	Highest in the first trimester	Serum IgM and PCR in blood, nasopharyngeal swab, urine, and CSF	Cataracts, cardiac defects, microcephaly, and microphthalmia
Cytomegalovirus (CMV): DNA virus, Herpesviridae family	Bodily fluids	Transplacental	PCR in blood, urine, and saliva	Retinitis, intracranial calcifications, microcephaly, and mental retardation; asymptomatic in 85% of cases
Herpes simplex virus (HSV): DNA virus, Herpesviridae family	Bodily fluids	Intrapartum	HSV 1–2 PCR surface, blood, and CSF	Microcephaly, intracranial calcifications, skin, and ocular findings
Treponema pallidum: Spirochete	Sexual contact	Highest in the third trimester	Non-treponemal test in blood	Multiple organ systems and skin rash
Zika virus: Flaviviridae	Mosquito-born	Highest in the first and second trimesters	PCR in blood, urine, and CSF, serum IgM	Severe microcephaly, ocular, and cardiac abnormalities

CSF cerebrospinal fluid, *DNA* deoxyribonucleic acid, *Ig* immunoglobulin, *PCR* polymerase chain reaction, *RNA* ribonucleic acid

6.3.1 Congenital Cytomegalovirus Infection

6.3.1.1 Epidemiology

Congenital CMVI (cCMVI) is the most common intrauterine infection in children, with an incidence of approximately 0.5–1.3% and 40,000 new cases annually in the USA and 0.64–0.7% of neonates worldwide [21–24]. The prevalence varies among populations. It is estimated that cCMVI leads to about 13–22% of all cases of neonatal HL, making it one of the most common nonhereditary causes [25]. Congenital CMVI is also the primary cause of long-term neurological and sensory sequelae, the most common of which is SNHL [26]. Congenital CMVI-related HL is underestimated because most newborns are undiagnosed, which might be related to no

symptoms at birth and the absence of universal screening during pregnancy and childbirth in many countries [27].

The transmission risk is 30–35% and 1.1–1.7% for primary and non-primary maternal infection, respectively [25]. Even if 85–90% of newborns with cCMVI are asymptomatic at birth, 10–15% of these babies may develop hearing, visual, or developmental impairment [28]. Vestibular involvement may also result in delayed motor skills [29]. Cytomegalovirus infection was first identified as a cause of congenital HL in 1964 [30]. For almost 60 years, many studies have explored the relationship between cCMVI and HL. Currently, cCMVI is the most common acquired cause of childhood SNHL and neurodevelopmental problems [31]. The hearing impairment may be progressive and require cochlear implants eventually [32].

6.3.1.2 Clinical Manifestations and Diagnosis

Congenital CMVI can be asymptomatic, with isolated SNHL, and mild and moderate-severe symptomatic. Although 90% are asymptomatic, 7–21% of children with cCMVI can develop SNHL [33]. When symptomatic, cCMVI can be related to growth retardation, prematurity, microcephaly, chorioretinitis, seizures, and other neurological abnormalities. Mild symptomatic cCMVI is related to mild and transient symptoms. Moderate-severe symptomatic cCMVI is associated with multiple problems, including central nervous system (CNS) involvement. Moderate-severe cCMV disease in newborns causes involvement of CNS, such as microcephaly, cortical malformations, ventriculomegaly, periventricular calcifications, germinal cysts, SNHL, chorioretinitis, and systemic manifestations, including hepatosplenomegaly, transaminitis, direct hyperbilirubinemia, petechiae, thrombocytopenia, and intrauterine growth retardation (IUGR).

Neonates with SNHL without any other clinical manifestations are considered a subgroup of asymptomatic infection. About 5–15% of newborns with cCMVI asymptomatic at birth may develop SNHL as late-onset sequelae [34]. In a systematic review, neonates with asymptomatic cCMVI were less likely to have delayed-onset SNHL than symptomatic cases [35].

Sensorineural HL occurs in 6–25% and 20–65% of infants with asymptomatic and symptomatic cCMVI, respectively [33, 36]. Hearing loss in cCMV-infected newborns rarely improves over time, and most asymptomatic and symptomatic children ultimately have loss progression [37]. Risk factors for SHNL were reported as primary CMVI before the 14th week of pregnancy, disseminated disease, and imaging abnormalities in the newborn in a prospective 22-year study [38]. Genetic causes should also be investigated in infants with asymptomatic cCMVI and isolated HL [39]. Early treatment with antiviral therapy has improved hearing outcomes for neonates with cCMVI.

Despite extensive research, no clinical or laboratory evidence to identify the disease has been found in children with CMV infection. A study of infants infected congenitally using viral whole-genome next-generation sequencing (NGS) found genes and variants that might be related to symptomatic and HL outcomes, representing an important step in understanding the impact of disease on CMV genetic

variation. These studies also identified potential markers in infants with cCMV at increased risk for adverse outcomes [40].

Universal screening programs may identify some asymptomatic newborns. Based on abnormal screening, a study identified 75% of infants with cCMVI [41]. Since there are no outcome predictors for asymptomatic neonates with cCMVI, future studies are needed to evaluate targeted or UNHS to identify children at risk for SNHL [42].

6.3.1.3 Treatment

In a study of 76 children with cCMVI followed through 18 years of age, SNHL, severe enough to require a cochlear implant, developed in most symptomatic patients treated with or without 6-week ganciclovir therapy [43].

A systematic review revealed that valganciclovir and ganciclovir use significantly improved hearing improvement and resulted in less deterioration for children with cCMV-related HL at birth [44]. However, there was insufficient evidence of the potential benefit on the hearing outcome of children with isolated HL, late-onset HL, and asymptomatic cCMVI.

In a multicenter, nonblinded, non–placebo-controlled randomized study, the antiviral treatment of cCMV-associated SNHL progression was evaluated [45]. The neonates with CNS disease and SNHL were randomized to get either 6 weeks of intravenous (IV) ganciclovir or no treatment. Treatment with ganciclovir resulted in hearing improvement or preservation at 6 months and most likely at 1 year. In a recently published study by Lanzieri et al. [43], the initial benefits of 6 weeks of IV ganciclovir in severely affected children with cCMV disease and HL on HL progression were shown not to be long-lasting through childhood.

Another nonblind, non-placebo-controlled study randomized the ganciclovir treatment in asymptomatic neonates who tested positive for cCMVI after birth [46]. Twenty-three neonates with cCMVI were randomized to receive either IV ganciclovir for 3 weeks or no therapy. At the follow-up, 2 children (18%) and none developed SNHL in the control and treatment groups, respectively.

Later, a multicenter, blinded, placebo-controlled randomized study compared 6-week and 6-month courses of valganciclovir [47]. In the trial, oral valganciclovir was given to all neonates for 6 weeks and then randomized to either receive a placebo or continue to receive valganciclovir for 6 months. Those in the 6-month treatment group had a higher hearing preservation rate at 12 and 24 months. However, the study could not examine the effect of valganciclovir treatment in isolated SNHL, which only one neonate had.

In 2017, a consensus statement was declared by the International Congenital Cytomegalovirus Recommendations Group [48]. In this statement, for neonates with moderate or severe cCMVI, oral valganciclovir for a 6-month course was recommended. Routine antivirals for neonates with mild disease or SNHL are not recommended since there is a lack of clear evidence of preserved or improved hearing with the treatment. There is a concern because of the risks associated with prolonged antiviral treatment. Also, recent data show that the initial short-term benefits

observed in randomized controlled trials are not long-lasting for progressive, long-term HL in cCMV disease after gancyclovir therapy [43].

Laboratory monitoring is vital in infants being treated with valganciclovir since the treatment may result in neutropenia. Absolute neutrophil counts should be followed weekly for at least 6–8 weeks, then monthly for the duration of therapy.

Treatment and monitoring of cCMVI are complicated and require a coordinated, team-based approach, including multiple specialists in pediatric infectious diseases, ophthalmology, audiology, otolaryngology, neurology, developmental pediatrics, occupational and physical therapy, orthopedic surgeons, and physical medicine and rehabilitation. Hearing aids, cochlear implantation, and speech/language therapies also may benefit children with cCMV-associated HL.

6.3.1.4 Outcome and Prevention

Most recently, a retrospective observational study evaluated 59 neonates with isolated SNHL [49]. Neonates received 12 months of antiviral treatment, either 6 weeks of IV ganciclovir followed by oral valganciclovir or only oral valganciclovir. At follow-up, 68.8% of affected ears showed an improvement, whereas 2.5% experienced worsening hearing. Of the improved ears, 96.3% improved to have normal hearing. Improvement in hearing was more likely to be seen in mild to moderate HL than in severe HL. No difference was found in hearing outcomes between neonates who initially received IV therapy and those receiving only oral therapy.

Antiviral treatment has been shown to improve hearing outcomes in neonates with symptomatic cCMVI and central nervous system involvement [50]. Limited studies suggest that antiviral therapy improves or preserves hearing in children with isolated SNHL [51].

It is recommended to have hearing evaluations every 3–6 months during the first 3 years of life and annually until 18 years of age since the HL with cCMVI is progressive [52]. In children with cCMVI-related HL, middle ear effusions can complicate the problem. Early referral for evaluation and possible tympanostomy tube placement will improve the outcomes. Also, monitoring individual hearing thresholds in both ears is essential for appropriate interventions [53]. Cochlear implantation (CI) has been an effective rehabilitation method for patients with severe-to-profound HL. However, the outcomes vary depending on the degree, onset, progression, and duration of the HL [54].

Since cCMVIs, asymptomatic and symptomatic, cause sequelae risk, there is a necessity for universal and targeted newborn screening, identifying more infants with infection. Passing hearing screening does not always exclude HL because of the possibility of late-onset and progressive HL in children with cCMVI. Close audiologic follow-up is required because of the process resulting in HL due to cCMVI [55].

For newborns who fail the neonatal hearing test, a targeted screening has been started in some states and hospitals in the USA, even if there is no universal screening. Also, multiple bills have been passed recently that require state health departments to provide educational resources, targeting healthcare providers and young

women of childbearing age. Such programs may facilitate timely diagnosis and early intervention [56].

Ultimately, the prevention of cCMVI most likely requires the development and implementation of effective vaccination. Investigations of several vaccines have been in phase I and II human studies; however, many questions remain about using the CMV vaccine in clinical practice [57]. One candidate is a purified, adjuvanted recombinant vaccine against the immunodominant glycoprotein B present in the CMV viral envelope that has demonstrated promising results in preventing primary CMVI in young women [58].

6.3.2 Congenital Toxoplasmosis

Toxoplasmosis is caused by congenital or acquired infection of the parasite *Toxoplasma gondii.* Congenital toxoplasmosis is a significant cause of morbidity and mortality in fetuses, neonates, and children, related to vertical transmission from infected mothers. Most newborns with congenital toxoplasmosis are asymptomatic, but 10–30% might have clinical symptoms and signs at birth or early infancy [59]. Severe symptomatic infection usually results from primary maternal infection during the first trimester. The classic triad of congenital toxoplasmosis, chorioretinitis, hydrocephalus, and intracranial calcifications, occurs in <10% of the cases [60].

Hearing loss is reported in about 20% of congenital toxoplasmosis [61]. All newborns with suspected congenital toxoplasmosis should be evaluated for HL [62].

There is evidence of risk for hearing impairment with congenital toxoplasmosis [63]. However, the details of the hearing outcomes are still unclear, and the assessment and follow-up details have not yet been validated.

6.3.3 Congenital Rubella

Rubella virus, a single-stranded RNA virus from the family of Matonaviridae, genus Rubivirus, causes congenital or acquired infection. Congenital rubella infection (CRI) may lead to fetal death in utero, preterm delivery, intrauterine growth retardation, or congenital abnormalities. Congenital rubella infection is also called congenital rubella syndrome (CRS) when it results in severe congenital anomalies, including microcephaly, congenital heart disease, SNHL, and eye problems, such as microphthalmia, cataracts, and glaucoma [64]. Hearing loss, cataracts, and cardiac disease are the classic manifestations of CRS; however, the rubella virus may infect every fetal organ and persist for a long time. Most infants with CRI are asymptomatic at birth but develop symptoms over time [65].

Nearly two-thirds of children with CRI have SNHL, usually bilaterally [64]. Once the most common viral cause of congenital SNHL, CRI is now rare due to maternal vaccination programs in high-income countries and was eliminated from the USA and Americas region in 2015 [66, 67].

The Pan American Health Organization (PAHO) called for rubella and congenital rubella syndrome (CRS) elimination in the Americas by 2010 in 2003. In 2015, the Americas were declared free of endemic rubella and CRS. The Americas region has sustained the elimination of rubella and CRS until now.

The last endemic rubella case in the PAHO region was documented in 2009 [68, 69]. In other parts of the world, rubella control is improving through the widespread implementation of vaccine programs.

6.3.4 Congenital Syphilis

Congenital syphilis occurs when the spirochete *Treponema pallidum* is transmitted to a fetus through the transplacental transmission of spirochetes in the bloodstream or, occasionally, through direct contact with an infectious lesion during birth. Transplacental transmission can occur at any time but more as gestation advances. Many cases are asymptomatic at birth [70]. Typical findings in symptomatic infants include nasal discharge, jaundice, hepatomegaly, rash, lymphadenopathy, and skeletal abnormalities. Rarely, it can also cause sepsis, myocarditis, pneumonia, eye involvement, and central nervous system infection. Infants with proven and probable diseases should be treated with penicillin [71].

Congenital syphilis has decreased for decades and is still very uncommon, but it is, unfortunately, rising [72]. Most cases are related to mothers who had no prenatal care or insufficient treatment for syphilis before or during pregnancy [73].

Sensorineural HL could be a late manifestation of congenital syphilis, typically developing at the ages of 8–10 [74]. Newborns with positive syphilis serology at birth should have hearing screening performed and should receive treatment with an appropriate course of penicillin therapy, preferably before 3 months of age. For all patients with congenital syphilis, close hearing screening is recommended. Sensorineural HL associated with late congenital syphilis typically develops suddenly by 10 years of age; often, the patient has interstitial keratitis and may respond to long-term glucocorticoid therapy [75].

6.3.5 Congenital Zika Virus Infection

Zika virus is an arthropod-borne flavivirus transmitted by mosquitos. Congenital Zika virus is associated with fetal growth restriction and sequelae related to the central nervous system. The Zika virus epidemic in the Americas was first recognized in 2015 and caused significant consequences during pregnancy resulting in congenital microcephaly and auditory changes [76]. The risk for vertical transmission exists throughout pregnancy; however, the most important risk of severe fetal sequelae appears to be first- and second-trimester infection. Fetal loss occurs in approximately 5–10% of pregnancies with documented Zika virus infection [77]. There is no specific treatment for the Zika virus infection, and management is supportive [78].

Little is known about HL in infants with congenital Zika virus infection, even though HL related to other congenital viral infections is well described. Of 70 children with microcephaly and evidence of congenital Zika virus infection, 5.8% were found to have SNHL [76]. Including the infants appearing normal at birth, all infants born to women with any evidence of Zika virus infection during pregnancy should have hearing testing [79]. In a report of infants with in-utero Zika virus exposure, who were prospectively followed, the overall rate of hearing impairment was 12% [80]. Hearing loss with delayed onset has not been reported. Further research is needed to evaluate whether the virus can cause HL later during infancy or childhood [81].

6.3.6 Congenital Lymphocytic Choriomeningitis Virus Infection

Lymphocytic choriomeningitis virus (LCMV), a member of the Arenaviridae family, is a single-stranded RNA virus. Ordinary house mice and other rodents, including rats, hamsters, the primary hosts, and reservoirs, carry and shed the LCMV in their saliva, urine, or feces. Humans acquire the virus by ingesting contaminated material, exposure to open wounds, or inhaling aerosols [82]. The LCMV infections are usually asymptomatic or characterized by upper respiratory tract infection symptoms.

Lymphocytic choriomeningitis virus is a rare cause of congenital infections and is generally underdiagnosed. Transmission to the fetus occurs with maternal viremia and can damage the developing brain. The fetus may be affected by LCMV infection, mainly if maternal infection occurs during the first or second trimester of pregnancy [83].

Congenital LCMV infection is associated with a high mortality rate. Survivors may have microcephaly (or macrocephaly), hydrocephaly, periventricular calcifications, cerebellar hypoplasia, ventriculomegaly, chorioretinitis, pachygyria, seizures, and neurodevelopmental sequelae, including intellectual disability and HL [83–85]. Minimal data exist about the prevalence of HL associated with congenital LCMV infection. Microcephaly and visual impairment are more common than HL in congenital LCMV infection [86]. No vaccine or effective treatment is available. Avoiding mice and hamsters during pregnancy can reduce the infection risk [83, 87].

6.3.7 Neonatal Herpes Simplex Virus Infection

Neonatal herpes simplex virus (HSV) infection caused by HSV-1 and HSV-2 incidence is estimated to be about 10 in 100,000 live births [88]. Transmission usually occurs during delivery from mothers with herpes simplex virus type 1 (HSV-1) or HSV-2 genital infection.

In most cases, the infection presents in the first 3 weeks of life with disseminated disease, encephalitis, or localized infection. Neurologic impairment, including HL, is found in most children with disseminated infection [89], 40% with encephalitis, and 25% with disease confined to the skin, mouth, or eyes [90].

Intrauterine or congenital HSV infection is rare and results from either maternal viremia with primary HSV infection or ascending infection during pregnancy. The development of SNHL in children with neonatal HSV infection occurs rarely, mostly seen with disseminated disease [91]. Hearing loss related to the neonatal infection can be severe to profound SNHL, bilateral or unilateral [92]. One study evaluated four children with mild to moderate SNHL after herpes encephalitis [93].

6.4 Conclusion

Hearing loss is common in congenital infections. Considering the natural process of HL with congenital infections, frequent audiologic follow-up is required. Universal screening should be considered because many children might have delayed HL after congenital infections. National hearing screening programs in different parts of the world vary considerably in quality, data acquisition, and accessibility of services [94].

Targeted screening of newborns for cCMVI is getting growing interest in conjunction with UNHS. The evolution of newborn screening and potentially effective vaccine efforts to prevent CMVI is promising with increased awareness.

Early identification can assist with prognosis and counseling families for all congenital infections. Frequent audiologic follow-up and universal screening will detect asymptomatic children at birth who may develop late-onset or delayed HL. A coordinated approach to diagnosis, treatment, and monitoring for HL is required for better outcomes. Cochlear implantation effectively improves speech and language in kids with HL related to congenital infections.

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Congenital Cytomegalovirus Infection and Hearing Loss

7

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7.1 Introduction

Cytomegalovirus (CMV) is the most frequent congenital infection and the leading cause of nongenetic sensorineural hearing loss (SNHL) in children worldwide. Congenital CMV (cCMV) infection (cCMVI) may be asymptomatic or symptomatic at birth. Although the minority of infants with cCMVI have symptoms at birth, these symptomatic infants are at significant risk for long-term sequelae. Sensorineural hearing loss (HL) is the most common sequela of cCMVI and can occur in asymptomatic and symptomatic cases [1, 2]. The association between cCMVI and HL was first described by Medearis in 1964 [3] and has been further described in numerous longitudinal studies since that time [4].

This chapter summarizes the current knowledge about the epidemiology, diagnosis, treatment, and prevention of cCMVI and focuses on the association of cCMVI with HL.

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7.2 Etiology

Human CMV, also known as human herpesvirus 5, is a member of the Herpesviridae family and the beta-herpesvirus subfamily. It is the largest member of Herpesviridae and shares many properties with other herpes viruses, including genome structure and the ability to cause latent and persistent infections. The complete virion consists of a linear, double-stranded deoxyribonucleic acid (DNA) genome within an icosahedral capsid of 162 capsomeres, which yields a final diameter of 200–300 nm [1, 2].

7.3 Epidemiology

Cytomegalovirus is the agent of the most frequent congenital viral infection, occurring in approximately 1–2% of live births worldwide [1, 5]. The birth prevalence of cCMVI is proportional to the seroprevalence of CMV among women of reproductive age in the population, which varies widely according to geographic regions and sociodemographic factors, such as age, race, and ethnicity [1]. Seroprevalence is higher among non-whites and individuals in low- and middle-income countries and groups with lower socioeconomic status in high-income countries [2, 5]. A recent review estimated a global CMV seroprevalence of 86% in women of reproductive age, with the highest (89–92%) seroprevalences in low- and middle-income countries in the Eastern Mediterranean, Western Pacific, African, and Southeast Asian regions and the lowest (70–79%) in the European region and the Americas [6]. However, even within the same geographic region, variable rates of CMV seroprevalence could be seen in women of different ethnic, racial, and socioeconomic backgrounds, reflecting the distinct epidemiological patterns of cCMVI [7].

Transmission of CMV can occur through contact with infected bodily fluids, such as saliva, urine, blood, or genital secretions. Children aged 1–3 years who excrete the virus in saliva and urine for extended periods are the most important CMV infection (CMVI) sources for young women [1, 2]. Maternal CMV acquisition usually occurs through frequent and prolonged contact with young children, especially children in the home and attending daycare or group care centers, as well as breast milk feedings and close contact situations.

Intrauterine transmission of CMV from mother to fetus can occur by primary (new) or nonprimary maternal infection during pregnancy. Nonprimary maternal infection, also called recurrent or secondary infection, may result from re-infection with a new strain or reactivation of latent CMV [1]. The rates of cCMVI due to nonprimary maternal infection are hard to determine and possibly underestimated due to difficulties in its diagnosis. It is highly difficult to identify by serologic and virologic markers which pregnant woman may experience a re-infection with a new strain or reactivation of the latent virus and to determine the timing of transmission due to nonprimary infection during pregnancy [7]. However, it contributes substantially to the burden of cCMVI because most women of reproductive age worldwide are CMV-seropositive [8].

Although it is estimated that 75% of cCMVIs in the United States of America (USA) result from nonprimary maternal infection [9], reliable estimates of prevalence from low- and middle-income countries are not available [7]. A previous meta-analysis estimated that the majority of cCMVIs in most populations result from nonprimary maternal infections [10]. Earlier studies suggested that symptomatic CMV disease and permanent sequelae are much more likely in infants infected due to a primary maternal infection than those infected due to nonprimary maternal infection [11, 12]. However, increasing evidence indicates that neither symptomatic CMVI nor the development of long-term sequelae, including SNHL, is correlated to the maternal infection type, and symptomatic disease and sequelae can be observed following nonprimary maternal infections [8]. The likelihood of maternal–fetal transmission is much greater during primary versus nonprimary maternal CMVI (32 versus 1.4%) [5].

At the time of primary maternal infection, gestational age is considered a significant factor affecting the intrauterine CMV transmission rate and the development of symptomatic disease and long-term sequelae [1, 2]. The vertical transmission rate appears to increase with advancing gestational age. A meta-analysis pooled data from ten studies (2942 fetuses) reported that vertical transmission rates increased, from 21% for infection at the periconceptional period to 36% in the first, 40% in the second, and 66% in the third trimesters [13]. Although symptomatic cCMVI may result from maternal infection at any time during pregnancy, severe sequelae and symptomatic diseases are more common when infection occurs earlier in pregnancy, particularly in the first trimester [1, 14].

7.4 In Utero Findings

The fetus with in-utero CMVI might show ultrasonographic abnormalities, including fetal growth restriction, microcephaly, ventriculomegaly, periventricular calcifications, neuronal migration abnormalities (polymicrogyria, pachygyria, and lissencephaly), cerebellar hypoplasia, large cisterna magna, enlarged liver or spleen, hepatic calcifications, echogenic bowel patterns, pleural effusion, and ascites. Although not pathognomonic or diagnostic, these findings could suggest fetal CMVI in the presence of maternal infection [1, 15].

7.5 Clinical Characteristics

The clinical presentation of cCMVI is highly variable and ranges from asymptomatic infection to severe multi-organ involvement. Infants with cCMVI are generally classified as “asymptomatic” or “symptomatic” based on the presence of clinical symptoms and signs at birth [1, 2].

7.5.1 Asymptomatic Congenital Cytomegalovirus Infection

Most newborns (~90%) with cCMVI have no apparent symptoms at birth and are thus termed asymptomatic. However, some of these infants may have detectable SHNL at birth and are classified as "asymptomatic with congenital SNHL" or "asymptomatic with isolated HL," or they may develop delayed-onset SNHL and are classified as "asymptomatic with normal hearing at birth, with later-onset SNHL" [1]. Approximately 7–11% of asymptomatic infants with cCMVI experience SNHL up to 5 years and 25% by age 18 [16, 17]. Lanzieri et al. [16] demonstrated that 2% of children with asymptomatic cCMVI developed SNHL severe enough to require cochlear implantation. Ocular abnormalities, such as small retinal lesions, were also reported in asymptomatic newborns; however, the visual impairment risk appears negligible [18, 19].

7.5.2 Symptomatic Congenital Cytomegalovirus Infection

Approximately 10% of newborns with cCMVI are symptomatic at birth [5, 20]. The clinical spectrum of symptomatic cCMV disease ranges from mild to moderate-severe manifestations [21]. At present, there is no standard definition for symptomatic cCMV disease. The informal International Congenital Cytomegalovirus Recommendations Group has categorized the symptomatic cCMV disease as "mildly symptomatic" or "moderately to severely symptomatic" [21].

The mildly symptomatic disease has been defined as the presence of isolated (one or two at most), mild, and transient manifestations of cCMVI (e.g., mild hepatomegaly or thrombocytopenia). In contrast, moderately to severely symptomatic disease includes central nervous system (CNS) involvement (e.g., microcephaly, neuroimaging findings consistent with cCMV disease, SNHL, and chorioretinitis) or multiple manifestations of cCMVI, such as petechiae, thrombocytopenia, hepatosplenomegaly, and hepatitis [21]. The characteristics of symptomatic cCMV disease are summarized in Table 7.1 [1, 2, 22, 23]. Figure 7.1 shows the *neuroimaging* findings associated with symptomatic cCMV disease.

Since cCMVI has a broad spectrum of clinical manifestations and can present with subtle or atypical signs and symptoms, a high suspicion index is necessary to identify cases. Some infants present with only CNS manifestations, such as microcephaly, seizures, and abnormal *neuroimaging findings, including* polymicrogyria or cortical dysplasia, and are classified as "primary neurophenotype." These infants may appear completely healthy at birth or have mild microcephaly without the classic somatic manifestations of cCMVI [1].

Approximately 10% of infants with symptomatic cCMVI have severe diseases, and among these severely affected infants, mortality rates might be as high as 10–30%. However, the overall mortality rate due to cCMVI is generally low (0.3–1.0%) [20].

Table 7.1 Clinical, laboratory, and *neuroimaging findings* in children with symptomatic congenital cytomegalovirus infection[a]

Clinical findings
Prematurity Small for gestational age (birth weight <10 percentile) Microcephaly Poor suck Hypotonia, lethargy
Seizures Jaundice at birth
Hepatosplenomegaly
Sensorineural hearing loss
Strabismus, chorioretinitis, cortical visual impairment, optic atrophy
Petechiae
Anemia
Laboratory findings
Anemia, hemolytic anemia
Thrombocytopenia
Neutropenia
Lymphopenia
Lymphocytosis
Leukemoid reaction
Elevated liver transaminases
Elevated direct and indirect serum bilirubin
Increased cerebrospinal fluid protein
Neuroimaging findings
Intracranial calcifications (typically periventricular)
Periventricular leukomalacia
Periventricular cystic abnormalities
Ventriculomegaly
Cerebral atrophy
White matter disease
Corpus callosum dysgenesis
Cerebellar hypoplasia
Migrational abnormalities (polymicrogyria, pachygyria, lissencephaly)
Lenticulostriate vasculopathy
Fetal brain sequence disruption or arrest syndrome

[a] Adapted and modified from Ref. [1, 2, 22, 23]

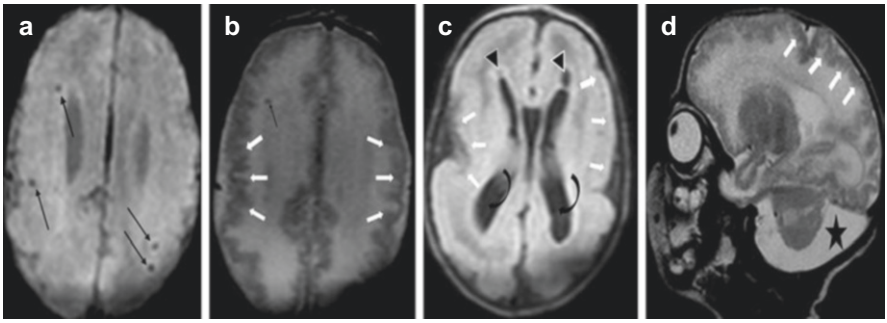

Fig. 7.1 Magnetic resonance images of the brain of a 1-month-old infant with symptomatic congenital cytomegalovirus infection. Sagittal T2-weighted images demonstrate scattered periventricular punctate foci of parenchymal calcifications (black arrows), neuronal migration abnormality leading to diffuse polymicrogyria in the bilateral frontoparietal region (white arrows), periventricular cysts (arrowheads), ventriculomegaly (curved arrows), and posterior fossa arachnoid cyst in the posterior fossa (star). (Courtesy Meltem Polat, MD)

7.6 Late Complications and Sequelae

Long-term sequelae can develop in asymptomatic and symptomatic infants with cCMVI, with the more frequent and severe sequelae occurring in symptomatic infants [20]. Approximately 40–60% of symptomatic infants had CMVI-related disabilities, with SNHL being the most common. Other reported late sequelae in children with symptomatic CMVI include motor and cognitive deficits, cerebral palsy, seizures, intellectual disability, chorioretinitis, strabismus, optic atrophy, cortical visual impairment, and dental abnormalities [20, 24].

Long-term sequelae in infants with asymptomatic cCMVI are less apparent because most have not been diagnosed [17]. It has been estimated that 13.5% of the asymptomatic infants with cCMVI will develop long-term sequelae, most commonly manifest as SNHL [20]. Although some earlier studies suggested that neurodevelopmental impairments might occur in children with asymptomatic cCMVI, recent studies concluded that these children do not have an increased risk of neurodevelopmental sequelae compared with healthy controls [17]. Additionally, Lopez et al. [25] found that infants with asymptomatic cCMVI who had normal hearing by age 2 years had no difference in intelligence, language development, or academic achievement during childhood compared with uninfected children. Conversely, intelligence and receptive vocabulary scores were lower than normal controls in children with asymptomatic cCMVI who developed SNHL by age 2 years [25]. Recent studies demonstrated that vestibular disorders can also occur in children with cCMVI, with or without associated SNHL [26].

7.7 Congenital Cytomegalovirus Infection and Hearing Loss

Congenital CMVI is the leading nonhereditary cause of SNHL in children worldwide, accounting for approximately 21% and 25% of cases of HL at birth and 4 years of age, respectively [4]. Congenital CMVI-related HL can occur following primary and nonprimary maternal infections [4, 8]. Sensorineural HL is the most common sequela of cCMVI and occurs in up to 50% of symptomatic and 15% of asymptomatic cases [4]. However, since there are many asymptomatic infants, most patients with SNHL due to cCMVI occur in this group [27]. Therefore, defining the actual contribution of cCMVI to permanent HL in childhood has been challenging.

The HL associated with asymptomatic or symptomatic cCMVI may be present at birth or later in life (late-onset). Late-onset HL occurs in up to 50% of children with cCMVI [4], mostly in the first 5–6 years [27–29]. There are considerable inter-study variabilities regarding the age at which children with cCMVI develop late-onset HL. Dahle et al. [30] reported the median age of late-onset HL to be 33 months in symptomatic and 44 months in asymptomatic children with cCMVI. Another study by Goderis et al. [31] reported the mean age of late-onset HL to be 18 months and found that 75% of the HL presented before 24 months of age, and none occurred after 61 months. In children with asymptomatic cCMVI, the risk of late-onset SNHL was reported to return to a level comparable to uninfected controls by age 5 years [16]. However, recent reviews have shown that late-onset HL can appear as late as the mid-teens [28, 32]. Riga et al. [32] found that late-onset HL was reported until 15.2 years in asymptomatic and 16.4 years in symptomatic children with cCMVI.

Recent systematic reviews have demonstrated that the nature of cCMVI-related HL (e.g., onset, severity, and course) is quite variable and unpredictable, as presented in Table 7.2 [17, 27–29, 32]. Regardless of symptomatic and asymptomatic statuses at birth, cCMVI-related SNHL may be unilateral or bilateral and has various patterns, including stable, fluctuating, progressive, and improving [27–29, 32]. These multiple patterns and changes can be seen in children with congenital, early onset, or late-onset SNHL and children treated or untreated with antiviral therapy [29]. The severity of HL can vary widely and range from unilateral high-frequency to bilateral severe to profound loss [4, 27]. Compared with asymptomatic children, symptomatic children with cCMVI tend to have more severe and often bilateral HL and are less likely to improve [27, 29, 32].

Progression of HL occurs at any time during childhood, even after years, in up to 50% of symptomatic and asymptomatic patients with cCMVI [32, 33]. A recent review found that SNHL has been reported to progress until 15.5 years in asymptomatic and 17.4 years in symptomatic children [32]. The reported age at which progression is first documented has varied from study to study. Fowler et al. [34] reported that the median age for asymptomatic children's first progression was 18 months. In another study by Dahle et al. [30], the median age for the first progression was 26 months in symptomatic and 51 months in asymptomatic children with cCMVI. Fluctuating HL is common and may occur in one or both ears [4]. Improvement of HL may also be seen among children with cCMVI and occurs

Table 7.2 Summary of literature reviews on the nature of congenital cytomegalovirus infection-related hearing loss according to symptomatic and asymptomatic status[a]

	Goderis et al. (2014) [27] Number of studies: 37		Bartlett et al. (2017) [17] Number of studies: 29		Fletcher et al. (2018) [28] Number of studies: 36		Riga et al. (2018) [32] Number of studies: 11		Vos et al. (2021) [29] Number of studies: 65	
cCMVI	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
Proportion of HL (% or range)	32.8	9.9	34–41	7–11	40.7–100	7–27	44.2	8.9	33.7–71.4	0–14.9
Characteristics of HL (% or range)										
Late-onset HL	18	9	–	–	9–29	11–18	–	–	0–27.1	0–24.2
Unilateral HL	28.8	56.9	–	–	–	–	32.2	55.9	–	–
Bilateral HL	71.2	43.1	–	–	–	–	67.8	44.1	–	–
Severe to profound HL	76.8	77.7	–	–	–	–	–	–	–	–
Bilateral severe to profound HL	65.1	42.6	–	–	–	–	–	–	–	–
Progressive HL	17.7	20.3	–	1.6–54	27–54	50–62.5	–	–	–	–
Fluctuating HL	21.5	24	–	16–54	–	–	–	–	–	–

cCMVI congenital cytomegalovirus infection, *HL* hearing loss

[a] Ref. [17, 27–29, 32]

predominantly in asymptomatic cases compared with symptomatic patients (40 versus 20%) [32].

It has been found that the presence of petechiae, intrauterine growth retardation (IUGR), microcephaly, and abnormal neuroimaging findings are predictive of the risk of SNHL in children with symptomatic cCMVI. Among asymptomatic cases of cCMVI, low birth weight and prematurity were associated with SNHL [1, 33]. An association between CMV viral load and HL has also been described [33]. However, despite these findings, there are no reliable virological and clinical markers to predict which children with cCMVI will have SNHL; it is also difficult to predict which children will develop late-onset or progressive SNHL [4, 33]. Studies have also suggested that inflammatory genes or genetic mutations might contribute to the development of cCMVI-related SNHL [1].

7.8 Differential Diagnosis

The differential diagnosis of cCMVI includes other intrauterine infections (e.g., toxoplasmosis, rubella, syphilis, herpes simplex virus, lymphocytic choriomeningitis virus [LCMV], and Zika virus infections). The differential diagnosis should also include bacterial sepsis or noninfectious disorders, such as genetic and metabolic disorders, and in-utero exposure to toxins or drugs [1].

7.9 Diagnostic Evaluation and Laboratory Diagnosis

For a timely diagnosis of cCMVI, a high clinical suspicion index is essential. In addition to the clinical, laboratory, and neuroimaging findings (Table 7.1) not explained by other causes and suggestive of cCMVI, laboratory testing for CMV should be considered in newborns born to mothers with suspected or known CMVI during pregnancy.

Laboratory diagnosis of cCMVI requires detecting the virus within the first 3 weeks of life since testing after this period cannot conclusively distinguish congenital from postnatal infection [1]. Viral culture is the traditional diagnostic test for cCMVI; however, it has been replaced by polymerase chain reaction (PCR) based tests in most clinical laboratories due to the requirement of tissue culture facilities and longer turnaround time. Saliva and urine are the preferred specimens for testing as most newborns with cCMVI have high viral loads in these fluids. Although saliva is the easiest to obtain, false-positive results may rarely occur due to breastfeeding. Therefore, it is recommended that samples be taken at least 60 min after breastfeeding to avoid contamination of the saliva with CMV from breast milk. A positive result should be confirmed with a repeat PCR test (preferably urine) [1, 21, 35]. For infants who have not undergone neonatal PCR testing within the first 3 weeks, CMV PCR testing on the archived dried blood spot (DBS) specimens obtained for routine newborn screening panels allows for diagnosing cCMVI retrospectively. However, a negative DBS PCR result cannot definitively exclude cCMVI because of this

Table 7.3 Post-diagnosis evaluation, monitoring during treatment, and follow-up of infants with congenital cytomegalovirus infection

Post-diagnosis evaluation: Asymptomatic or symptomatic cCMVI at birth
Physical, neurologic, and neurodevelopmental examination
Laboratory tests: complete blood count, kidney and liver function tests, coagulation studies (in patients with liver disease), and quantitative CMV PCR in whole blood or plasma (used for monitoring of infant receiving antiviral therapy)
Hearing assessment: auditory brainstem response
Ophthalmic assessment
Cranial imaging with ultrasound, computed tomography, or magnetic resonance imaging (depending on clinical presentation)
Monitoring during antiviral treatment
Absolute neutrophil counts should be monitored weekly for 6 weeks, then at week 8, and then monthly for the duration of antiviral treatment
Liver function tests should be monitored monthly during treatment
Long-term follow-up
Audiological testing (all children with cCMVI)
Neurologic consultation and developmental assessments (on a case-by-case basis)
Ophthalmologic evaluations (in cases with clinically detectable disease)
Dental visits

CMV cytomegalovirus, *cCMVI* congenital cytomegalovirus infection, *PCR* polymerase chain reaction

testing method's low and highly variable sensitivity [21, 35]. Serologic methods are not recommended for routine diagnosis of cCMVI. A positive serologic test for CMV immunoglobulin (Ig) G antibody may indicate the passive transfer from the mother; however, a negative test makes cCMVI unlikely. The CMV IgM antibody is insensitive and may be falsely negative in more than 50% of infected newborns [1, 2].

Once the diagnosis of cCMVI is confirmed virologically, a multidisciplinary and comprehensive evaluation should be performed to detect the presence of end-organ involvement, even in asymptomatic newborns, to determine subclinical or subtle symptoms (Table 7.3). Findings might also help determine potential candidates for antiviral treatment and counseling about prognosis and long-term outcomes [21, 35].

7.10 Newborn Screening for Congenital Cytomegalovirus Infection

As the most common congenital infection and a significant public health problem worldwide, cCMVI meets many criteria for screening. Cytomegalovirus is more common and causes more cases of congenital disabilities than the several metabolic or endocrine disorders included in newborn screening panels. Unlike other causes of SNHL in children, cCMVI-related SNHL is potentially treatable, making screening and early diagnosis highly important. Early diagnosis improves patient outcomes and may provide opportunities for timely antiviral treatment and earlier interventions. On the other side, delay in diagnosis and initiating interventions lead

to poor patient outcomes, such as speech and language delays and cognitive and hearing impairments.

Most infants born with cCMVI are asymptomatic or have nonspecific clinical presentations that do not prompt the physician to order a CMV test that must be performed within the first 3 weeks of life. Detection of CMV after this period cannot distinguish congenital from postnatal infection, which is not associated with SNHL and developmental disabilities. All of these, coupled with the substantial health and economic burden of the disease that mainly stems from long-term cognitive and hearing impairments, many CMV experts advocate the implementation of targeted and/or universal newborn screening for cCMVI. Despite the potential benefits mentioned above, it is possible that a false- or true positive screening result, since most infants with cCMVI never develop SNHL or other sequelae, may lead to increased parental stress and inappropriate antiviral treatment, or unnecessary medical visits and tests [21, 36, 37].

Although cCMVI is the leading nonhereditary cause of SNHL in children and is more common than any other screened newborn disorders, there is no universal neonatal screening program to identify infected infants. The main goals of newborn screening for cCMVI include identifying asymptomatic infants at risk for delayed HL, requiring more frequent audiologic assessment, and early identifying infected infants with subtle, nonspecific, or atypical symptoms that might benefit from antiviral treatment [36, 37].

The two types of proposed newborn screening for cCMVI are the universal (screening of all newborns) and targeted (testing of newborns who fail newborn hearing screening) programs [1, 37]. The hearing-targeted CMV screening approach has been implemented in many hospitals. In the USA, Utah became the first state to mandate CMV screening in 2013, and a 2015 cost-benefit analysis found targeted newborn screening to be cost-effective [38]. However, this screening approach is insufficient to detect all CMV-infected infants since most infants with cCMVI have normal hearing at birth. A recent study from seven medical centers in the USA demonstrated that the targeted screening approach failed to detect 43% of infants with CMV-related SNHL in the newborn period and identify infants with cCMVI at risk of late-onset SNHL [39].

Without universal screening, asymptomatic and many symptomatic cCMVIs presenting with milder or nonspecific symptoms will go undiagnosed [24]. For these reasons, many experts advocate for universal newborn screening, which appears to be cost-effective. However, the most reliable and cost-effective method for universal newborn screening for cCMVI has yet to be determined. It may include the detection of CMV DNA by PCR in saliva (both liquid and dried) and urine samples collected at birth or DBS samples from newborn screening Guthrie cards [1]. It has been demonstrated that saliva and urine are reliable samples for neonatal cCMVI screening [40]. Previous reports revealed that DBS PCR has lower sensitivity than traditional methods, possibly because not all infected infants are viremic at birth or the methods used [41]. However, recent studies demonstrated improved sensitivity for DBS, possibly because of improved PCR testing methodologies [42].

7.11 Treatment

Treatment of cCMVI includes supportive treatment, antiviral treatment, hearing amplification and/or cochlear implantation, speech-language therapy, physical therapy, and special education [1].

Antiviral treatment (intravenous ganciclovir or oral valganciclovir) is recommended only for newborns with moderate to severe symptomatic cCMV disease to improve hearing and neurodevelopmental outcomes [21, 35]. Antiviral treatment should be initiated within the first 30 days of life, and the standard duration of treatment is 6 months. There is no definitive clinical evidence or benefit in starting antiviral therapy beyond the first 30 days of life, and this issue is an area of active study. The clinical benefit and safety of antiviral treatment in infants with asymptomatic cCMVI, including those with isolated SNHL, are unknown. Two international consensus groups recommend that asymptomatic infants with or without isolated SNHL should not receive antiviral treatment [21, 35]. Several clinical trials are underway to determine whether valganciclovir treatment is beneficial in asymptomatic infants with and without SNHL.

In infants with severe, life-threatening diseases or gastrointestinal disorders affecting drug absorption, intravenous ganciclovir is preferred initially. Antiviral treatment's commonly reported side effects are neutropenia, thrombocytopenia, hepatotoxicity, and catheter-related events during ganciclovir treatment, such as infection or extravasation [1, 21, 35]. Therefore, *blood tests should be monitored* regularly during antiviral treatment. In animal models, ganciclovir is gonadal toxic and carcinogenic, but these long-term adverse effects have not been reported in humans [43].

In addition to antiviral treatment, managing symptomatic infants with severe disease includes supportive measures, such as control of seizures, nutritional support, and platelet transfusion [1].

If undetected or untreated, HL can lead to speech and language delays and cognitive impairments in children. Therefore, a multidisciplinary team should manage children with cCMVI-associated SNHL, including otolaryngologists, speech-language pathologists, and HL educators. The treatment of children with cCMVI-related SNHL is not different from any child with SNHL. The first stage of treatment is early amplification. Cochlear implantation can be considered for children with severe to profound HL who do not receive adequate hearing amplification benefits [33].

7.12 Long-term Follow-Up

To detect late complications and sequelae, long-term follow-up is necessary for all children, asymptomatic and symptomatic, with cCMVI (Table 7.3).

Due to the absence of well-defined predictors of SNHL, monitoring all infants with asymptomatic or symptomatic cCMVI is essential. Additionally, the

late-onset and progressive nature of SNHL in children with cCMVI necessitates long-term audiologic follow-up for early detection and intervention of HL. Most changes seem to occur within the first few years of life, and most children with cCMVI will develop progressive HL into adolescence. Considering these findings, hearing evaluations are recommended every 3–6 months for the first 3 years of life and annually through adolescence. If HL is determined, audiological assessments should be carried out into adulthood to monitor the progression of HL [1, 21, 35].

Neurodevelopmental assessments should be performed regularly to determine cognitive and motor disabilities. Neurology consultation may be required in children with cerebral palsy or seizure management. Repeat ophthalmologic evaluations should be performed to follow up on symptomatic infants with chorioretinitis or other abnormalities present at birth and to monitor for the development of late sequelae, such as later-onset retinitis, strabismus, and vision impairment. Congenital CMVI is also associated with hypoplasia and hypocalcification of tooth enamel. Therefore, regular dental visits are also required for the long-term care of these children [1, 44].

7.13 Prevention

Currently, no effective and safe therapies are available to treat maternal and fetal CMVI. Therefore, prevention rather than treatment is a promising option for reducing the risk of cCMVI. Until today, several promising interventions have been proposed to prevent cCMVI [45].

At present, no licensed vaccine is available to prevent CMVI. Randomized trials of CMV hyperimmune globulin use to prevent cCMVI have not shown a benefit [46]. A recent randomized study by Shahar-Nissan et al. [47] reported a 70% reduction in vertical transmission of CMV with the oral valaciclovir treatment after primary maternal infection acquired early in pregnancy. However, the routine use of antiviral therapy to prevent cCMVI during pregnancy is not recommended due to insufficient clinical evidence [21].

A significant risk factor for maternal CMVI is close contact with young children who excrete the virus in saliva and urine for months or years. Several studies have shown that most pregnant women are unaware and uninformed about cCMVI and its consequences in infants. Similarly, low awareness rates have also been reported among healthcare providers [1, 21]. This lack of awareness is a critical problem, given that the only way to prevent maternal CMVI is through hygiene precautions and behavioral interventions. Therefore, all pregnant women, seropositive and seronegative, should be educated about cCMVI and preventive measures, such as careful hand-washing after exposure to young children's body fluids, avoiding kissing children on the mouth, and not sharing food, drink, or oral utensils with young children [21, 45]. The www.nationalcmv.org website may be advised as a good resource for families and professionals.

7.14 Conclusion

Congenital CMVI is the leading cause of nongenetic SNHL in children worldwide. The recognition of cCMVI as a cause of SNHL is underestimated for the following reasons. First, there is a lack of awareness about cCMVI among healthcare workers and the general population. Second, there is no universal systematic newborn screening for cCMVI. Third, most maternal and newborn infections are asymptomatic and, therefore, not tested and diagnosed with cCMVI at birth. Also, most children with cCMVI have normal hearing at birth and develop subsequent late-onset HL, at which point a retrospective diagnosis is challenging. Consequently, universal neonatal hearing screening programs will miss many of these children even if combined with targeted testing for cCMVI.

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Congenital Toxoplasmosis and Hearing Loss

8

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8.1 Introduction

Normal hearing is one of the most critical factors affecting the neurocognitive development of humans. While the peripheral part of structures related to hearing is fully formed until birth, the central part takes up to 2 years after delivery to mature. In this maturation period, the quantity and quality of external stimuli reaching the infant are critical. Therefore, early diagnosis and treatment of hearing loss (HL) are vital to neuromotor development, speech development, and socialization [1].

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Permanent congenital HL occurs in 2–4 of every 1000 live births [2, 3]; inherited disorders cause more than half, and acquired causes, including congenital infections, about a quarter [2]. Almost all congenital infections can adversely affect fetal hearing function development. Because congenital toxoplasmosis may also result in hearing impairment, it should be considered among the preventable causes of hearing loss. Current guidelines on early hearing detection and intervention recommend that infants with congenital infections be monitored to detect late-onset hearing loss, even if the initial audiological evaluation was normal [4].

8.2 Etiology and Epidemiology

Toxoplasmosis is a parasitic disease caused by *Toxoplasma gondii*, an obligate intracellular protozoan that infects almost all warm-blooded animals. It is estimated that about one-third of the world's human population is infected with *T. gondii*. Infection rates vary extensively from 10 to 80% between geographical regions. Socioeconomic status and hygiene behaviors are important factors determining the prevalence of infection [5].

The prevalence of *T. gondii* infection was reported at quite different rates in epidemiological studies conducted in different geographical areas or populations. The incidence and prevalence data may also differ over the years. Europe, Central America, Brazil, and Central Africa have the highest rates of *T. gondii* infections [6]. Among European countries, seroprevalence rates vary widely between regions. For example, while the overall seroprevalence was reported as 10.7% in pregnant women in Norway [7], it was 37–42% in France [8]. The seroprevalence and incidence rates, reported to be higher in the past years, have been decreasing in recent years. In France, seropositivity for toxoplasmosis was decreased in pregnant women, from 83% in 1965 to 37% in 2010 [8].

The differences in the seroprevalence for toxoplasmosis are also observed for congenital toxoplasmosis as 18–34, 20–24, and 6–8 per 10,000 live births in South America, Africa, Europe, and North America, respectively [9]. The global congenital toxoplasmosis burden is estimated to be 190,000 cases annually [9].

In the last 20 years, a dramatic decrease occurred in the incidence and prevalence of toxoplasmosis, even in countries with a high prevalence of *T. gondii* infections [8, 10]. It is thought that this is related to raising awareness in the population, especially about food preparation hygiene, educating pregnant women, and prenatal screening [6, 10, 11]. In some countries, prenatal screening for toxoplasmosis is strongly recommended [6, 11]. A significant decrease in congenital toxoplasmosis incidence after prenatal screening programs was reported [6, 11].

8.3 Life Cycle of *Toxoplasma gondii* and Transmission

Toxoplasma gondii can live in animals in three forms; tachyzoite, bradyzoite, and oocyst [5]. Tachyzoite is the rapid-proliferating form, and bradyzoite is the slow-proliferating form in animals and humans [6]. Oocysts are found in cat feces. The

sexual life cycle of *T. gondii* occurs mainly in felines, and the asexual cycle occurs in humans and animals [6].

Cats become infected directly by ingesting oocysts or ingesting intermediate hosts' tissue or organs harboring bradyzoite-containing tissue cysts [12]. Then, the sexual life cycle begins in the cat's intestine, and macrogametocytes and microgametocytes develop from ingested bradyzoites and/or oocysts and fuse to form zygotes [13, 14]. The zygotes become encapsulated within a thick wall and are dispersed as oocysts. Oocysts are resistant to ultraviolet light, chlorinated water, and ozone. Thus, oocysts can survive and contaminate water sources, soil, and the environment through cat feces. Oocysts are responsible for the spread of infection from cats to humans or animals [5, 15].

Humans and animals may acquire toxoplasmosis from oocyst-contaminated soil and vegetables. When orally ingested, oocysts reach the intestines and rupture to release sporozoites. Then, sporozoites transform into tachyzoites. Tachyzoites can spread throughout the body via the bloodstream and lymphatics. If the host's immune response is adequate, tachyzoites reaching the end organs are confined to tissue cysts and transform into bradyzoites. Bradizoites are responsible for the chronic stage of infection and can persist throughout the host's life. A cyst may contain several or hundreds of bradyzoites responsible for latent infection [15]. Tissue cysts can be found in the eye, brain, heart, and skeletal muscles [5, 15]. The shape of the cysts may differ according to the involved organ; a spherical shape in the brain parenchyma and a more elongated shape in the muscle are seen [5].

Transmission of *T. gondii* to humans also occurs by eating undercooked meat containing tissue cysts. Cysts are found in the muscles of pigs and cattle, and their ingestion by humans is critical for transmitting toxoplasmosis to humans. Bradyzoites, more resistant to temperature changes than tachyzoites, should be stayed for 3 days at minus (−) 12 °C or be exposed to a temperature above 67 °C to lose the infectivity potential [15]. Therefore, it is essential to cook the meat at the appropriate temperatures for bradyzoites' inactivation [5, 6, 15].

Congenital toxoplasmosis happens due to transplacental transmission of the tachyzoites to the fetus [5]. Rarely, the infection can be transmitted to humans by transplantation of an infected organ or transfusion of blood products containing tachyzoites [5, 6].

8.4 Clinical Features

The incubation period is around 1 week for acquired toxoplasma infection. Parasitemia occurs through the spread of tachyzoites and is responsible for acute symptoms, generally lasting 2 weeks after infection. Following the acute phase, the latent phase begins with transforming the tachyzoites into bradyzoites [15].

Toxoplasmosis is usually asymptomatic, benign, and self-limited in immunocompetent individuals [6]. Severe end-organ damage may occur in immunocompromised patients and congenitally infected infants. Patients with congenital infections are at high risk for retinal disease throughout their lives, even if they are asymptomatic in early life [6].

When symptomatic, toxoplasmosis may present with mild symptoms, such as fever, flu-like syndrome, lymphadenopathy, hepatosplenomegaly, infectious mononucleosis, arthralgia, or rarely with severe end-organ involvement, such as chorioretinitis, pneumonia, central nervous system (CNS) infections, and myocarditis. Severe toxoplasmosis is more common in patients with high parasite load and countries with more virulent and antigenic sub-types, such as Mexico, Colombia, French Guiana, and Brazil [5, 6, 15, 16].

Chorioretinitis has particular importance for a person infected with *T. gondii* because it is the most common late manifestation of infection. The patients usually suffer from blurred vision. Rarely, chorioretinitis may also present with photophobia, epiphora, and scotoma. Fundoscopic examination shows focal necrotizing retinitis. Vision loss, retinal detachment, and neovascularization on the optic nerve and retina may occur. Cataracts, microphthalmia, strabismus, and nystagmus are the other ocular complications of *Toxoplasma* infections [6, 17]. Approximately 90% of children who do not receive appropriate treatment may develop new retinal lesions later in life. These lesions usually develop in late childhood or adolescence. In cases that received proper treatment, chorioretinitis attacks may also be seen in the following years [6, 18].

Toxoplasma gondii is an important opportunistic pathogen in immunocompromised patients. Reactivation of bradyzoites in tissue cysts may occur in these patients, resulting in prolonged fever, meningoencephalitis, brain abscess, lower respiratory tract infection, myocarditis, hepatitis, skin rash, uveitis, chorioretinitis, disseminated disease, multi-organ failure, and death [5, 6, 15]. Hematopoietic stem cell and solid organ transplant recipients are at risk of severe toxoplasmosis without antimicrobial prophylaxis. *Toxoplasma* infection has particular importance for pregnant women. In pregnant women, the fetus may be infected transplacentally when the primary infection develops or the reactivation of bradyzoites in tissue cysts during latent infection [5, 6, 15, 16].

8.5 Congenital Toxoplasmosis

Primary *T. gondii* infection in pregnant women is usually asymptomatic. During primary or reactivated toxoplasma infection in pregnant women, the probability of transmission to the fetus is 50% [5]. The transmission rate varies according to the stage of pregnancy, geographical region, and subtypes of the parasite [5].

The probability of maternofetal transmission is low in early pregnancy; this risk becomes almost 100% in the last weeks. If the fetus is infected early in pregnancy, the risk for severe congenital toxoplasmosis is high [6, 15, 16]. However, if the fetal infection occurs in late pregnancy, neonates are usually born asymptomatic. The treatment for toxoplasmosis during pregnancy reduces the risk of developing complications in the newborn but does not eliminate the risk [5, 6, 19]. The severity of congenital toxoplasmosis mostly depends on the timing of fetal infection, genotypic subtypes of *T. gondii* strains, parasite burden, and immune responses of infants and pregnant women [6, 20].

Congenital toxoplasmosis is 90% asymptomatic in the neonatal period. The physical examination of a newborn with congenital toxoplasmosis is usually normal. If there is a high index of suspicion for intrauterine infection, additional tests, including cerebrospinal fluid (CSF) examination, neuroimaging, and ophthalmologic examination, should be performed [6, 15]. These tests are abnormal in half of the asymptomatic infants with congenital toxoplasmosis [21].

In early infancy, clinical findings may present in only 10–30% of infants with congenital toxoplasmosis [6, 15]. In neonates with symptomatic congenital toxoplasmosis, microcephaly, microphthalmia, seizures, rash, jaundice, generalized lymphadenopathy, hepatosplenomegaly, strabismus, meningoencephalitis, hepatitis, retinitis, choroiditis, HL, anemia, and thrombocytopenia may occur [5, 15]. Severe congenital toxoplasmosis manifestations usually result from the primary infection of pregnant women in the first trimester [6, 15].

The classic triad of congenital toxoplasmosis consists of chorioretinitis, cerebral calcifications, and hydrocephalus. Retinal involvement is usually characterized by unilateral macular scars [6]. Cerebral calcifications may be seen as small, focal, and scattered lesions. Cerebrospinal fluid shows mononuclear pleocytosis and increased protein levels. However, these findings occur in <10% of patients [6].

Even if congenital toxoplasmosis is asymptomatic in the perinatal period, it may present with chorioretinitis, vision problems, HL, learning disabilities, endocrine abnormalities including growth retardation, and precocious puberty, or severe developmental delay later [5, 6, 15, 16].

8.6 Diagnosis

The diagnosis of toxoplasmosis is often challenging due to the interpretation of diagnostic tests. Many different techniques can be used for the diagnosis of *Toxoplasma* infections. Test selection is made by considering the patient's age, clinical status, and whether the tests are available. The most commonly used diagnostic method is serological tests [5, 6, 15, 16].

Isolation of *T. gondii* from sterile body fluids, or blood, inoculated into the mice or cell cultures indicates acute infection [16]. *Toxoplasma* can also be isolated from tissues in acute and chronic (latent) infections. If the placental infection exists, the fetus is often infected with *T. gondii*. Tachyzoites may be demonstrated in histopathological examination of tissues or cytologic preparations of body fluids. Tissue cysts can also be shown by specific immunoperoxidase staining in tissue specimens, including the placenta and fetus [16].

Toxoplasma-specific immunoglobulin (Ig) M and IgG tests are widely available in commercial laboratories. The results should be confirmed in reference laboratories when serological tests are positive in pregnant women and newborns. *Toxoplasma*-specific IgM test results may be falsely positive. Confirmatory tests may include IgM, IgA, IgE, IgG avidity, and differential agglutination [15].

Toxoplasma-specific IgM becomes positive 1–2 weeks after infection, reaches the peak level in 1 month, and decreases to undetectable levels in 6–9 months.

Rarely, it may remain positive for years. This prolonged *Toxoplasma*-specific IgM positivity is the most common diagnostic error in pregnant women [16]. *Toxoplasma*-specific IgM positivity may indicate a recent infection, latent infection, or a false-positive result [15]. The acute infection is excluded if Toxoplasma-specific IgM by enzyme-linked immunosorbent assay (ELISA) or immunosorbent agglutination assay (ISAGA) methods is negative [16].

Toxoplasma-specific IgG antibodies reach the highest level 1 month to 5 months after infection and usually remain positive lifelong [15, 16]. If *Toxoplasma*-specific IgG is positive in low-titers and *Toxoplasma*-specific IgM is negative, it may indicate the infection occurred at least 6 months ago. *Toxoplasma*-specific IgG avidity tests can help differentiate between recent and chronic infections. If the avidity of the *Toxoplasma*-specific IgG test is high, it indicates that the infection was acquired before, not within the last 3 months. If the avidity of the *Toxoplasma*-specific IgG test is low, it indicates that the infection may have been acquired within the previous 3 months [16]. Avidity tests are helpful when *Toxoplasma*-specific IgG is positive in the first trimester of pregnancy [16].

An acute (recent) infection diagnosis can be made when an initially negative test result turns positive or if the specific-antibody levels rise fourfold or more in serum samples taken at least 3 weeks apart [16].

Differential agglutination tests can help distinguish acute and chronic infections [16]. High agglutination with acetone fixation suggests acute infection; high agglutination with formalin fixation indicates chronic infection. For the most accurate evaluation of infection in pregnant women, differential agglutination tests should be combined with the Sabin–Feldman dye test, IgM ELISA, IgA ELISA, IgE ELISA/ISAGA, and avidity studies [16].

For the accurate diagnosis of congenital infection, it is essential to determine when it is acquired or reactivated in pregnant women. A positive result of *Toxoplasma*-IgM should be confirmed with additional tests (IgG avidity, IgA-, and IgE-specific antibodies) [5, 6, 15, 16].

Polymerase chain reaction (PCR), an essential, widely used diagnostic test, can detect the deoxyribonucleic acid (DNA) segments of *T. gondii* in both tissue samples, such as muscle, myocardium, placenta, and brain parenchyma, and sterile body fluids, including blood, CSF, vitreous fluid, bronchoalveolar lavage fluid, and urine [6, 15]. When PCR positivity is detected in tissue samples, it primarily indicates that this may be due to bradyzoites responsible for latent infection or tachyzoites responsible for acute illness [15]. In a study conducted on 339 pregnant women in France, PCR tests in amniotic fluid and umbilical cord blood sampling were entirely compatible with diagnosing congenital infection [16].

8.6.1 Diagnosis of Congenital Toxoplasmosis

Early diagnosis of congenital toxoplasmosis and, thus, early initiation of antimicrobial therapy are crucial to reducing morbidity and mortality. Serological screening during pregnancy, screening of newborns in the postnatal period, or diagnostic tests

performed on amniotic fluid or a neonate born with compatible clinical findings provide the congenital toxoplasmosis diagnosis [6, 15, 22].

The indications for the evaluation of a newborn for congenital toxoplasmosis are listed below [6, 23];

1. Serologic evidence of primary *T. gondii* infection during pregnancy
2. Serologic evidence of past infection with *T. gondii* in a pregnant woman with immunodeficiency
3. Infants born with compatible clinical findings
4. Infants with a positive result for *Toxoplasma*-specific IgM if newborn screening is performed.

Given the potential difficulty in interpreting serologic tests in newborns, all infants with a presumed diagnosis of congenital toxoplasmosis should undergo additional clinical, laboratory, and neuroimaging evaluations for evidence of infection.

Tests that can be used to demonstrate fetal infection are as follows: (1) Toxoplasma-PCR in amniotic fluid, (2) Fetal ultrasonography, which can detect anatomical abnormalities, (3) Histopathological examination of placental tissue, fetus, or newborn, and (4) Toxoplasma-PCR in placental tissue [5, 16].

In neonates, serologic evaluation should be performed with *Toxoplasma*-specific IgG, IgM, and IgA measurements and *Toxoplasma*-PCR test in blood or sterile body fluids, including urine and CSF. *Toxoplasma*-specific IgM and/or IgA and IgG positivity suggest the diagnosis of congenital toxoplasmosis. Transfusion of blood products may cause false-positive serological test results. If an infant is still positive for *Toxoplasma*-specific IgG after 12 months, this also supports the diagnosis of congenital toxoplasmosis [5, 15].

A newborn with positive *Toxoplasma*-specific IgG but negative IgM and IgA tests and no supporting findings for congenital toxoplasmosis should be monitored with serological tests. Repeating the Toxoplasma-specific IgG test is recommended every 4–6 weeks. If initial *Toxoplasma*-specific IgG positivity is due to transplacentally transmitted maternal antibodies, the IgG level is expected to decrease gradually and disappear before 1 year of age [15]. If initial serological tests are performed in the first 10 days of life, tests should be repeated later to exclude false positivities [6]. The pyrimethamine and sulfadiazine treatments during pregnancy may affect the infant's serological test results for toxoplasmosis [6].

Complete blood count, liver function tests, serum total IgM, IgG, IgA, albumin, CSF analysis including cell count, protein, and glucose levels, CSF IgG level, CSF dye test, *Toxoplasma*-specific IgM, head and abdominal ultrasonography, and brain magnetic resonance (MR) imaging should be performed in a newborn with suspected congenital infection [5, 6, 15, 16]. In a newborn with congenital toxoplasmosis with CNS involvement, CSF protein level increases and glucose level decreases.

Maternal serologic tests, including the Sabin–Feldman dye test, *Toxoplasma*-specific IgM, IgA, IgE, and differential agglutination, should also be performed during newborns' evaluation for congenital toxoplasmosis [16].

Calcifications localized to the brain parenchyma can be detected by ultrasonography, computed tomography (CT), or MR imaging. Among the imaging methods, CT is recommended as it is more sensitive to calcifications [5, 15]. Dilated eye examination and audiological assessments should be performed on every neonate evaluated for congenital infection.

If initial laboratory test results are within normal limits despite high clinical suspicion, serological evaluation should be repeated every 4 weeks until 3 months of age [6].

8.7 Treatment

Acute-acquired toxoplasma infections usually do not require specific antimicrobial therapy. However, *Toxoplasma*-specific treatment should be given in the following indications: (1) Infection during pregnancy, (2) Ocular involvement, (3) Severe end-organ damage, (4) Infection in patients with immunodeficiencies, and (5) Congenital toxoplasmosis.

When congenital toxoplasmosis is strongly suspected or a definite diagnosis is made, antimicrobial therapy should be started as soon as possible. The preferred regimen is the combination of pyrimethamine, sulfadiazine, and folinic acid. The treatment should be given for at least 12 months. The treatment regimen and doses are summarized in Table 8.1 [15].

In children and adolescents with severe acute toxoplasmosis or severe reactivated toxoplasmosis, if the preferred drug regimen (pyrimethamine, sulfadiazine, and folinic acid) is not available or drug-related adverse effects have developed, the following antimicrobial therapy options can be given [15]:

1. Trimethoprim-sulfamethoxazole (TMP-SMX) monotherapy, intravenous or peroral)
2. Pyrimethamine + folinic acid + clindamycin
3. Pyrimethamine + folinic acid + atovaquone

Table 8.1 Drugs and doses used in the treatment of toxoplasmosis[a]

Drugs	Pyrimethamine	Sulfadiazine	Folinic acid (leucovorin)	Prednisone[b]
Doses	First 2 days: 1 mg/kg every 12 h orally Then, 1 mg/kg once daily for at least 2–6 months Remaining months to complete 12 months: 1 mg/kg once daily, 3 days/a week	50 mg/kg every 12 h orally (for 12 months)	10 mg/dose, 3 days/a week orally	0.5 mg/kg every 12 h (maximum 20 mg/dose)

[a] Adapted and modified from Ref [15, 16]

[b] Only given if the cerebrospinal fluid protein is ≥1 g/dL or detection of vision treating chorioretinitis

4. Pyrimethamine + folinic acid + clarithromycin
5. Pyrimethamine + folinic acid + azithromycin
6. Atovaquone + sulfadiazine

Alternative therapies should be changed to the preferred drug regimen when available.

Spiramycin treatment is recommended in pregnant women with *Toxoplasma* infection [13]. However, if fetal infection occurs despite spiramycin treatment, a combination of pyrimethamine, sulfadiazine, and folinic acid should be started [6, 16]. If antitoxoplasmal therapy during pregnancy is started within the first 3 weeks after seroconversion, the probability of maternofetal transmission is reduced by 52% [24].

8.8 Prophylaxis

Primary or secondary prophylaxis with TMP-SMX is indicated in patients with primary and secondary immunocompromising conditions, including hematopoietic stem cell and solid organ transplantation and human immunodeficiency virus (HIV) infection.

In HIV-infected patients, if the absolute CD4(+) T-cell count is low and *Toxoplasma*-specific IgG is positive, antimicrobial prophylaxis against toxoplasmosis should be given. Trimethoprim-SMX is the preferred agent for primary prophylaxis and can be given thrice per week [25]. Alternative regimens also can be given, such as dapsone + pyrimethamine + leucovorin and atovaquone ± pyrimethamine ± leucovorin [25].

Toxoplasmosis is a rare but fatal infection after solid organ transplantation. Since *T. gondii* tends to settle in the muscles, the disease can be problematic, especially after heart transplantation [26]. If the donor is seropositive and the recipient is seronegative, the risk of *T. gondii* infection in the posttransplant period is high. If appropriate antimicrobial prophylaxis is not given in this patient group, 50–70% of patients may develop toxoplasmosis [26]. Although rare, toxoplasmosis was also transmitted by liver, kidney, and lung transplantation. Although no standard recommendation for antimicrobial prophylaxis exists in these patient groups, primary prophylaxis is given with TMP-SMX or TMP-SMX + pyrimethamine for 6 weeks to 6 months, especially after heart transplantation [26]. Sulfadiazine, dapsone, clindamycin, and atovaquone are the other alternative agents for prophylaxis against toxoplasmosis.

When acute Toxoplasma infection is detected during pregnancy, antimicrobial therapy is given to prevent congenital *T. gondii* infection in the infant, regardless of whether the mother has symptoms or not [27]. The parents should be informed that this prophylaxis approach does not eliminate the infection risk in the fetus. When acute infection is detected in the mother, treatment should be started as soon as possible, preferably before amniocentesis. Treatment should be initiated before tachyzoites in the fetus transform into bradyzoites, known to be resistant to

antimicrobial therapy, within the first 3 weeks after seroconversion occurs. Spiramycin or pyrimethamine-sulfadiazine treatment is given to pregnant women. Studies report that pyrimethamine-sulfadiazine is more successful in prophylaxis [28].

8.9 Complications and Prognosis

A fetus with disseminated congenital toxoplasmosis may die in utero or within the first few days of life. In infants with severe congenital toxoplasmosis, although early diagnosis and treatment have been applied in the neonatal period, neurocognitive and visual functions may be affected later in life. However, symptomatic infants without signs of severe disease or asymptomatic infants can recover completely without sequelae with early diagnosis and treatment [15]. Asymptomatic and symptomatic newborns should be followed up regarding neurocognitive, ocular, and hearing functions.

In long-term follow-up, motor and cerebellar dysfunctions, microcephaly, and intellectual disabilities can be noticed [6]. An infant with congenital toxoplasmosis may present with seizures later. A study conducted in the United States of America (USA) in 2011 reported that when prenatal or postnatal treatment was not applied for toxoplasmosis, more than 90% of infants had mental or visual impairment when they reached the age of 12 [29]. Therefore, monitoring and supporting neurocognitive functions during or after treatment is vital in improving the patient's quality of life.

Infants diagnosed with congenital toxoplasmosis should be examined every 3 months in the first 2 years of life, every 6 months in the third year, and once a year after that until they can report vision problems [6].

All infants with congenital toxoplasmosis should be evaluated for hearing function and kept on close follow-up. Hearing screening programs are routinely performed in many countries. However, hearing should be monitored with auditory brainstem response (ABR) tests in infants with congenital toxoplasmosis. These tests are more sensitive than automated tests used in routine screening to evaluate hearing functions [6].

It is also reported that congenital toxoplasmosis may result in precocious puberty and growth retardation by disrupting the hypothalamohypophyseal axis [6, 30].

8.10 Prevention

Another compelling feature of toxoplasmosis is that it is impossible to suggest a single protection method because *T. gondii* can transmit to humans by different mechanisms. Increasing knowledge and awareness about toxoplasmosis and its transmission in society are essential. However, special consideration should be given to pregnant women and those with primary or acquired immunodeficiency at high risk for severe complications of toxoplasmosis.

To prevent the transmission of toxoplasmosis, the following precautions should be recommended:

1. Contact with cat feces should be avoided. Cat litter should be changed daily, and hands should be washed carefully after this process.
2. Domestic cats should be prevented from hunting birds or rodents infected with *T. gondii*.
3. Gloves should be worn during contact with the soil, and hands should be washed carefully after removing the gloves. Contamination of water with soil or waste should be prevented.
4. Meat should be well cooked. Bradyzoite-containing tissue cysts will be inactivated when their internal temperature rises above 65.5 °C. Keeping the meat in the freezer for at least 2 days at minus (−) 20 °C also inactivates the bradyzoites. Foods should be prevented from being contaminated with raw meat. Shellfish should not be consumed raw.
5. Vegetables and fruits should be washed carefully, and the materials and benches used while preparing the food should be adequately cleaned [15].

The approaches to prevent congenital toxoplasmosis in infants can be summarized as follows; performing serological screening in pregnant women, treating the acute maternal infection with spiramycin, and administering pyrimethamine, sulfadiazine, and folinic acid when a fetal infection is documented. Therapeutic abortion should be discussed with parents when fetal abnormalities are detected by ultrasound or MR imaging to prevent the birth of a severely affected infant [16].

Standard isolation precautions are recommended when a patient with congenital or acquired toxoplasmosis is hospitalized [15].

8.11 Screening Programs

In some countries, including Austria, Denmark, France, Slovenia, and only a few states in the USA, prenatal serological screening is mandatory to detect congenital toxoplasmosis early [6, 11]. In the study of Prusa et al. [11], the cost of the screening program implemented in Austria and the costs of diagnosing and treating infants with congenital toxoplasmosis who would be born in the absence of screening were compared and was reported that prenatal serological screening is cost-saving. However, pregnant women are not screened routinely for toxoplasmosis in many countries.

In newborn screening programs, blood samples taken for routine metabolic screening are tested for *Toxoplasma*-specific IgM; if positive, detailed serological testing is performed on the mother and the infant [6].

8.12 Congenital Toxoplasmosis and Hearing Loss

Hearing loss is one of the most important but challenging to detect complications of congenital toxoplasmosis. In cases with congenital toxoplasmosis, educationally significant HL was reported as 10–15% and all HLs up to 30% [31–33].

In the ear involvement of congenital toxoplasmosis, severe inflammation, necrosis, and calcium deposits are seen in histopathological examinations, similar to the lesions seen in CNS involvement [34, 35]. The calcium deposits are primarily found in the spiral ligament of the cochlea [35]. Another important mechanism in HL caused by congenital toxoplasmosis is that the *T. gondii* tachyzoites can also damage the auditory pathways during brain involvement [5, 32]. In these cases, tachyzoites were found in the middle ear fluid, temporal bones, internal auditory canal, spiral ligament, stria vascularis, and saccular macula [5, 34]. Antimicrobial therapy suppresses the replication of *T. gondii* and reduces inflammation, and cell destruction caused.

Inflammatory changes caused by tachyzoites are not observed in the presence of encysted organisms, bradyzoites [34]. The mechanism responsible for HL is thought to be the host's inflammatory response to tachyzoites. It has also been reported that vacuolization and nucleus–nucleolus distinction are lost in cochlear neurons. Therefore, neuronal pathways of hearing are also affected. Thus, timely initiation of antimicrobial therapy, suppressing the replication of tachyzoites, can decrease hearing damage [34].

In the 1940s, the relationship between toxoplasmosis and HL began to draw attention, demonstrating parasites in the mastoid and temporal bones in autopsies of cases with toxoplasmosis. A study by Kelemen [35] in 1958 emphasized the effect of congenital toxoplasmosis on hearing; autopsy findings of two infants showed the CNS and hearing effects. In the following years, studies focused on the long-term effects of congenital toxoplasmosis on hearing and treatment success in preventing complications. In 1980, Wilson et al. [36] reported clinical outcomes of 24 cases with asymptomatic congenital toxoplasmosis without treatment. They reported chorioretinitis in 19 patients and varying degrees of HL in five cases (Tables 8.2 and 8.3).

Table 8.2 Summary of studies reporting hearing outcomes in infants with congenital toxoplasmosis[a]

Degree of hearing impairment				Results		
	Auditory brainstem responses (Db/HL)	Audiogram (Db/HL)	Wilson et al. (1980) [36]	McGee et al. (1992) [32] *n*	Wilson et al. (1980) [36] *n*	De Andrade et al. (2008) [37] *n*
Normal	≤20	0–20	<25 dB	30	14	15
Mild	>20–40	25–40	25–50 dB	0	3	2
Moderate	>40–60	>40	51–80 dB	0	2	1
Severe	>60	>70–90		0	0	1
Profound		>90		0	0	
Total number of cases				30	19	19

Db indicates decibel, *Db/HL* decibel/hearing loss, *N/A* not applicable

[a] Adapted from Ref. [32, 36, 37]

Table 8.3 Summary of studies reporting diagnostic tools, treatment modalities, and hearing outcomes in infants with congenital toxoplasmosis[a]

Study/ Reference number	Number of cases	Diagnostic criterion	Treatment	Audiometric test	Prevalence of hearing loss
Stagno et al. (1977) [38]	1	Toxoplasma-specific-IgG antibody persistence after 12 months	None	Air-bone conduction used to exclude conductive hearing loss	0% (0/1)
Wilson et al., (1980) [36]	19	Toxoplasma-IgM testing in neonatal/cord blood and Toxoplasma-specific-IgG persistence after 6 months	None/ insufficient	Pure-tone and speech reception threshold audiometry	26% (5/19)
McGee et al. (1992) [32]	30	Toxoplasma-IgM testing in neonates (17 infants) or in CSF (two infants), and/or Toxoplasma-specific IgM or Sabin–Feldman dye test in maternal blood plus clinical findings of congenital toxoplasmosis	>12 months	ABR	0% (0/30) (in six cases, conductive type hearing loss was detected due to acute otitis media)
McAuley et al. (1994) [22]	7	Serological test in the reference laboratory	None	ABR, soundfield, and behavioral audiography	14% (1/7)
McLeod et al. (2006) [39]	68	Serological test in the reference laboratory	>12 months	ABR, soundfield, and behavioral audiography	0% (0/68)
Andrade et al. (2008) [37]	19	IgM/IgA <6 months and IgG persistence after 12 months	Partial /12 months	Interacoustics pediatric audiometer, impedanciometer, behavioral audiometry, otoacoustic emissions, and BAEP	21%, (4/19)

(continued)

Table 8.3 (continued)

Study/ Reference number	Number of cases	Diagnostic criterion	Treatment	Audiometric test	Prevalence of hearing loss
Resende et al. (2010) [40]	106	Toxoplasma-IgM positivity in infants' dry blood samples, confirmatory serum tests, and Toxoplasma-specific IgG persistence >12 months	12 months	Behavioral audiometry, ABR, otoacoustic emission, and tympanometry	12.3% conductive hearing loss in 13/106, 3.8% sensory-neural hearing loss (4/106), and 27.4% central hearing abnormality (29/106)

ABR indicates auditory brainstem responses, *BAEP* brainstem auditory evoked potentials, *CSF* cerebrospinal fluid, *Ig* immunoglobulin

[a] Adapted and modified from Ref. [31, 33, 40]

In a study by McGee et al. [32], 30 infants with congenital toxoplasmosis were treated for 1 year and followed up prospectively. The infants' hearing was monitored by an auditory brainstem response (ABR) test and behavioral audiometry. Although half of the patients had severe end-organ involvement, such as hydrocephalus, chorioretinitis, and systemic illness, the audiometry tests were normal and consistent with the ages of the cases. The authors concluded that these positive results are related to the timely and adequate administration of antimicrobial treatment. The authors also recommended that infants with congenital toxoplasmosis be closely followed-up for hearing between the ages of 6 months and 2 years, which is considered the critical period for language acquisition.

McLeod et al. [39] conducted a prospective multicenter study to detect the long-term effects of congenital toxoplasmosis. They reported that 68 children with congenital toxoplasmosis developed HL with appropriate and adequate antimicrobial therapy. They concluded that early diagnosis and long-term treatment positively affect neurocognitive functions and vision (Table 8.3).

Andrade et al. [37] followed all newborns born in Belo Horizonte, Brazil, for 1 year with serological diagnostic methods (*T. gondii*-specific IgM and/or IgA). They detected congenital toxoplasmosis in 20 of 30,808 newborns (1/1590). One of these 20 newborns, diagnosed with congenital toxoplasmosis, died due to systemic disease in the early period. The hearing of the other infants was tested with behavioral audiometry, otoacoustic emission, and brainstem evoked responses audiometry (BERA), and HL was detected in four (21.1%) infants (Tables 8.2 and 8.3). One of these four infants had other risk factors for HL. The HL in the other three infants was attributed only to toxoplasmosis. Contrary to the literature, HL persisted in two infants despite receiving timely and adequate antimicrobial therapy composed of pyrimethamine, sulfadiazine, and folinic acid for 12 months.

Resende et al. [40] reported that 106 infants with congenital toxoplasmosis were followed up. Antiparasitic treatment was started before 2.5 months old, and detailed hearing tests, including tympanometry, transient evoked otoacoustic emissions, distortion product otoacoustic emissions, behavioral observation audiometry, and brainstem auditory evoked potentials, were performed. Normal hearing in 60 children (56.6%), conductive HL in 13 children (12.3%), sensorineural HL (SNHL) in 4 children (3.8%), and central hearing abnormality in 29 children (27.4%) were detected. The authors emphasized that hearing and language problems can be seen in congenital toxoplasmosis despite early diagnosis and treatment.

Fontes et al. [41] reported that children with congenital toxoplasmosis have a five times higher risk of abnormality in the brainstem auditory evoked potential test and higher latency of wave V. In the study conducted by Al-Amari et al. [42] in Saudi Arabia, 50 infants, aged 11–30 months, followed up with the diagnosis of congenital HL were compared with the age-matched control group. *Toxoplasma*-specific IgG positivity was significantly higher in infants with hearing loss. Potasman et al. [43], in a similar study in Israel, screened the *Toxoplasma*-specific IgG levels of 109 patients aged 1–15 years and followed up with the diagnosis of idiopathic epilepsy, cerebral palsy, and deafness. The seropositivity was 2.5 times higher in the disease group compared to the control group, and the relative risk ratio for hearing abnormality was 7.1.

In a meta-analysis, 114 cases of congenital toxoplasmosis in 5 longitudinal studies analyzed were divided into no or short-term treatment, treated for 12 months but started after 2.5 months, and treated for 12 months but started before 2.5 months of age groups [31]. Hearing loss developed in these groups at 28%, 12%, and 0%, respectively (Table 8.3).

In 2018, Corrêa et al. [33], in a review summarizing eight research articles published between 1980 and 2015, reported that 3.8–30% of HL due to congenital toxoplasmosis are of the sensorineural type and 10–20% of the conductive type. No SNHL was encountered in one of the studies reviewed [39].

Studies focused on congenital toxoplasmosis report that early diagnosis and appropriate antimicrobial therapy for 12 months effectively reduce hearing damage. The risk of HL is low when adequate and timely treatment (before 2.5 months) is started in cases with congenital toxoplasmosis. However, the hearing should be monitored closely, especially in cases where treatment was started late, inadequate, or not given [6, 31].

8.13 Conclusion

Congenital toxoplasmosis, reported with different rates in different geographical regions, is an important intrauterine infection. It is mostly asymptomatic but may cause severe end-organ damage. The most critical factors determining the rate of congenital toxoplasmosis in society are hygiene behaviors, the knowledge and awareness of pregnant women about toxoplasmosis, the dominant *T. gondii* strains in the geographical region, and whether pregnant women and/or newborn screening for toxoplasmosis is performed.

If maternal *T. gondii* infection occurs early in pregnancy, the possibility of transplacental transmission to the fetus is low. However, severe illness is more likely when the fetus is infected early in pregnancy. Suppose an acute maternal toxoplasmosis infection diagnosis is made, early and appropriate antimicrobial therapy should be started, and microbiological and radiological tests should be planned to determine whether the fetus is affected. Infants with congenital toxoplasmosis usually remain asymptomatic. However, both symptomatic and asymptomatic infants should be followed up for long-term sequelae, such as chorioretinitis, motor mental retardation, growth retardation, and HL. Hearing loss is an important but sometimes overlooked complication of congenital toxoplasmosis. The rate of HL in infants with congenital toxoplasmosis is 0–30%. Studies reported that appropriate and early (within the first 10 weeks of life) antimicrobial treatment could reduce the HL rate. Since the sensitivity of commonly used routine hearing screening tests is relatively low, ABR should be preferred for hearing screening in infants with congenital toxoplasmosis. Early diagnosis and treatment of HL can improve the affected infant's psychosocial, motor, and intellectual development.

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Congenital Rubella Infection and Hearing Loss

9

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9.1 Introduction

Rubella is generally mild, self-limited, and vaccine-preventable contagious viral infection, mainly affecting children aged 2–12 years. Rubella virus infection is specified with maculopapular rash, lymphadenopathy, and sometimes fever. Arthritis might accompany rubella, especially in women, but is observed less in men and children. Although rare, encephalitis can also develop during rubella infection, more commonly in adults [1].

Many postnatal rubella infections are subclinical and asymptomatic. However, pregnant women in their first trimester with rubella infection might experience miscarriage, stillbirth, and even congenital disabilities of the fetus, known as congenital rubella syndrome (CRS) [2].

Congenital rubella syndrome was first recognized in 1941 and could have various symptoms, such as mild to severe sensorineural hearing loss (SNHL), cataracts, mental retardation, and congenital heart disease [1, 3, 4]. During pregnancy,

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maternal rubella infection causes roughly 105,000 children to be born with CRS annually worldwide [5], a potentially fatal condition that could be prevented with vaccination. After reinfection, a few confirmed CRS cases have been observed, and this event is rarely teratogenic [4, 6].

In 1969, after the license of the rubella vaccine, rubella and congenital rubella cases decreased rapidly in countries employing national immunization programs. Nevertheless, CRS and rubella remain a significant public health threat in countries lacking rubella immunization programs worldwide [7].

9.2 Etiology

In 1962, Weller and Neva [8] and Parkman et al. found a positive-sense, enveloped, and single-stranded ribonucleic acid (RNA) virus called rubella virus [9, 10]. Rubella virus is considered in the Rubivirus genus the sole member within the Togavirus family. Only one serotype of the rubella virus has been recognized, and humans are the only identified reservoirs [7, 8].

Three structural polypeptides are observed in the rubella virüs; a single nonglycosylated core protein, C, surrounding the virion's RNA, and two envelope glycoproteins of E1 and E2. The rubella virus E1 prevailing exterior molecule is the primary target of the humoral reaction, and it is responsible for viral attachment, fusion, hemagglutination, and neutralization. The E2 glycoprotein is embedded into the envelope [7, 11].

9.3 Pathogenesis

The rubella virus enters the target cell by binding the E1 protein on its surface to the host cell's myelin oligodendrocyte glycoprotein (MOG), mainly identified in human central nervous system (CNS) cells and the placenta [12, 13]. The rubella virus is transmitted to the fetus by the placental route and infects all fetal organs. When a maternal infection develops in the first trimester of pregnancy, the risk of fetal defects is as high as 85–90%, as organogenesis occurs during this period [7]. The risk decreases to 50% with maternal infection at 13–16 weeks and 25% at 15–16 weeks [7]. Although fetal defect risk is infrequent in maternal infections that develop after the 16th week, hearing loss (HL) may develop with maternal infection as late as 20 weeks [7, 14]. Whether rubella reinfection during pregnancy is transmitted to the fetus is controversial [7, 14, 15].

The pathogenesis of congenital rubella infection remains unclear. A few studies demonstrated the histopathological changes related to the CRS in multiple organs. Cytopathic damage occurs in blood vessels, and ischemia develops in affected organs [16]. Noninflammatory necrosis was detected in infected fetuses' eye, ear, heart, brain, and liver structures [8, 17]. Lachrymal glands in the eye and the direct viral infection in epithelial cells of the ciliary body, pycnotic nuclei, inclusion bodies, and cytoplasmic vacuoles detected in primary lens cells could play an influential

role in developing cataracts [18]. Histopathological analysis of rubella virus-infected fetuses showed cellular damage in the cochlear duct and/or stria vascularis epithelium. These findings may explain the cause of deafness in CRS [17, 18].

Tropism of the rubella virus to the fetal endothelial cells was detected [19]. Vascular pathologies such as thrombosis and surrounding tissue necrosis in CRS result from persistent rubella virus infection of the endothelium [7, 19]. Vascular necrotic changes cause cellular destruction, leading to ischemic damage to the myocardium and brain [6, 17] and significant histopathological changes in the liver [18]. Necrotizing and inflammatory changes were presented in the liver of the infected fetus [18].

9.4 Epidemiology

Rubella was a more common disease before the rubella vaccine's global use, which occurs most often during spring, mainly among young children. Epidemics occur every 6–9 years, and large-scale epidemics arise for up to 30 years [1]. In the pre-vaccine era, in the United States of America (USA), 62 CRS and 57,600 rubella cases were reported every year [20]. The last major American epidemic occurred in 1964–1965. There was a report of 12.5 million rubella cases and approximately 20,000 CRS cases in this epidemic [1, 2]. After national vaccination campaigns in the USA, rubella incidence has decreased by more than 99% and declined by 86% worldwide [21]. After 2004, rubella and CRS elimination were declared from the USA [7, 22]. However, rubella is still commonly circulated in different parts of the world, and an estimated 100,000 infants are born with CRS yearly [7]. As a result of the failure to manage vaccination programs, large rubella outbreaks were reported in low- and middle-income countries such as Ethiopia, Oman, Uzbekistan, Romania, Argentina, Brazil, and some other Latin American countries [23].

In 2021, the World Health Organization (WHO) reported that the current rubella vaccine global coverage was 69%, with 90% in America, 95% in Europe, 45% in Eastern Mediterranea, 32% in Africa, 83% in South-East Asia, and 94% Western Pacific [5]. Twelve and a half million disability-adjusted life years (DALYs) and 131,000 deaths because of CRS could be prevented from 2001 to 2030 with expanded coverage for the rubella vaccine. Eighty-one of 194 (42%) member states in WHO regions confirmed eradicating rubella until September 2019 [5].

9.5 Clinical Manifestations of Congenital Rubella Syndrome

During pregnancy, and especially in the first trimester, CRS is the most severe consequence of rubella virus infection. Manifestations of CRS vary depending on the timing of maternal infection. The defect risk is quite high if maternal rubella infection develops in the first trimester. The risk is considerably reduced after 18–20 weeks of pregnancy [7, 24, 25].

Congenital rubella syndrome presents different manifestations during intrauterine, early (neonatal), and later periods. Congenital disabilities and death in the affected fetus and premature birth may develop. A literature review evaluating articles between 1991 and 2014 reported that 17 of 32 fetuses showed 56 various disabilities detected before labor [24]. Amniotic fluid anomalies (40%), cardiac malformation (34.3%), brain anomalies (12.5%), and ocular abnormalities (6.25%) were identified. Placentomegaly, hepatosplenomegaly, hyperechogenic bowel, ascites, short femur, micrognathia, hyperechogenic scrotal mass, and single umbilical artery were among the other ultrasound findings [24].

9.5.1 Early Manifestations

In 1970, abnormalities were reported in a systematic review of 1109 children having CRS [24]. Early manifestations of CRS include intrauterine growth retardation, low birth weight, blueberry muffin lesions, generalized lymphadenopathy, hepatosplenomegaly, hepatitis, jaundice, diarrhea, bleeding underneath the skin, hemolytic anemia, congenital heart disease, pneumonitis, meningoencephalitis, cataract, microphthalmia, retinopathy, bony radiolucencies, cryptorchidism, and inguinal hernia. Some manifestations may be temporary, while others may be permanent (Table 9.1) [1, 2, 26]. In a study following the 1964 rubella epidemic in the USA, 68% of newborns with CRS were subclinical, and 71% of subclinical patients developed clinical signs in the first 5 years [27].

9.5.2 Cardiac Defects

Patent ductus arteriosus (PDA), pulmonary valvular stenosis, pulmonary artery stenosis, pulmonary hypertension, coarctation of the aorta, aortic stenosis, atrial septal defect (ASD), and ventricular septal defect (VSD) are the cardiac defects detected in 38–70% of CRS patients [2]. The most common cardiac finding is PDA in newborns with CRS. In evaluating 36 children having CRS using echocardiography, PDA was found in 67%, ASD in 19%, pulmonary stenosis in 8%, VSD in 3%, and atrioventricular septal defect in 3% [28]. In another study evaluating more patients with CRS, similar to previous studies, the most frequently detected defect was PDA (87%), tricuspid regurgitation (65%), ASD/patent foramen ovale (50%), pulmonary hypertension (44%), mitral regurgitation (26%), pulmonary stenosis (23%), pulmonary regurgitation (15%), aortic stenosis (14%), VSD (9%), aortic regurgitation (7%), coarctation of the aorta (4%), and atrioventricular septal defect (1%) [2]. Affected newborns may also develop myocarditis, which can result in death. In addition to cardiac defects, vascular problems may also occur in children with CRS. Many vessels, such as coronary, cerebral, and peripheral arteries, with obstructive lesions were reported [29].

Table 9.1 Clinical manifestations of congenital rubella syndrome[a]

	Temporary	Permanent
General	Low birth weight	
Skin effects	Dermal erythropoiesis	Chronic rash
		Dimples
Ocular effects	Cloudy cornea	Cataracts
	Iridocyclitis	Microphthalmos
		Glaucoma
		Pigmentary retinopathy
		Hypoplasia of the iris
		Severe myopia
Auditory effects		Central hearing impairment
Cardiovascular effects	Myocarditis	Pulmonary arterial stenosis
		Aortic stenosis
		Coarctation of aorta
		Atrial/ventricular septal defects
		Patent ductus arteriosus
		Tetralogy of Fallot
		Pulmonary hypertension
Pulmonary effects	Interstitial pneumonitis	Interstitial pneumonitis
		Tracheoesophageal fistula
Gastrointestinal effects	Hepatosplenomegaly	
	Hepatitis	Duodenal stenosis
	Jaundice	Jejunal or rectal atresia
	Chronic diarrhea	
Central nervous system	Meningoencephalitis	Microcephaly
	Large anterior fontanel	Spastic diplegia
	Hyperirritability (tremors)	Brain calcification
	Seizures	Cerebral arterial stenosis
	Hypotonia	
Hematologic effects	Hemolytic anemia	
	Hypoplastic anemia	
	Thrombocytopenia with/without purpura	
Urogenital anomalies	Vesicoureteral reflux	Hypospadias
		Cryptorchidism
		Vesicoureteral reflux
		Inguinal hernia
Orthopedic effects	Radiolucent bone disease	Clubfoot
	Pathologic fractures	
	Myositis	
Immunologic effects		Thymic hypoplasia
		Asplenia

[a] Adapted and modified from Ref. [1, 2, 26]

9.5.3 Congenital Rubella Infection and Hearing Loss

The most characteristic manifestation of CRS is congenital SNHL due to disease, damage, and other causes impacting the inner ear (e.g., the cochlea) and the auditory nerve (eighth cranial nerve). Few histopathological studies examining the placenta have shown emboli in the placental vessels [7, 17]. This causes thrombosis and surrounding tissue necrosis that will affect the development of fetal organs. Cytopathic action, mitotic inhibition, and increased chromosomal breaks have been identified in congenitally infected human embryonic cells and fetuses [17]. Reduced cell numbers and hypoplasia may occur in infected organs [6].

Histopathological evaluations showed cellular damage in rubella virus-infected fetuses' cochlear duct and stria vascularis epithelium. These findings may explain the cause of HL in infants with CRS [14, 18].

Temporal bone studies have been performed to explain the HL that develops in CRS. Data on temporal bone pathology in infants with CRS were reported. Six sets of temporal bones were examined in Baltimore and Houston studies, and a cochleosaccular change was detected in most of the bones [17]. No pathological changes were reported in the utricle, spiral ganglia, or semicircular canals. The collapse of the sacculi and a few changes in the organ of Corti were observed in bones. Ward et al. [30] and Alford showed atrophy and destruction of the stria vascularis [17].

In studies, pathologies in the middle ear were also investigated to explain the cause of HL in CRS. Only moderate perivascular infiltration was recognized in the middle ear mucous membrane in a small number of bones [17]. However, there are still unanswered questions about the pathogenesis of HL related to CRS.

Hearing loss may be the only manifestation of CRS. Previous studies have reported that 66–90% of children with CRS have a hearing impairment after maternal infection in the 18th to 20th pregnancy weeks [2]. Although CRS-related HL is usually detected in early childhood, progressive hearing problems beginning in later years have also been reported [12].

Congenital rubella syndrome was reported as the cause in 32–41% of children with hearing impairment [31, 32]. The HL in CRS generally is bilateral (%61), and sensorineural but can be unilateral [26, 33]. The severity of HL in children with CRS ranges from mild to severe and may progress over time. Fifty-seven percent of infants with rubella virus isolated have SNHL; however, 41.5% of cases were confirmed serologically [34]. In a recent study from China, among 720 children with HL, CRS was detected as the cause in 42 (5.83%) [35].

In studies investigating the causes of HL after the widespread application of the rubella vaccine, rubella was found to be a significantly less common cause of SNHL. This result is related to the overall decline in rubella prevalence following universal childhood vaccination programs [36].

Hearing loss in children with CRS may be overlooked in infancy. Children with HL may be mistakenly evaluated as developmentally delayed. Furthermore, progressive hearing impairment beginning several years after birth may also develop [37]. Experiencing HL in the first years of life could lead to cognitive, language, speech, and developmental delays. Early diagnosis of SNHL due to CRS is the most

critical management aspect. Special rehabilitative measures and education programs prevent the development of weak language skills and speech delays. Otoacoustic emissions (OAEs) and automated brainstem auditory evoked responses (BAERs) should be tested in infants of mothers with rubella experienced during pregnancy at regular intervals until age 5 to assess HL [38].

9.5.4 Ophthalmological Manifestations

N. McAlister Gregg, an Australian ophthalmologist, first reported that maternal rubella infection could cause congenital disabilities [3]. Every part of the fetal eye is impacted via transmission of the rubella virus by the bloodstream and rarely lymphatic fluid [4]. The rubella virus may remain in the crystalline lens for more than one year [27]. Fifty-three to 78% of patients with CRS had ocular defects [2]. Cataracts, microphthalmia, pigmentary retinopathy, chorioretinitis, myopia, hyperopia, strabismus, and nystagmus are among the ocular findings found in newborns with CRS [2, 4, 24]. Ocular defects may progress postpartum.

Congenital rubella syndrome's most common ocular manifestation is "salt and pepper" pigmentary retinopathy. It is seen in 24–60% of cases with CRS [2]. Cataract, usually unilateral, is also a common sequela of CRS (17–63%) [2] due to partial arrest in cell development and lens maturation [4]. Microphthalmia, another frequently seen complication of CRS and often associated with cataracts, may be unilateral or bilateral [39].

9.5.5 Delayed Manifestations

Some delayed manifestations of CRS resulting from directly or indirectly damaging the embryo by the rubella virus occur later in life. Although the exact relationship between late-onset findings and CRS is not conclusively proven, endocrine, cardiovascular, ocular, neurological, and psychosocial problems have been observed as delayed manifestations among CRS children [40].

Delayed manifestations of CRS are summarized in Table 9.2 [1, 26, 40]. None of these delayed manifestations seen in patients with CRS are reported as the results of studies using control groups. Contrary, some studies concluded that CRS does not cause a higher risk for these diseases [40].

9.5.5.1 Endocrine Abnormalities

Diabetes, thyroid disorders, early menopause, osteoporosis, and possible growth hormone deficiency are endocrine problems as delayed manifestations of CRS. The relationship between endocrine problems and autoimmunity is vital in these patients. It is thought that diabetes develops in CRS patients due to damage to pancreatic cells by the rubella virus. In a study from Japan, diabetes prevalence was 1% in patients with CRS, higher than in Japanese society [40].

Table 9.2 Delayed manifestations of congenital rubella syndrome[a]

Auditory effects	Sensorineural hearing impairment
Ocular effects	Keratic precipitates Keratoconus Corneal hydrops Lens absorption
Endocrine effects	Diabetes mellitus Hypothyroidism Thyrotoxicosis Idiopathic hypothyroidism Hyperthyroidism Thyroiditis Growth hormone deficiency Addison's disease Early menopause Osteoporosis
Cardiovascular effects	Hypertension Mild aortic valve sclerosis
Neurological and psychosocial problems	Progressive rubella panencephalitis Learning disorder Psychomotor developmental delay Ataxia Cerebral palsy Psychosi Intellectual disability Autism spectrum disorder Behavior problems

[a] Adapted and modified from Ref. [1, 2, 40]

Hypothyroidism, hyperthyroidism, and thyroiditis are also seen in cases with CRS as delayed health issues. In a study of adolescents with CRS having HL, thyroid disorders were found in 19.6% [26]. Autoimmune mechanisms are considered effective in the pathogenesis of endocrine abnormalities.

Early menopause and osteoporosis are other delayed manifestations of CRS. A study evaluated patients with CRS 60 years after intrauterine infection [41]. Eight of the 11 women had early menopause, and 4 had osteoporosis. Endocrine abnormalities due to CRS may cause these conditions [42]. In 1977 growth hormone deficiency was reported in two boys with CRS [43]. However, this sole case report is insufficient to prove CRS's association with this disorder.

9.5.5.2 Cardiovascular Abnormalities

It is suggested that intimal fibromuscular proliferation and arterial sclerosis may develop in vascular structures in CRS [38]. These vascular sequelae may cause peripheral, cerebral, and coronary vascular disease in adulthood. Obstructive arterial lesions and systemic hypertension may develop secondary to renal disease [27, 42].

9.5.5.3 Ocular Abnormalities

Glaucoma and spontaneous lens absorption have been reported as delayed manifestations in patients with CRS [26, 44].

9.5.5.4 Neurologic and Psychosocial Abnormalities

Chronic progressive encephalopathy simulating measles-related subacute sclerosing panencephalitis (SSPE) was observed in a few patients with CRS as a late-onset manifestation [26]. Psychiatric disorders, intellectual disability, and behavioral problems have also been reported [26, 42].

Children having CRS may develop mild to severe psychomotor disorders. Among these disorders, intellectual disability (41–42%), hyperactivity (18%), spastic diplegia (14%), seizure disorder (7%), autism (7.4%), spastic quadriplegia (2%), and hemiparesis in a few cases were reported [2, 45–48]. A prospective study detected communication or language disorders in children evaluated with the Denver test and Ages and Stages Questionnaire (ASQ) [48]. Ninety-five percent of children with CRS having intellectual disabilities experienced hearing or visual disorders simultaneously [48]. Hearing and vision defects are important causes of these disorders [48]. Twelve to 15% of children with CRS were evaluated with a Modified Checklist for Autism in Toddlers, and the Diagnostic and Statistical Manual of Mental Disorders-V was diagnosed for autism spectrum disorder [2, 48].

9.6 Diagnosis and Laboratory Findings

In newborns whose mothers have a rubella history during pregnancy, microcephaly, generalized lymphadenopathy, hepatosplenomegaly, ocular abnormalities, or thrombocytopenia suggest congenital rubella infection, and the neonate should be evaluated for CRS. Serological and molecular tests are used in the diagnosis of rubella infection. Viral isolation or reverse-transcriptase polymerase chain reaction (RT-PCR) is the best method to diagnose CRS definitively. A positive test for viral RNA on cerebrospinal fluid, amniotic fluid, urine, nose swabs, or the throat is beneficial for diagnosing congenital rubella infection [49].

In the neonatal period, antibodies to the rubella virus should be investigated in infant and maternal sera for serologic diagnosis of rubella infection. Congenital rubella syndrome is diagnosed in newborns with rubella immune globülin (Ig) M positivity in serum or cord blood [1, 7]. Rubella IgG antibodies detected in a newborn passed from the mother will drop over time [26]. Continuation or rising rubella IgG antibody levels over several months is also diagnostic for CRS [49]. Congenital rubella syndrome can be diagnosed when a woman has a rubella infection during pregnancy by detecting rubella virus RNA in the amniotic fluid [4].

9.7 Treatment

There is no specific treatment for CRS. Infants with suspected CRS should have pediatric, cardiac, auditory, ophthalmological, and neurological evaluations. Appropriate treatments should be planned according to the affected system. The introduction and maintenance of physical, speech, behavioral, and occupational therapies at an early age are essential. A multidisciplinary team should evaluate the need for hearing aids, cochlear implants, cardiac interventions, ophthalmological surgeries, glasses or contact lenses, and appropriate treatments [1, 7].

9.8 Prevention and Control

Isolation of patients with rubella should be done 7 days after the rash onset. Standard and droplet precautions are suggested, especially for hospitalized patients. Infants with CRS are contagious via urine and nasopharyngeal secretions until one year of age. Contact isolation should be applied to children with suspected or proven CRS until the rubella PCR test is negative in two clinical samples taken 1 month apart after the 3rd month. And also, isolation measures should be applied in hospitalized children smaller than 3 years old for congenital cataract surgery [1, 49].

Immunoglobulin administration is not recommended for rubella-exposed pregnant women because studies have reported that this approach failed to prevent anomalies related to congenital rubella infection in the fetus [50].

The best protection against rubella infection is provided by vaccination. Rubella vaccine is a live virus vaccine administered by subcutaneous injection. The rubella vaccine is combined with the measles and mumps (MMR), or measles, mumps, and varicella (MMRV) vaccines. The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend the first dose of rubella-containing vaccination at 12–15 months, followed by the second dose at the age of 4–6 [50–52]. In postpubertal women without a record of rubella immunization, the rubella vaccine should be administered before planning a pregnancy. It is recommended not to become pregnant for 28 days after vaccination [50].

9.9 Conclusion

Rubella is an infectious disease transferred primarily via droplet or direct contact from nasopharyngeal secretions. Rubella in pregnancy may cause CRS leading to severe medical problems. Sensorineural HL is one of the most prevalent complications of CRS. Vaccination is the best protection against rubella, CRS, and related SNHL. After the widespread implementation of the rubella vaccine, rubella and CRS cases have decreased globally.

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Congenital Syphilis and Hearing Loss

10

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10.1 Introduction

Congenital syphilis (CS) occurs secondary to transmitting *Treponema pallidum* from an infected mother to her fetus. Mother-to-child transmission (MTCT) of syphilis can lead to a broad spectrum of clinical outcomes, including prematurity, fetal loss, stillbirth, neonatal death, and congenital defects if untreated or treated late [1, 2]. Stillbirth and infant death may be observed in one-quarter of the cases [3]. The disease may be asymptomatic at birth, and some congenital deformities may not be apparent until adulthood. Thus, CS is a significant global health problem that can be preventable and treatable.

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10.2 Etiology and Epidemiology

Treponema pallidum, the causative agent of syphilis, is a spirochete, a helix-shaped, fastidious microorganism (6–15 μm long and 0.1–0.2 μm wide) that exhibits characteristic corkscrew motion with flexing and back-and-forth movement [3].

Although *T. pallidum* was first identified in 1905, the disease's history dates back to the middle ages. According to the Columbian Theory, which dates back to the fifteenth century, syphilis was transmitted to Europe after the arrival of Columbus to the New World (America) [4]. While this appears to be the most widely accepted theory, another well-supported hypothesis suggests that syphilis was already present in Europe at the time of the outbreaks in the late fifteenth century (pre-Columbian) [5]. Syphilis first took the name "morbus gallicus" or "The French disease," eponymous for the country which Italian physicians blamed for this epidemic as part of King Charles VIII's invasion of Italy in the fifteenth century [6]. Predictably, though, the disease began to take the name of whoever was felt to be to blame, earning the name "The German disease" in Poland, "The Polish disease" in Russia, "The Chinese ulcer" in Japan, and many others [7]. Despite first appearing as "syphilis" in print in the sixteenth century [8], it was not until the mid-eighteenth century that physicians began to commonly use this term to refer to the infection caused by *T. pallidum* [9]. Its venereal transmission was not recognized until the eighteenth century [3]. Early therapies for syphilis, like guaiac, mercury bismuth salts, and arsenic compounds, had worse outcomes than the disease [10]. The discovery of penicillin by Alexander Fleming in 1940 dramatically changed the course of the disease. However, syphilis has been a public threat in many parts of the world in the last two decades.

The World Health Organization (WHO) reported nearly 19.9 million prevalent cases of syphilis in the reproductive age group in 2016 [11]. The annual incidence of CS was 661,000 cases leading to more than 200,000 stillbirths and neonatal deaths [1]. The statistical data indicates that CS cases have increased [12]. The 2018 case rate represents a 40% increase relative to 2017 and a nearly 400% increase relative to 2012 [2]. Parallel to human immunodeficiency virus (HIV) infection worldwide, the incidence of syphilis and CS is rising. While recent studies have shown that a fewer percentage of pregnancies with syphilis in the United States of America (USA) have resulted in congenital infection [13], recent data from the Centers for Disease Control and Prevention (CDC) paints an alarming trend for the coming decade [14].

10.3 Transmission

In the case of maternal infection, spirochetes may transmit via the transplacental route at any time during pregnancy [12]. Although some reports defend the hypothesis that there is a protective effect of the Langerhans' cell layer of the placenta inhibiting spirochetal passage before the sixth month of pregnancy, much evidence suggests otherwise [15]. For example, *T. pallidum* was isolated up to 74% in

amniotic fluid analyzes of pregnant women with early syphilis [16]. This finding indicates that spirochetes cross the fetal membranes, reach the amniotic fluid, and cause infection in the fetus. Findings consistent with CS are detected in utero, and immunoglobulin (Ig) M antibodies specific for *T. pallidum* are detected in blood samples taken from fetuses or newborns [16]. Moreover, the Langerhans cell layer persists throughout pregnancy.

Mother-to-child transmission of syphilis varies with the stage of maternal syphilis. The highest transmission rates are detected in early syphilis, especially secondary syphilis [16]. Sheffield et al. [17] determined the vertical transmission rates as 29%, 59%, 50%, and 13% during primary, secondary, early latent, and late latent infection, respectively. Transmission can also occur through contact with infected maternal lesions during delivery. Breastfeeding is not considered a route for infection unless the mother has an infectious lesion on her breast [3, 12].

Syphilis is also associated with increased sexual transmission of HIV. However, the contribution of syphilis and HIV coinfection to MTCT of either syphilis or HIV has not been elucidated fully [3].

10.4 Pathogenesis

Treponema pallidum spirochetemia leads to disseminated infection and widespread inflammation of the fetus's almost all visceral organs [3, 12, 18]. Perivascular structure and interstitial stroma, rather than the parenchyma, are intensely affected. The liver, gastrointestinal system, kidneys, spleen, and bone are frequently involved in symptomatic CS. Skeletal changes are attributed to syphilitic granulation of the periosteum and epiphyses that interfere with bone formation. Extramedullary hematopoiesis in the fetus is prominent [3, 12]. The placenta of the neonates with CS presents enlarged villi, the proliferation of the vascular structures, and inflammation [3, 19]. The umbilical cord may also show signs of inflammation, necrosis, and abscess-like foci called necrotizing funisitis [19]. Histochemical staining may yield spirochetes within both the umbilical cord and placenta.

10.5 Clinical Presentation

Transplacental transmission of syphilis can result in adverse fetal outcomes [2, 3, 12]. In a comprehensive meta-analysis, Gomez et al. [20] documented that 52% of the pregnancies with untreated syphilis ended up with complications, including fetal loss or stillbirth (21%), neonatal death (9%), prematurity or low birth weight (LBW, <2500 g; 6%), and symptomatic CS (15%).

Clinical findings appear broadly from asymptomatic infection limited to only laboratory or radiologic abnormalities to life-threatening involvement of multiple organ systems. In a South African study of 50 newborns diagnosed with early symptomatic CS, 34 infants required intensive care and 38% died [21].

Table 10.1 Clinical, laboratory, and radiologic findings of congenital syphilis[a]

Early congenital syphilis (first 2 years of life)
Physical examination findings:
Hepatomegaly with or without jaundice
Splenomegaly
Skin rash
Adenopathy (characteristically epitrochlear)
Rhinitis (snuffles)
Condyloma lata
Mucus patch
Pseudo paralysis of parrot
Eye: chorioretinitis, cataract
Central nervous system: asymptomatic, cranial nerve palsies, seizures.
Laboratory findings:
Blood analysis: anemia, thrombocytopenia, hypoglycemia, increased liver transaminases, direct hyperbilirubinemia.
Cerebrospinal fluid analysis: pleocytosis, elevated protein levels
Radiographic findings:
Periostitis, osteochondritis, pneumonia alba
Other: Nephrotic syndrome, pancreatitis, myocarditis, fever, gastrointestinal malabsorption, hypopituitarism (diabetes insipidus)
Late congenital syphilis (>2 years)
Eye: interstitial keratitis, chorioretinitis
Eight nerve deafness
Hutchinson's teeth, Mulberry molars
Rhagades
Central nervous system: mental retardation, hydrocephalus, seizures, optic nerve atrophy, cranial nerve palsies
Bone and joint: frontal bossing, saddle nose deformity, protuberant mandible, short maxilla, saber shin, high palatal arch, Higoumenakis sign (sternoclavicular joint thickening), Clutton joints

[a] Adapted and modified from Ref. [22, 23]

Congenital syphilis is divided into two clinical syndromes according to the presentation time as early or late CS [3]. Clinical, laboratory, and radiologic findings of CS are summarized in Table 10.1.

10.5.1 Early Congenital Syphilis

Early CS is the disease in which clinical findings are observed in the first two years of life [2, 3, 12, 22]. Most neonates born to untreated syphilitic mothers may appear normal at birth and develop the symptoms of the disease months later. In untreated cases, clinical findings occur most frequently in the first 3 months.

Bone involvement, sometimes the only manifestation of CS, occurs in up to 80% of infants born to mothers with untreated syphilis. Periostitis and osteochondritis have diagnostic values, mainly in the femur and humerus [3]. Although skeletal changes may heal spontaneously in the first year of age, they may be very painful initially, leading to disability in the child termed pseudoparalysis of Parrot. Long bone involvement may also cause pathologic fractures.

Almost all symptomatic CS cases have hepatomegaly which may also be together with splenomegaly. Jaundice may also be observed at physical examination. Biochemical findings of liver dysfunction, most commonly after the initiation of therapy due to immune response, and elevated serum alkaline phosphatase levels are expected [20, 24].

Neonates with CS may have white, translucent nasal discharge, usually appearing in the first week of life. Snuffles may be hemorrhagic or purulent in the case of bacterial superinfection. It lasts longer than the common cold. The darkfield examination may yield spirochetes [2, 3].

Generalized non-tender-firm lymphadenopathy may be as large as 1 cm. Lymphadenopathy in the epitrochlear region is highly suggestive of CS [2]. An erythematous maculopapular rash may be observed during the first weeks of life. The rash then may desquamate and appear in a coppery color. Palm and soles are usually affected, and peeling can occur (Fig. 10.1a, b). If the infant has thrombocytopenia, petechial lesions may also be seen. Infectious vesiculobullous lesions called "pemphigus syphiliticus" are characteristic of CS [2, 3, 12]. Less commonly, easily bleeding fissures around the mucocutaneous junctions may be observed. Flat, wart-like lesions called "condylomata lata" containing spirochetes can also be encountered.

Central nervous system (CNS) invasion by *T. pallidum* occurs in approximately 50% of infants with clinical, laboratory, or radiographic signs of CS [2, 3, 12]. Involvement of CNS may be asymptomatic at birth. Cerebrospinal fluid (CSF) analysis can yield pleocytosis, increased protein levels, and a reactive Venereal Disease

Fig. 10.1 (**a, b**) Peeling on hands and feet in an infant with congenital syphilis (Courtesy of Tuğçe Tural Kara, MD)

Research Laboratory (VDRL) test. Symptomatic infants generally present with two clinical syndromes. The "acute syphilitic leptomeningitis" form usually occurs in the first year of life and is hardly indistinguishable from bacterial meningitis [2]. Yet, the CSF findings mostly mimic aseptic meningitis. In the other scenario, the infant may come to clinical attention with signs of progressive hydrocephalus, neurodevelopmental regression, and seizures [2, 3, 12, 25]. The presentation, which typically occurs at the end of the first year, is called "chronic meningovascular syphilis."

Early CS can rarely manifest itself with non-immune hydrops, hematologic abnormalities, ocular findings (loss of eyebrows, glaucoma, chorioretinitis, etc.), myocarditis, pneumonia, gastrointestinal involvement (necrotizing enterocolitis), nephrotic syndrome, failure to thrive, or prolonged fever. However, the latter is prominent when the infant's mother is affected late in the pregnancy [25].

10.5.2 Late Congenital Syphilis

In late CS, the clinical findings occur after 2 years of age [3]. The disease results from chronic inflammation rather than active infection; therefore, patients are not contagious [2, 16]. Although some clinical findings can be preventable by treating the expectant mother in the late pregnancy or the neonate after birth, particular manifestations like keratitis and saber shins may occur even with treatment [2].

In the nineteenth century, British surgeon and pathologist Jonathan Hutchinson defined the classical triad of "interstitial keratitis, 8th nerve deafness and the defects in the incisor teeth" as characteristic of CS [26]. In addition to these, there are specific findings related to various systems. For instance, infants with CS have characteristic facial features, including frontal bossing, saddle nose, protuberant mandible, and short maxilla, resulting from osteochondritis [25]. An ophthalmologic examination may also reveal corneal scarring, glaucoma, and optic atrophy. Interstitial keratitis is quite specific for CS, is usually bilateral, and can occur at any time in the first three decades of life [25, 27, 28].

Dental developmental disorders, widely spaced notched central incisors, known explicitly as Hutchinson's teeth, are typical features of late CS. Mulberry molars and perforation of the hard palate are rare but almost pathognomonic for syphilis. In addition, perioral fissures (rhagades) can be observed [2, 3, 12, 16].

Skeletal abnormalities may involve long bones. "Saber shins" (anterior bowing of the shins), "Clutton joints" (painless arthritis of the knees), and "Higoumenakis sign" (enlargement of the sternoclavicular joint) are the hallmarks of physical examination. Neuromotor development abnormalities and rare hematologic conditions such as paroxysmal nocturnal hemoglobinuria are exceptional manifestations [2, 3, 12].

10.6 Congenital Syphilis and Hearing Loss

In utero, syphilis exposure is a risk indicator for developing congenital, delayed-onset, or progressive hearing loss (HL) in childhood [3]. Although it is a constant but the least common element of the Hutchinson triad described many years ago,

there is scarce information about CS-associated HL in the literature data and leading textbooks in the field [2, 3, 12, 15, 29]. Few contemporary studies have looked at HL in these children. While most evidence suggests that HL occurs late in the disease [3], typically in the absence of treatment, other more recent publications suggest that there could be an association with hearing deficits in the neonatal period [30, 31]. Accordingly, as disease incidence is relatively low and can occur at any time in childhood, the incidence of CS-associated HL is hard to estimate. As a result of the plummeting incidence of this disease in children, driven by timely diagnosis and treatment in pregnancy, estimates for the prevalence of HL in children and adolescents with CS come from studies conducted a decade ago. One of the first studies to investigate HL in children with CS found a prevalence of 14% [32]. In another study, the prevalence was higher at 38%; however, critics of this estimate note that the diagnosis of CS remained questionable as specific serologic or clinical criteria were not provided [33].

It has become generally accepted that hearing disturbances in the neonatal period are rare. This belief has been primarily driven by a study by Gleich et al. [33], in which none of the 75 children diagnosed with CS had evidence of HL during the neonatal period, and all infants demonstrated symmetric waveforms with normal amplitudes and latencies. While these findings are reassuring because no frequency-specific audiometric assessments were performed, some degree of HL could have been missed, and perhaps more importantly, so could have progressive HL as the study lacked reevaluation of those patients. Although contemporary studies have cast doubt on neonatal HL as a consequence of CS, screening for HL at birth remains part of the evaluation guidelines, as otosyphilis can present at any time during infection.

While the incidence of HL in CS may be distributed over a much wider age range, onset is often clustered around 8–10 years [34]. In a study by Tamari et al. [32] of 310 syphilitic patients, the onset of HL occurred in the first two decades of life. This finding is supported by another study which found that 12% of patients with CS developed symptoms of hearing disturbances before the age 10 [33]. In the case of HL attributable to CS, the presentation is often sudden and bilateral, with loss of high frequencies preceding those found in normal conversational [15, 34, 35]. Despite the fact that most cases appear to affect both ears equally, there have been reports of children with unilateral HL [36].

The pathogenesis of syphilis sheds light on why HL may be seen in both congenital and acquired forms. The most common form of HL involves the eighth cranial nerve, which can be affected by *T. pallidum* within or outside the CSF space, the cochlea vestibular apparatus, or the temporal bone [37]. Though some clinical differences exist, it is not always easy to distinguish CS-related late-onset HL from adult-type syphilitic HL. In the former, vestibular symptoms usually do not accompany deficits in hearing. When HL occurs in adults, it is typically asymmetric, fluctuating with sudden onset of tinnitus and vertigo [38]. However, if the spirochetes invade only the perilymph of the inner ear and the inflammation is restricted to the cochlea and vestibular system, the patient may experience HL together with vertigo [37]. If the infection is limited to the inner ear, CSF indices will typically be within normal limits. When spirochetes spread through the CSF and invade the perilymph

of the inner ear via the cochlear aqueduct, CSF analysis is usually abnormal. In these cases, abnormal auditory brainstem responses (ABRs) indicative of upper brainstem pathways or cochlear nerve dysfunction may occur.

Cochlear degeneration and fibrous adhesions due to osteochondritis of the otic capsule, osteitis, and periostitis of the temporal bone and the ossicles in the middle ear can be observed in untreated CS or chronic adult infection [15, 37]. Histological obliterative endarteritis appearance can cause a decrease in vascular supply contributing to bony necrosis [39]. As can be seen from the diversity in pathophysiology, symptomatic, audiometric, and laboratory (CSF findings), differences and therapeutic responses may be observed among patients [37].

Syphilis-related morbidity was markedly reduced after penicillin treatment. Therefore, publications describing the otologic complications of CS often belong to the pre-antibiotic era. However, even in these studies, data on children are limited. When steroid treatment was being investigated as an adjuvant in treating bacterial and tuberculous meningitis, prednisone was suggested as a potential treatment that could potentially benefit HL, especially in adults [40]. While no contemporary studies have evaluated these findings in syphilis, a meta-analysis found that, in high-income countries, adjuvant glucocorticoid therapy reduced severe HL in bacterial meningitis [41].

Long-term follow-up of these children is important since the true incidence and age of onset of CS in children are not known precisely, and newborn screening tests may be completely normal. Therefore, a repeat hearing screening should be performed later, between 2 and 3 years of age, for all children with CS who have received appropriate treatment in the neonatal period. For those, who did not get proper treatment, at least an annual audiological examination should be provided [35].

10.7 Diagnostic Approach

The Centers for Disease Control and Prevention recommends that all infants born to seropositive mothers should be evaluated with a thorough physical examination (including the examination of the placenta and umbilical cord), laboratory tests (complete blood count, liver transaminases, CSF pleocytosis analysis, protein level, and VDRL) radiologic investigation (long bone radiographs, neuroimaging, HIV test), and additionally quantitative nontreponemal tests (NTTs) as clinically indicated (Fig. 10.2) [3, 12, 27, 29].

10.7.1 Laboratory Evaluation

Routine blood tests are inconclusive in CS. Complete blood count can yield hematologic abnormalities in up to 75% of symptomatic infants [29]. Approximately half of the cases present elevated white blood cell count, prominently monocytosis [29]. Thrombocytopenia may be encountered. An increase in liver enzymes may often be observed after the initiation of the therapy.

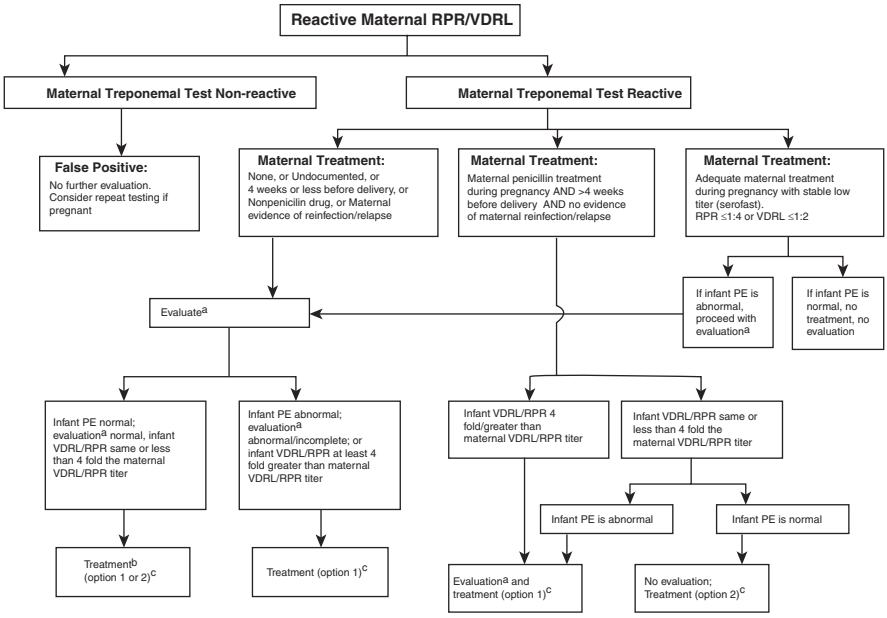

Fig. 10.2 Evaluation and management of congenital syphilis[*]. *PE* indicates physical examination, *RPR* rapid plasma reagin, *VDRL* Venereal Disease Research Laboratory. [a]Evaluation includes complete blood cell and platelet count; cerebrospinal fluid examinationfor cell count, protein, and quantitative VDRL; other tests as clinically indicated (e.g., chest and long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response). [b]Many experts recommend option 1. [c]Treatment options: Option 1: Aqueous penicillin G 50,000 units/kg, intravenous, q12h (≤1-week old), q8h (>1-week and ≤4-week old), q6h (>4-week old) × 10 days, or procaine penicillin G 50,000 units/kg, intramuscular × 10 days (≤4-week old). Option 2: Benzathine penicillin G 50,000 units/kg, intramuscular as a single dose. ([*]Adapted and modified from Refs. [3, 12, 26, 28, 42])

Cerebrospinal fluid analysis may reveal pleocytosis, elevated protein level, and reactive VDRL test, the only test approved for testing CSF [2, 3, 29]. Since the VDRL test in the CSF may yield false-negative or false-positive results, detecting *T. pallidum* by polymerase chain reaction (PCR) can be a more reliable alternative [43].

10.7.1.1 Tests for Organism

It is difficult to culture *T. pallidum* in the laboratory environment; therefore, various methods are used in clinical practice. The first is the direct visualization of *T. pallidum* by darkfield microscopy or fluorescent antibody methods [3, 12, 29]. Thin, delicate, corkscrew-shaped organisms with rigid, tightly spiral-shaped, typical back-and-forth rotational motion of *T. pallidum* can be observed with darkfield microscopy, which can be studied in body fluids such as runny nose or samples taken from moist skin lesions. However, spirochetes are exquisitely susceptible to antimicrobials, so microscopic examination may be unrevealing if done after

starting therapy [29]. Microorganisms can also be detected by staining histopathological samples or autopsy materials.

Historically, the reference test in the diagnosis of CS was the rabbit infectivity test (RIT) which involves the serial passage of infected material such as CSF or other body fluids in the testes of rabbits to detect alive *T. pallidum* [38, 39]. Once considered the gold standard for measuring infectivity, RIT is no longer suitable for clinical use due to animal testing [44].

10.7.1.2 Serological Tests

Serological tests can be evaluated under two headings: Nontropenemal tests (NTTs: Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and treponemal tests (TTs: fluorescent treponemal antibody absorption [FTA-ABS], *T. pallidum* particle agglutination [TP-PA], enzyme immunoassay [EIA], chemiluminescence immunoassay [CIA], micro hemagglutination test for *T. pallidum* [MHA-TP]) [2].

Nontropenemal tests are inexpensive, performed quickly, and have high sensitivity; however, they are not specific. They detect IgM and IgG antibodies to cellular lipids and lecithin [29]. A false-positive NTT result (usually has a titer $\leq$1:4) may occur in various clinical syndromes, including connective tissue disorders, infectious diseases (e.g., hepatitis, chickenpox, and infectious mononucleosis), and pregnancy [3, 12, 29]. A false-negative reaction called the "prozone effect" can result from excessive antibody production inhibiting antigen–antibody interaction [2, 29]. The prozone effect should be suspected when an infant presents signs of CS but the mother is seronegative. The prozone effect can be overcome with serial dilution of the samples.

There are several differences between TTs and NTTs. Treponemal tests become positive slightly earlier and stay positive for a lifetime, but they cannot reflect the infection activity [29]. False positivity mainly occurs in other spirochetal infections, such as Lyme disease [44], and can also be seen with endemic trypanosomoses [45]. Recombinant *T. pallidum* antigen tests, EIA, and CIA are often used for population-level screening, with confirmation done by a different TT, and a quantitative NTT is referred to as reverse sequence testing [46].

10.7.2 Radiology

Radiological evaluation of long extremities is of great importance to the newborn assessment of suspected CS, as radiographic abnormalities are common in early syphilis [47]. Abnormalities can be detected in 95% of symptomatic infants and up to 20% with asymptomatic disease [29, 47]. The changes are usually present at birth, sometimes appearing in the first weeks of life.

Symmetric localized demineralization and osseous destruction of the medial portion of the proximal tibial metaphysis, referred to as Wimberger sign, or irregular areas of increased density and rarefaction called moth-eaten appearance can be observed [3, 47]. Sometimes these pathological changes in the long bones cause

pain and fractures, leading to a limitation of movement of the affected extremity. This condition is called pseudoparalysis of Parrot [48]. Multiple layers of periosteal new bone formation are referred to as periostitis and can be encountered [47]. Lesions in the bone often heal spontaneously within months [16]. In untreated cases, opacification of both lungs, characteristically called pneumonia alba, may be observed on chest radiography.

10.8 Evaluation and Management

All newborns born to mothers with a reactive test for syphilis at birth should be evaluated for the possibility of CS. A negative NNT result at delivery does not rule out the possibility of CS owing to the case of the prozone effect [42], and the decision to treat an infant according to the diagnosis of CS should be made after evaluating the clinical, serological, and epidemiological findings together. Risk analysis of the mother for syphilis, serological examination, adequacy of the treatment if treated, and the possibility of reinfection or relapse should be evaluated. Case definitions for CS have been made to provide a standardized and applicable treatment algorithm. The evaluation and management algorithm and treatment options are summarized in Fig. 10.2 and Table 10.2 [3, 12, 23, 27, 29].

If a neonate has any of the following indicators, including abnormal physical findings compatible with CS or a reactive (≥four-fold the corresponding maternal titer) serum NTT (VDRL or RPR), or a positive darkfield or fluorescent antibody test for *T. pallidum in* neonatal nasal discharge, umbilical cord or other body fluids, is defined as "proven or highly probable CS" [12, 23, 27].

"Possible CS" is the term used to define neonates with normal physical examination who have a reactive NTT (<four-fold the maternal titer) born to untreated or inadequately treated syphilitic mothers. These infants should be further evaluated according to the American Academy of Pediatrics (AAP) and the CDC recommendations [12, 23, 27].

An asymptomatic neonate (normal physical examination) with a reactive NTT (<four-fold the maternal titer) whose mother received adequate and proper treatment (for more than 4 weeks before delivery) and has no evidence of relapse or reinfection is considered as "CS less likely." Such infants should be treated with a single dose of intramuscular (IM) penicillin G benzathine [12, 27, 47]. However, some experts recommend not treating neonates under close serologic follow-up provided their mothers' NTT decreased at least four-fold after therapy or remained stable at low titer [12, 23].

The distinction between congenital and acquired syphilis is challenging after >1 month of age. The possibility of sexual abuse must always be evaluated [27]. The child's examination should include CSF analysis (cell count, protein, and VDRL), complete blood test, HIV test, and other tests (long-bone and chest radiographs, liver function tests, abdominal ultrasonography, ophthalmologic examination, ABR, and neuroimaging studies) as clinically indicated. Those infants should be treated with parenteral penicillin therapy [12, 23, 27].

Table 10.2 Evaluation and treatment of infants with congenital syphilis[a]

Case	Evaluation	Treatment
Proven or highly probable congenital syphilis	CSF analysis: VDRL, cell count, and protein; CBC and platelet count; other tests as clinically indicated (e.g., long-bone radiographs, liver function tests, ophthalmologic examination, hearing evaluation, neuroimaging)	Aqueous penicillin G 50,000 U/kg IV q12h (≤1 wk old), q8h (>1 wk old, ≤4 wk old), q6h (>4 wk old) × 10 d, or Procaine penicillin G 50,000 U/kg IM × 10 d (≤4 wk old)
Possible congenital syphilis	CSF analysis: VDRL, cell count, and protein; CBC and platelet count; long bone radiographs	If complete evaluation is normal: (a) Benzathine penicillin G 50,000 U/kg IM × 1[b] or (b) Aqueous penicillin G 50,000 U/kg IV q12h (≤1 wk old), q8h (>1 wk old, ≤4 wk old), q6h (>4 wk old) × 10 days, or (c) Procaine penicillin G 50,000 U/kg IM × 10 d (≤4 wk old)
Congenital syphilis less likely	No evaluation	Benzathine penicillin G 50,000 U/kg IM × 1 (preferred), or Clinical, serologic follow-up
Congenital syphilis unlikely	None	None or Benzathine penicillin G 50,000 U/kg IM × 1 (some experts) if follow-up is uncertain
Congenital syphilis in infants aged >28 d	CSF analysis: VDRL, cell count, protein; CBC and differential; platelet count As clinically indicated: radiographs of long bones, liver function tests, neuroimaging (cranial ultrasonography), eye examination, hearing evaluation	Aqueous penicillin G 50,000 units/kg q4–6h × 10 d[d]

CBC indicates complete blood count, *CSF* cerebrospinal fluid, *d* day, *h* hour, *IM* intramuscular, *IV* intravenous, *q quaque* (every), *U* unit, *VDRL* Venereal Disease Research Laboratory

[a] Adapted and modified from Ref. [3, 12, 23, 27, 29]

[b] Clinical and serologic follow-up must be certain

[c] If the infant's nontreponemal test is non-reactive, no evaluation is required, but the infant should receive a single IM dose of benzathine penicillin G 50,000 U/kg

[d] Some experts prefer prolonged therapy by administering a single dose of benzathine penicillin G after the 10-day course of IV aqueous penicillin G

10.9 Treatment

Penicillin is the only drug with proven efficacy in treating CS and the only treatment option with a low side-effect profile [12, 23, 49]. There is insufficient data on the efficacy of non-penicillin drugs. Thus, the AAP and CDC insist on penicillin therapy after desensitization in infants with penicillin allergy [12, 27]. The same diagnostic and treatment algorithm should be applied to syphilitic infants born to HIV-infected mothers [50].

Two different 10-day course penicillin options exist in the treatment of CS: intravenous (IV) aqueous penicillin G (50,000 units/kg, q12h [every 12 h] in infants ≤1 week old, q8h [every 8 h] in infants >1-week to ≤4-week old, and q6h [every 6 h] in infants >4-week old) × 10 days, or IM procaine penicillin G (50,000 units/kg as a single daily dose for 10 days). Although the CSF penicillin levels are lower when applied in IM procaine penicillin G form than IV aqueous penicillin G, no treatment failures have been reported, and the clinical significance is unknown [12, 51].

The single-dose regimen (penicillin G benzathine, 50,000 units/kg, IM) is strongly discouraged in infants of inadequately treated mothers unless the newborn undergoes a complete evaluation and is found to be normal [12, 50]. In addition, CNS involvement should undoubtedly be excluded since it requires a 10-day regimen.

For infants >1 month of age, either the late diagnosis of early CS, late CS, or acquired syphilis, aqueous penicillin G (50,000 units/kg, IV, q4–6h for 10 days) treatment is recommended. In the presence of CNS involvement, some experts recommend an additional single dose of penicillin G benzathine (50,000 units/kg, IM) before the 10-day aqueous penicillin G course [23].

In the early course of the treatment (most commonly in between 2 and 12 h), an adverse reaction with penicillin, the so-called Jarisch-Herxheimer reaction, may occur. Endotoxin-like compounds released from the fragmented *T. pallidum* are thought to cause this reaction. Jarisch-Herxheimer reaction consists of fever, headache, and myalgia, although hypotension, tachycardia, and tachypnea can occur in some cases [23, 52].

10.10 Follow-Up and Outcome

For long-term follow-up, infants with CS and all serologically reactive infants should be evaluated with a thorough clinical and serologic examination via NTTs (VDRL or RPR) every 2–3 months until they are non-reactive [29]. A hearing screen, ophthalmologic examination, and the evaluation of neurodevelopmental progress should be performed yearly [3]. Maternal-origin NTTs usually become negative within 3 months, and if the child is not infected, they should be negative at 6 months [15]. The response may be slower in infants and children treated after the neonatal period [23]. Positivity of the maternal origin TTs may persist beyond 12–15 months of age in a proportion of uninfected children. Thus they have limited

value in the follow-up. However, a positive TT titer in a child older than 18 months indicates CS [3].

After ages 6–12 months, in cases where NTT titers do not decrease or, on the contrary, increase, patients should be completely reevaluated and treated with a 10-day course of penicillin, whether or not they had been treated before. A complete reevaluation should include CSF analysis (for VDRL, cell count, and protein), complete blood and liver function tests, hearing and ophthalmologic examinations, and long bone radiographs as clinically indicated [15, 23, 37]. In the past, serial CSF examinations were recommended to be performed every 6 months in children with initially abnormal CSF results; however, recent recommendations [12, 27] state that serial examinations may be deferred in patients who do not exhibit signs of progressive disease and have normalization of their NNT [42]. Nevertheless, detailed neuroimaging may be warranted in children with persistent CSF abnormality [23].

Congenital syphilis has a 6–8% case fatality rate among infants of mothers with non or inadequate prenatal care [23, 53]. Proper treatment within the first 3 months of life may prevent late complications of early CS, although some of them, like interstitial keratitis and "saber shins," may persist despite therapy [15, 23]. Osseous lesions heal over time regardless of treatment [23].

10.11 Prevention

In prevention, screening pregnant women and international adoptees, contact tracing, and long-term follow-up of CS cases with appropriate treatment are essential [23].

10.12 Conclusion

Congenital syphilis is a preventable and treatable infectious disease insidious global health problem. Besides several clinical manifestations, bilateral, sudden sensorineural HL may occur in the late form of the disease. However, the literature data on HL related to CS is limited. Penicillin is the drug of choice for the treatment of CS. Infants with CS require long-term follow-up and may experience late manifestations despite appropriate therapy.

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Congenital Zika Virus Infection and Hearing Loss

11

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11.1 Introduction

Zika virus (ZIKV) is a member of the family Flaviviridae. In common with the other members of this group, it is a single-stranded RNA virus with an envelope and an icosahedral morphology [1]. The viral envelope consists of a lipid membrane densely studded with projecting glycoproteins [1].

In the majority of patients, ZIKV infections are of mild severity and resolve spontaneously. The time from initial viral exposure to the first appearance of symptoms is approximately 3–14 days [2]. The features of Zika infection share similarities with other arthropod-borne viral diseases, although a maculopapular exanthem, probably due to an immune reaction, is generally the key feature [2]. One feature differentiating ZIKV from other arthropod-borne infections is that it may also be transmitted by sexual contact. There is an association of congenital central nervous system anomalies and maternal ZIKV infection in the initial trimester of pregnancy.

The earliest description of ZIKV dates from 1947, when a rhesus macaque held in captivity in the Zika forest, Entebbe, Uganda, was found to be pyrexial and the causative pathogen was identified as a newly discovered virus. This was followed

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the next year by the discovery that the *Aedes africanus* mosquito was the vector within the Zika forest. The existence of Zika infection in humans was confirmed in 1952 [1, 3]. Since then, Zika infection has been noted in several areas beyond Africa, notably Micronesia and French Polynesia [4, 5]. A major epidemic occurred between 2015 and 2016, in the Americas, with the majority of cases in the United States found to be linked to travel. The World Health Organization (WHO) declared a public health emergency in 2016 in response to this epidemic [6]. Confirmed Zika infections fell after 2017, and in 2021, it was reported that there were no current new infections occurring anywhere in the world [7, 8].

11.2 Pathophysiological Features

The ZIKV genome consists of 10,700 base pairs, with structural and nonstructural regions. The structural regions code for three structural proteins, C, prM and E, standing for core, pre-membrane, and envelope. The nonstructural region encodes seven proteins of nonstructural kind. The virus gains entry to the cell by attaching itself to a transmembrane tyrosine kinase enzyme, the AXL receptor. This involves the prM and E proteins. The virus is absorbed by endocytosis, after which the nucleocapsid coat is removed to allow viral RNA to enter the cytoplasmic compartment. This RNA is a negative sense strand, from which positive sense RNA is transcribed by a complex of proteins of viral origin encoded by the nonstructural region of the viral genome. The viral proteins are synthesized as a polyprotein, which then undergoes modification within the endoplasmic reticulum, forming virions. These are then released from the infected cell within secretory vesicles. The nonstructural viral proteins and the structural core protein cause the cell to stop progress through the cell cycle and eventually to undergo programmed cell death (i.e., apoptosis) [1, 2].

Cryogenic electron microscopic techniques were used by Sirohi et al. to determine the structure of the fully formed Zika virus. The overall structure is similar to that of the other flaviviruses but displays a unique structure in the Asn154 glycosylation site on the glycoproteins, which make up the viral envelope. This site consists of ten amino acids. ZIKV has an icosahedral shell, consisting of 180 envelope proteins. The glycosylation site appears to be how the virus binds to human cells before entry [9].

Phylogenetic analysis reveals that the ZIKV has two separate lineages, one in Asia and one in Africa, and has three different genotypes, namely, West, East African, and Asian. The Asian variant originated in Asia but was then transmitted to the Americas and islands of the Pacific. So far, the extent to which the viral lineage affects the clinical picture is unclear. One hypothesis links the Asian variant to severe outbreaks and may result in congenital defects, rather than death of the fetus, whereas the African variant may cause an acute infective episode that harms the outcome of pregnancies [10].

ZIKV has evolved to be able to replicate effectively in a variety of animal hosts, both arthropods and vertebrates. It has a tropism in humans for certain tissues such

as the skin, blood, placenta, testis, and retina. It also infects neural stem cells and neuroprogenitor cells. The virus can also replicate inside monocytes, which means it can be transported through the placental and blood–brain barriers. Cells respond to ZIKV infection by dying, either through apoptosis or necrosis. Both congenital neurological anomalies and intrauterine death can be explained in this way, the former resulting from death of neuroprogenitor cells and the latter through placental damage [11].

The initial response to ZIKV infection occurs through activation of innate immunity. Viral replication is inhibited through secretion of type 1 interferons, which induce expression of specific genes. The viral nonstructural proteins can block the signals leading to interferon expression and synthesis of interferon gene products, thereby evading attack by the immune system. It has been shown that ZIKV can prevent stress granules being formed and take control of nonsense-mediated mRNA decay, thereby increasing the ability of the virus to make copies of itself. The exact mechanisms by which ZIKV avoids destruction by the immune system are, however, still imperfectly understood, and more research is needed in this area [8, 12].

11.3 Epidemiological Features

There are few data available on how prevalent ZIKV infections are worldwide. The picture is complicated by asymptomatic infections, clinical confusion with other diseases caused by flaviviruses (such as dengue and chikungunya), and problems with achieving diagnostic certainty [8].

A study that collated evidence from reports of epidemics, entomological research and serological prevalence data in July 2019 ascertained that ZIKV had been found in 87 different countries or territories, covering Africa, North and South America, Southeast Asia, and the Western Pacific, and in humans, monkeys, and mosquitoes [3].

Ugandan data from 1952 indicated a prevalence of 6.1% for Zika infection, based on a sample of 99 individuals [13]. When patients in Java, Indonesia, admitted to hospital for pyrexia were examined between 1977 and 1978, ZIKV was identified in 7.1% of cases [14]. A West African study from 2007 to 2012 covering Mali, Gambia, and Senegal found serological evidence of ZIKV infection in 20–22% of those tested [2].

There has been an extension in the range of ZIKV infection since 1947, when the virus was first identified in Africa. Its range now included Southeast Asia and North and South America. There were occasional reports of ZIKV infection prior to 2007. In that year, an epidemic of ZIKV infection affected some 73% of the inhabitants of the island of Yap in Micronesia. The virus was transmitted by the *Aedes hensilli* mosquito [5]. There were Zika outbreaks in French Polynesia, New Caledonia, the Cook Islands, Easter Islands, and other islands of the Pacific between 2013 and 2015 [6]. Guillain-Barré syndrome was noted to occur as a complication of Zika infection in cases from French Polynesia [8].

11.4 Prognosis

The majority of ZIKV infections are of mild severity and resolve without intervention. The lack of severe symptoms probably explains why at least 80% of infections do not come to clinical attention [2].

Rarely, ZIKV infections cause severe nervous system complications, such as Guillain-Barré syndrome [2, 15].

The most concerning aspect of ZIKV infections may, however, be when they occur in pregnant women. In these cases, the risk of an adverse outcome rises, and transmission from mother to fetus carries a poor prognosis in the long term [14, 16].

Furthermore, infection with ZIKV causes temporary infertility [8].

11.5 Transmission

Transmission of ZIKV can occur both via vectors and in other ways [8].

11.5.1 Transmission Via Vectors

In common with several other flaviviruses, transmission may occur via an arthropod vector [17], especially different species within the mosquito genus *Aedes*, such as *A. aegypti*, *A. africanus*, *A. luteocephalus*, *A. albopictus*, *A. vittatus*, *A. furcifer*, *A. hensilii*, and *A. apicoargenteus* [1, 2, 5, 18]. Isolation of ZIKV is also reported from the southern house mosquito, *Culex quinquefasciatus*. The virus passes from human or other vertebrate hosts into mosquitoes and is then passed onto another host. ZIKV transmission occurs enzootically among nonhuman primates, while human-to-human transmission is described as the urban life cycle. Two species, *A. aegypti* and *A. albopictus*, are generally resident in tropical and subtropical areas, although they may also exist elsewhere. The former species is a major disease vector, whereas the latter has only occasionally been implicated as vector. The geographical areas of the United Staes where ZIKV has the potential to become endemic have been mapped by the Centres for Disease Control, based on the likely habitats for *A. aegypti* or *A. albopictus*.

For the United States, new cases are most common between June and October, corresponding to the period when mosquitoes are most likely to feed on human blood. ZIKV resides in the salivary glands of the arthropod vector, passing via the bite into the host's circulation, whence it can arrive at the skin and other tissues for which it has a tropism [19].

11.5.2 Viral Transmission Not Involving Vectors

Analysis of ZIKV epidemics has revealed that the virus may also be transmitted without the need for a vector [8].

For pregnant women infected at any stage of the pregnancy, the risk of transmission to the fetus is between 20 and 30%. The initial trimester is the period during which vertical transmission produces the gravest consequences and is when Zika syndrome occurs. Despite the isolation of ZIKV from breast milk, there are no data to show that the virus may be transmitted to infants through nursing. Accordingly, even where a mother is definitely or potentially infected by ZIKV, breastfeeding should continue, since its benefits exceed the risks [2, 20].

Within the first month of becoming infected, ZIKV is found in the semen of 50–60% of infected male patients, with a case recorded where the virus could still be isolated after 281 days. There are reports indicating transmission of ZIKV from a male to female sexual partner in the United States and French Polynesia. Furthermore, cases where the virus has been transmitted sexually from a woman to a man, or between men, have also been described. It has been calculated that the period between 32 and 44 days after initial symptoms appear in ZIKV-infected patients is the most likely time for sexual transmission to occur [1, 2, 21].

There is a brief window of opportunity for serological detection of ZIKV in acutely ill patients. RNA from ZIKV has been estimated to be present in approximately 1 in 100 donated blood samples, which means that iatrogenic transmission via transfusion is still a potential problem. Although ZIKV has also been detected in other body fluids (urine, saliva) or solid organs, it does not appear currently that the virus is transmitted during organ transplantation [1, 2, 8, 22].

11.6 Symptomatology and Physical Findings

Cases of VIKV are usually symptomatic for between 2 days and 1 week [2]. The most common presentation is an exanthem. Other frequent findings are pyrexia, joint pain (affecting the finger and toe joints), headache localized to behind the eyes, and conjunctival inflammation [1, 5, 15].

On rare occasions, ZIKV infection triggers Guillain-Barré syndrome [2, 15]. There is a case report in the literature of a young doctor with no other health problems who suffered hypertensive iridocyclitis, probably caused by infection with ZIKV [13].

The most usual clinical picture is one of swift, total resolution of symptoms. A study in 2007 where ZIKV infection cases from Yap Island, Micronesia, were retrospectively reviewed, found no patient had been admitted to hospital and no hemorrhage or fatality had occurred [5, 8].

11.7 Factors to Consider in Clinical Approach

It is challenging to confirm a diagnosis of ZIKV infection by laboratory testing, since the tests used have low sensitivity and specificity and the frequency of infections is generally low. There are both molecular and serological techniques available for diagnostic confirmatory purposes [23]. The standard way to confirm the

diagnosis during the acute phase is nucleic acid amplification testing (NAAT). However, this test may produce a false negative in the active phase, since viraemia may be only transient. NAAT has FDA approval for emergencies where ZIKV infection is suspected and suitable samples include serum, plasma, whole blood, urine, and cerebrospinal or amniotic fluid [8].

Quantification of IgM by serology is possible after just 7 days of the patient being symptomatic. However, the absence of IgM specific for ZIKV is not proof that the virus is absent as the stage at which IgM begins to be synthesized varies from patient to patient. Testing too soon may be falsely negative if the synthesis of IgM has not yet properly begun. Likewise, a delayed test may appear falsely negative due to the immune system decreasing the synthesis of IgM as the infection resolves. Another complication is that IgM synthesis potentially continues for a maximum of 12 weeks following ZIKV infection, and thus, a positive result may represent acute infection or persistence of the immune response beyond the acute phase. There is cross-reactivity with IgM specific to other flaviviruses, such as yellow fever, dengue, Japanese encephalitis, and West Nile fever, which may cause false positivity to occur. The serological tests for ZIKV are suitable for the following specimens: blood (whole, serum, or plasma) and cerebrospinal fluid (CSF) [8].

If there is a suspicion that serological false positivity has occurred due to cross-reaction with IgM for other flaviviruses, plaque reduction neutralization tests (PRNTs) may be used. PRNTS can quantify the levels of immunoglobulin specific for several flaviviruses, notably Zika and dengue. The CDC employs the following criteria for test positivity: for serum, a titer of at least 10 for 90% plaque reduction, whereas for CSF a titer of at least 2. If the titer for ZIKV neutralizing immunoglobulins is at least four times above that for other flaviviruses, the diagnosis is confirmed. PRNT can be used to distinguish ZIKV infection from other flaviviruses and can retrospectively confirm the diagnosis even if more than 3 months have elapsed since the acute infection. However, if PRNT is employed more than 1 year after the episode, it may be difficult to interpret the result. A study in Florida found that 27% of cases still had raised IgM titers more than a year after the initial viral episode, and PRNT could not differentiate Zika from dengue [8].

At the time of writing, there have been no positive NAATs for ZIKV infection in the continental United States since September 2017, nor in other US territories since May 2018. The low prevalence of Zika does, however, mean that false positivity of Zika testing is more probable [8].

For cases of suspected Guillain-Barré syndrome, the recommendation of the WHO is to employ the Brighton criteria [24].

11.8 Laboratory Investigations

Initial clinical diagnosis and laboratory confirmation of ZIKV infection is difficult to achieve in a timely fashion [8].

11.8.1 Serology

Laboratory confirmation of suspected ZIKV infection depends on detecting and isolating viral RNA with the NAAT and is performed on serum. NAAT is most sensitive in the first 7 days of symptoms, when the level of viraemia is elevated. Following the first 7 days, detection of specific IgM and neutralizing immunoglobulins is possible with an ELISA assay [25]. Following a negative NAAT, IgM serology is advised, irrespective of the timing of specimen submission to the laboratory [8].

If NAAT serology is positive less than a week after the patient becomes symptomatic, this result implies an acute ZIKV infection. A positive result, however, needs to be confirmed by extracting RNA a second time from the specimen to repeat the NAAT procedure. On the other hand, if both NAAT serology and IgM levels are normal in a patient whose symptoms are of less than 1 week's duration, ZIKV infection is unlikely [8].

IgM levels in the normal range in a patient who has been symptomatic for between 1 week and 12 days imply ZIKV is not present [8]. Where IgM levels are equivocal, IgM serology should be performed once again or use made of PRNT testing [8]. Cases where IgM levels are raised but NAAT is negative should be investigated further using PRNT testing [8].

In patients who have previously experienced Zika or a similar flavivirus, or who have undergone vaccination, the criterion generally used to distinguish immunoglobulins specific to ZIKV from cross-reacting, other immunoglobulins, that is, a titer at least four times higher on PRNT, does not apply [8].

Where IgM serology points to ZIKV or dengue infection, or the results are unclear, PRNT results should be interpreted as follows [8]:

- If the PRNT titer to one particular flavivirus is at least 10 and the PRNT to other flaviviruses is below 10, that particular flavivirus is the likely pathogen responsible for infection.
- PRNT titers that are lower than 10 show that the virus to which those immunoglobulins are specific is not the cause of the infection.
- PRNT titers for a variety of flaviviruses that are simultaneously above 10 may be interpreted as the patient responding to a recent infection with some sort of flavivirus.

The tables that follow are based on the CDC guidance on how to interpret diagnostic tests for dengue or Zika. The guidance applies to patients who present with characteristic clinical findings following exposure to a source of the virus and can be used in all patients, including those who are pregnant [8].

11.9 Congenital ZIKV Infections

11.9.1 Congenital Anomalies, Including Microcephaly

Despite the general mildness of ZIKV infections, an area of significant concern is the occurrence of congenital anomalies caused by vertical transmission of ZIKV. A spike in the frequency of congenital microcephaly was noted in Brazil 6 months after an epidemic of ZIKV, the level being 20 times higher than usual. The background rate of microcephaly was 2 in 10,000 live births. However, for 2015, 1248 potential cases of microcephaly were noted [14, 26], with 4810 potential cases notified in January 2016. Of the cases reported, 270 underwent diagnostic confirmation, but in 462 cases, the criteria for microcephaly were not met [26].

A number of anomalies affecting the eyes have been linked to babies with congenital microcephaly, where fetal ZIKV was believed responsible. The anomalies include absent foveal reflex, mottled areas of pigment on the macula, chorioretinal thinning, and hypoplasia of the optic nerve, which presents as the double-ring sign [14].

It is important to be cautious, however, about interpreting these findings, given the potentially inaccurate data regarding the frequency of microcephaly in the past, which may lead to a spurious impression that congenital abnormalities have increased [26].

A Brazilian study defined microcephaly as a head circumference smaller than the mean, adjusted for sex and gestational age, by a minimum of 2 standard deviations. When 35 cases of microcephaly across the whole of Brazil and occurring between August and October 2015 were examined in detail, it was ascertained that all the mothers had had some degree of exposure to Zika, while pregnant, either through residing in an affected area or by visiting there [27]. Of the 35 cases examined, 27 represented severe microcephaly occurring in isolation from any other form of congenital anomaly. It was recently reported from Brazil that ZIKV RNA was present in amniotic fluid, the placenta, or the fetus in cases involving congenital anomalies of the nervous system [8, 26].

11.9.2 ZIKV Tests in Pregnancy

Expectant mothers who present with symptoms of Zika infection and a history indicating exposure should be tested for ZIKV with molecular techniques and serology. Serum and urine should be tested using NAAT, accompanied by serological quantification of IgM. The specimens should be gathered no later than 12 weeks after symptoms began. Interpretation of the results of these investigations should follow a diagnostic protocol, allowing Zika and dengue infections to be differentiated from each other [8]. One such diagnostic protocol suitable for use in suspected cases of congenital acquisition is the one developed by the CDC [8].

11.9.3 Congenital ZIKV and Auditory Impairment

Congenital ZIKV infection puts the infant at risk of auditory impairment. In cases where the initial audiological screen does not detect any abnormality, regular follow-up screening is needed, since auditory impairment may present insidiously and gradually worsen, as is noted with other causes of congenital viral infection [28].

The most fully characterized congenital anomaly found in cases of ZIKV is microcephaly [17, 18]. This malformation seems to mostly affect the nervous system. Imaging of the brain reveals calcified regions between the cortex and subcortex, malformed cortex, and pachygyria or agyria [17, 18, 29]. Alongside its effects on the nervous system, there appear to be abnormalities of the eyes [30] and musculoskeletal system [31]. One Brazilian study looked at 23 newborn infants with microcephaly who were believed to have contracted congenital ZIKV. As a result of otoacoustic testing, 9% were found to have hearing loss, albeit this was not confirmed by other examination [29]. The diagnosis of Zika was made in these cases by exclusion of competing diagnoses, since specific testing was not feasible due to the circumstances of the study.

It is well known that congenital infections of various types cause auditory impairment, such as cytomegalovirus (CMV), rubella, toxoplasmosis, herpes simplex, and syphilis. In such cases, auditory impairment generally affects both ears, is of sensorineural type, and is of very great or profound severity. In many cases, hearing loss does not become evident at birth, but may progressively deteriorate or fluctuate [32, 33].

Fetal infection with ZIKV and auditory loss in the early years of childhood appear to be connected. However, for this potential association to be better understood, future research will need to control for potentially confounding variables, such as the presence of microcephaly. Furthermore, children exposed in utero to ZIKV should be followed up for lengthy periods in order to identify auditory impairment occurring after a protracted delay [34].

The location of the neurological insult, which causes deafness following Zika infection, is still unknown. Studies where the inner ear was imaged have failed to note any potential structural defect. It is worth bearing in mind, nonetheless, that there is often no apparent abnormality of the cochlea in children with auditory impairment caused by other infections acquired in utero. Thus, it is wrong to assume that the absence of apparent anatomical abnormality means no hearing loss will occur. Indeed, a child who received a cochlear implant following congenital viral infection, despite no demonstrable anatomical injury to the inner ear, was reported to demonstrate benefit. His behavior changed, with more independence-seeking, positive responses to auditory stimuli, smiles when the device was activated, greater interest in music, and being able to respond to sound at an intensity of 30 dB [35]. The explanation for this response is that the auditory nerve and auditory pathways of the central nervous system must have remained functional, with auditory loss attributable to cochlear dysfunction. The same conclusion had already been proposed in a study of infants exposed in utero to ZIKV and whose auditory function

was assessed by measuring otoacoustic emissions, although without a formal diagnosis being made [29, 36].

Infants who present with signs of congenitally acquired ZIKV infection should be thoroughly assessed clinically, and appropriate investigations should be undertaken. The US CDC has published guidelines on optimal practice in managing such patients. The usual workup includes complete physical examination, recording of growth parameters, ongoing observation of development, and audiological screening in accordance with the advice of the American Academy of Paediatrics, which suggests neonatal auditory function testing at the time of birth. The ideal technique for this purpose is automated auditory brain stem response testing [8].

Additionally, the following investigations may be valuable [8]

- Ultrasound of the central nervous system
- A complete ophthalmological assessment within the initial month of life, by a specialist with expertise in evaluating and treating infants
- If the child passes neonatal screening by otoacoustic emissions testing, but no other investigations were performed at that stage, automated auditory brain stem testing should be undertaken within the initial month of life.

Involvement of a specialist with knowledge on care of infants is also recommended.

Patients with congenitally acquired Zika syndrome should also be closely followed up for potential complications, and any such issues call for timely investigation [17].

- An infant who has distressed breathing or goes into respiratory failure and been placed on ventilatory support may be unable to restart breathing when the ventilatory is withdrawn, due to paralysis of the diaphragm.
- Dysphagia or choking, coughing or gasping while feeding, or very slow feeding is indications for a swallowing assessment.
- If there are any indications of raised intracranial pressure (such as raised head circumference, irritability, or vomiting), postnatal hydrocephalus should be suspected. Imaging of the central nervous system is required.

Care should be taken that such children receive preventative interventions routinely, are fully vaccinated, and are under regular pediatric follow-up. The advice about performing auditory brain stem response (ABR) testing has changed. It used to be recommended that ABR measurement be repeated at age 4–6 months in children with congenital ZIKV infection. The assumed low probability of developing auditory impairment after a delay in such cases makes this test unnecessary.

Furthermore, infants who lack evidence of congenital ZIKV infection, but where there is laboratory confirmation of maternal infection or a history of exposure to an area where Zika is endemic, require careful follow-up in a pediatric clinic. If the child subsequently shows any indications of congenital Zika syndrome, he or she should be referred to a subspecialty clinic to advise on further assessment and treatment [17].

11.10 Pharmacotherapy

In the first instance, bed rest and plentiful fluids are recommended. If the patient becomes pyrexial or complains of pain, paracetamol may be administered. Itching and an exanthem are treated with an antihistamine. Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered if the diagnosis of Zika has not been confirmed. The reason for this avoidance is that these drugs may cause hemorrhage in patients with dengue and is a risk factor for Reye's syndrome in children [37].

According to WHO guidelines, patients who develop Guillain-Barré syndrome should receive high level supportive care. There should be regular physical examination of the nervous system, checking of vital signs and careful monitoring of breathing, since respiratory failure may supervene or a thrombotic event occur. In cases where the symptoms swiftly deteriorate or where the patient can no longer walk, immunoglobulin treatment should be administered intravenously or plasma exchange performed [24]. Specialist involvement is required if ZIKV occurs in pregnancy or where the patient is a child with congenital Zika syndrome [8].

No medications are specifically licensed by the FDA for the treatment of ZIKV infections. There are, however, several drugs currently being evaluated as potential treatments for Zika [2, 10, 38]. The agents currently being developed either directly inhibit various stages in viral replication or inhibit cellular processes involved in the viral life cycle. Examples of the former are nucleoside analogues and polymerase inhibitors, including those acting on RNA-dependent RNA polymerase, such as sofosbuvir and galidesivir, while examples of the latter are inhibitors of purine or pyrimidine synthesis or drugs that interfere with viral entry into cells. There have been encouraging results so far from a number of studies, both in vitro and in vivo. There are some agents that are already licensed by the FDA for other indications that may be of benefit in combating ZIKV. Examples include interferon (which exhibits antiviral actions in vitro), Chloroquine and Mefloquine (licensed in treating malaria and with low teratogenicity potential throughout pregnancy), Ivermectin (an antiviral), and Azithromycin (licensed as an antibacterial but may also reduce infectivity). These agents are potentially effective against ZIKV, but further research is needed to establish how safe and efficacious they are. The development of anti-Zika medications faces the difficulties that any agent needs to have the ability to cross both the blood–brain barrier and the placenta but have low teratogenicity. One further constraint is that any new agent needs to be affordable by patients who are mostly found in low- or middle-income countries within the tropics or subtropics [39].

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Hearing Loss in Neonates Exposed to Herpes Simplex Virus

12

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12.1 Introduction

Although neonatal herpes simplex virus (HSV) infections primarily develop due to transmission of the virus from the mother's genital tract during delivery, it can also develop as a result of viremia in the intrauterine period [1]. The essential factor in determining mother-to-child transmission is the classification of the infection in the mother. Compared to the risk of transmission from mother with primary infection, transmission from mother to newborn with recurrent infection is very low; the presence of antibodies in the mother is a protective factor for the newborn [1]. The absence of HSV symptoms and signs in the mother does not exclude the diagnosis of congenital HSV because even if the mother is asymptomatic, virus shedding may continue [2, 3].

Symptomatic fetal HSV is an infrequent clinical entity, while it can cause significant morbidity and mortality [4, 5]. A high index of suspicion is required for early diagnosis, especially in the absence of skin lesions.

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12.2 Etiology

Herpes simplex viruses are enveloped, double-stranded DNA viruses of the Herpesviridae family and are highly prevalent among humans. There are two types of HSV: HSV-1 and HSV-2 [6]. Herpes simplex virus-1 is usually related to labial herpes and HSV-2 to genital herpes. However, either virus can be present in areas other than their familiar territories [6, 7]. Herpes simplex virus-2 is the leading cause of HSV infection in newborns, while HSV-1 can also occur after the neonatal period [8, 9].

12.3 Epidemiology and Transmission

The incidence of neonatal HSV infection is reported as 1 in 3200–10,000 live births [10]. This wide range in incidence is due to the prevalence of genital HSV infection in different parts of the world. Since 2000, an increasing incidence of severe neonatal HSV infection has been reported [11]. Herpes simplex viruses are most commonly transmitted by contact at birth from the maternal genital tract; however, they can also be transmitted by ascending route from ruptured or intact amniotic membranes. More rarely, HSV can be transmitted by the transplacental intrauterine route [6].

Despite the general opinion that HSV-1 causes oral infections and HSV-2 causes genital infections, HSV-1 is the cause of 40% of genital herpes cases in some populations. Both HSV-1 and HSV-2 can infect the newborn [4, 10, 12]. It has been reported that congenital HSV infection develops not only in association with genital HSV infection but also due to the maternal viremia caused by HSV gingivostomatitis [13].

12.4 Pathogenesis and Immunity

Herpes simplex virus penetrates the human body through the oral, genital, or conjunctival mucosa or cutaneous injury, infecting the sensory nerve endings. Following primary infection, HSV migrates to the dorsal root ganglion in a retrograde manner via the axonal fibers. Then HSV remains dormant in the sensory ganglia with reactivation potential [2]. Herpes simplex virus-1 usually remains dormant in the trigeminal and/or sacral ganglions, while HSV-2 usually remains dormant in the sacral ganglion [1]. After the latent period, HSV-1 and HSV-2 may reactivate. Reactivation can cause asymptomatic infection causing only viral shedding or recurrent symptomatic disease. Genital infection caused by HSV-2 recurs more frequently than caused by HSV-1 [6].

Definitions of primary, non-primary first-episode, and reactivation infection for the different types of maternal infection are used. In primary infection, the mother has experienced a recent infection with HSV-1 or HSV-2 without a history of being infected with the other type. In non-primary first-episode infection, the mother is

infected with one of the HSV virus types, mostly with HSV-2, but has antibodies against the other type [14]. Reactivation is when the dormant virus wakes up and results in infectious HSV on mucosal or skin surfaces as detected by the polymerase chain reaction (PCR) test or cultures [14, 15].

The virus can be transmitted to the newborn transplacentally due to viremia during primary infection. Recurrent maternal infection can also result in congenital HSV [15, 16]. The probability of developing congenital HSV is higher after primary infection than reactivation or a non-primary first episode [2, 15]. The transmission rate from the mother to the baby is more than 50% in primary HSV infection and can go up to 60% when the infection occurs close to birth. The transmission risk is less than 3% in non-primary infection and less than 2% with reactivation in the first half of pregnancy. This variance is due to the difference in genital viral load and maternal antibodies. The protective antibodies present in the mother may protect the newborn and limit the disease during reactivation [17].

Less than one-third of women with a primary infection during pregnancy are symptomatic. After the first attack, cervical scatter can continue asymptomatic for as long as 2 months [14]. The person may be asymptomatic during reactivation; ulcers do not constantly occur in these cases, as some present only with vaginal discharge. Therefore, the absence of HSV symptoms and signs in the mother does not exclude congenital HSV, and virus scatter can occur even when the mother is asymptomatic [2, 3].

12.4.1 Herpes Simplex Virus Transmission to the Fetus

Herpes simplex virus transmission to the fetus may occur by the transplacental route in the intrauterine period (congenital or in utero infection) or by the ascending route in the perinatal period (perinatal infection) [5].

Congenital infection is an extremely rare condition that develops due to maternal viremia resulting from primary HSV infection during pregnancy [11]. Congenital HSV infection's estimated incidence is 1 in 250,000 deliveries, representing less than 5% of neonatal HSV cases. Peripartum transmission is much more common (85%); the neonate is exposed to the virus in the birth canal during labor. Ten percent of neonatal HSV infections are acquired postnatally [5, 8, 18, 19].

Congenital and perinatal transmitted infections have different clinical presentations [5]. Intrauterine transmission can occur due to viremia developing after oral, genital, or skin lesions. Perinatal transmission can occur with or without ruptured amniotic membranes. Neonatal HSV infection was also reported in infants born by cesarean section with intact amniotic membranes. Congenital HSV infection is more likely to result in encephalomalacia, ventriculomegaly, calcifications, and microcephaly than perinatally acquired disease [19].

12.5 Clinical Manifestations

12.5.1 Congenital (In Utero) Herpes Simplex Virus Infection

Intrauterine-acquired HSV infection is an extremely rare condition. The typical triad of congenital HSV infection is chorioretinitis, microcephaly or hydranencephaly, and active skin lesions together with skin scarring [18]. However, this triad is seen in less than one-third of the patients. Congenital HSV infection manifests with signs and symptoms within the first 2 days of life [18]. Death occurs within the first month of life in 60% of babies with intrauterine HSV infection [20].

The most common finding in congenital HSV infection is skin anomalies [13]. The skin manifestations may be localized or widespread and consist of skin ulcers, erosions, scars, and mucocutaneous vesicles; corneal or retinal damage is also common [21, 22]. Central nervous system (CNS) findings in newborns with in utero HSV infection may include microcephaly, microphthalmia, cerebral hemorrhage, anencephaly, intracranial calcifications, hydrocephalus, ventriculomegaly, porencephaly, encephalomalacia, corpus callosum agenesis, and cerebellar anomalies [5, 10]. Possible findings of congenital HSV infection are presented in Table 12.1.

12.5.2 Perinatal Herpes Simplex Virus Infection

Symptoms may appear at birth or within the first 6 weeks [5]. The prognosis is good with early diagnosis and treatment; however, the risk of progression to encephalitis and disseminated disease is high if treatment is delayed. The condition can be insidious and nonspecific in early [5, 24].

Table 12.1 Possible findings of congenital herpes simplex virus (HSV) infection

Fetal death
Premature birth
Intrauterine growth retardation
Hydrops fetalis
Limb hypoplasia
Skin anomalies
Heart anomalies
Herpetic keratitis, retinitis, retinal scar
Cardiomegaly, pericardial effusion
Hepatomegaly, elevated liver enzymes, liver calcification, liver necrosis
Splenomegaly
Hyperechogenicity in the intestines

Adopted from Refs. [3, 5, 10, 13, 18, 20, 21, 23]

There are three types of neonatal HSV infection

- Disease localized to the skin, eyes, and mouth (SEM)
- Central nervous system (CNS) disease (with or without SEM involvement)
- Disseminated disease (may include the symptoms and signs of the first two groups)

12.5.2.1 Skin, Eyes, and Mouth (SEM) Disease

Skin, eyes, and mouth (SEM) disease constitutes 45% of neonatal HSV infections [18]. It appears in the first 2 weeks and is most commonly localized to the skin, eyes, and mouth. Skin lesions may be individual vesicles, large bullous lesions, and desquamation. Eye involvement may be asymptomatic; however, keratoconjunctivitis, chorioretinitis, cataracts, and permanent vision loss are also possible. The prognosis of SEM disease is excellent when antiviral treatment is started early. Still, the condition can progress to CNS and/or disseminated diseases if not diagnosed and treated [1, 5].

12.5.2.2 Central Nervous System Disease

This form represents 30% of neonatal HSV infections [18]. It can result from retrograde viral spread from the nasopharynx and olfactory nerves or hematogenous spread in newborns with disseminated disease. Central nervous system disease can present with a bulging fontanel, lethargy, irritability, seizures, tremors, and body temperature imbalance [14]. The patients usually become symptomatic on the 8–17th day of life. Two-thirds of the cases have concomitant skin lesions. The probability of sequelae in the long term is high [24].

12.5.2.3 Disseminated Disease

Disseminated HSV disease form constitutes 25% of neonatal HSV infection cases, and a sepsis-like clinical picture with multiple organ failure is common [14, 18]. Two-thirds of the babies have concomitant skin lesions. However, skin vesicles do not occur in more than 20% of newborns with disseminated disease [14]. Disseminated HSV disease may present with signs of hepatic, pulmonary, and neurologic dysfunction or failure [1]. Table 12.2 summarizes the signs and symptoms of neonatal disseminated HSV disease.

The neonatal disseminated HSV disease diagnosis is often delayed by mimicking bacterial sepsis [18]. In a newborn presenting a sepsis-like clinical picture with thrombocytopenia, elevated liver enzymes, *disseminated intravascular coagulation (*DIC), and cerebrospinal fluid (CSF) pleocytosis, disseminated HSV disease should also be suspected [6, 16]. It has the worst prognosis among neonatal HSV disease forms in terms of mortality, with a mortality rate of 80%. However, the mortality rate decreases to 30% with timely treatment [13].

Table 12.2 The manifestations of neonatal disseminated herpes simplex virus (HSV) disease

Fever or hypothermia
Lethargy
Apnea
Pneumonia, hemorrhagic pneumonia
Myocarditis
Hepatitis, acute liver failure
Central nervous system (CNS) involvement
Necrotizing enterocolitis
Neutropenia, thrombocytopenia
Disseminated intravascular coagulation (DIC)

Adopted from Refs. [3, 18]

12.6 Diagnosis

Early findings are indistinct and nonspecific, especially in disseminated disease [11]. In the absence of skin lesions, diagnosing neonatal HSV infection can be troublesome and maybe late [14]. The maternal history is usually not helpful because there is no history of genital ulcers in 80% of the cases [2, 3, 14]. Newborns with disseminated HSV infection often appear at 1 week old with signs and symptoms that mimic neonatal sepsis. The patient may experience fever or hypothermia, irritability, lethargy, and respiratory distress and rarely present with fever only. In advanced neonatal disseminated HSV disease, fever is usually absent, and hypothermia is predominant [11, 25, 26].

In newborns, SEM disease presents with skin vesicles in 80% of patients; in the absence of vesicles, the infection is localized to the eye and/or oral mucosa. More than half of the neonatal disseminated or CNS HSV disease accompanied skin lesions. However, skin lesions may not be present on admission [6]. Newborns with a sepsis-like clinical picture, meningoencephalitis, progressive pneumonia, severe hepatic dysfunction, or DIC should be tested for HSV infection, and empiric antiviral therapy should be initiated [6, 11, 27–30]. Herpes simplex virus should also be considered in newborns with fever, vesicular rash, and abnormal CSF findings in the first 3 weeks of life, especially when a history of seizures is present [6].

12.7 Laboratory Features

The diagnosis of HSV infection is made with PCR, surface viral culture, and direct immunofluorescence tests. Serology does not help diagnose neonatal HSV infection at presentation.

12.7.1 Surface Viral Culture

Surface viral culture is the gold standard for diagnosing neonatal HSV infection [2]. The material can be aspirated from unruptured vesicular lesions, swabs from the floor of ruptured vesicles, and the conjunctiva, mouth, nasopharynx, or anus [14, 31].

A single stick is used to take a surface swab. Swab samples from the mouth, nasopharynx, conjunctiva, and anus can be taken with a single swab, starting from the conjunctiva and ending at the anus. The swab is then placed in a viral transport medium. Viral culture aims to determine the presence or absence of proliferating virus instead of localizing the virus. Positive cultures result 12–24 h after birth, indicating viral replication and suggesting infection, not contamination at birth. This is the most critical information from such cultures, except for CNS involvement. A moistened cotton swab should be preferred because a calcium alginate-impregnated swab inhibits virus growth. Surface viral cultures are transferred on ice with the appropriate transport medium [5, 14].

Every patient with neonatal HSV infection should have a conjunctival HSV culture and an ophthalmologic examination, regardless of the type of disease [6, 11].

12.7.2 Polymerase Chain Reaction (PCR) Test

The polymerase chain reaction test is used for HSV deoxyribonucleic acid (DNA) detection in CSF and blood samples. Viremia can occur in all three forms of neonatal HSV disease and is detectable by PCR. The polymerase chain reaction test is precious in the diagnosis of HSV encephalitis. The sensitivity and specificity of PCR in CSF for the diagnosis of neonatal HSV infection are 75–100% and 71–100%, respectively [14]. A negative CSF PCR result does not exclude CNS involvement; as a result, it can also be negative in the early stages [6]. In patients with a strong presumption of CNS HSV disease but CSF PCR tests are negative more than once, a histopathological survey and viral tissue culture of the brain biopsy specimen is the most reliable investigation to diagnose HSV encephalitis [6]. Cerebrospinal fluid viral culture is usually negative in patients with HSV CNS disease [6].

Some authors report that PCR is acceptable if cultures from the surface swab are not possible. However, studies on PCR in newborn surface swab samples are inadequate [14]. Using the PCR assay on surface swabs or scraping samples has not been evaluated, but skin PCR should be used in addition to (and not in place of) a surface culture, the gold standard. False-negative results are possible [14].

12.7.3 Direct Immunofluorescence Antibody (DFA) Test

The test provides fast results, but the sensitivity is 60–80%. A scraping sample from the skin lesions is used. The test reliability increases if the sample is taken appropriately but is not as sensitive as culture. Therefore, samples negative for DFA must be confirmed with another test [11, 32].

12.7.4 Other Tests

Serology does not help diagnose neonatal HSV infection but helps diagnose and classify maternal disease. Cross-reactions and false positivity are commonly seen with serology.

The cytological changes on Papanicolaou (Pap) stain or the Tzanck test are not specific, as these changes are also seen with cytomegalovirus (CMV) and varicella-zoster virus (VZV). The sensitivity of these tests varies with the pathologist's experience [5].

Complete blood count and liver function tests, especially alanine aminotransferase (ALT), are recommended in neonates with suspected congenital HSV infection [11, 14].

All newborns with suspected HSV infection, including SEM disease, should undergo lumbar puncture. CSF results may be normal at the onset of the disease. However, typically mononuclear cell pleocytosis, normal or slightly low glucose, and a slightly increased protein level are detected [5, 14]. In contrast to general knowledge, erythrocytes do not increase significantly in the CSF in CNS disease; HSV PCR should also be studied in the CSF sample [14].

Blood and CSF cultures should be taken to exclude bacterial sepsis, one of the most frequently confused diagnoses. Although most newborns with HSV infection have a negative blood culture, there may be a possibility of positive blood culture results due to bacterial co-infection [8].

12.7.5 Cranial Imaging

Cranial imaging is recommended for all infants with neonatal HSV infection, irrespective of disease category [23]. Initially, it may be normal, but this does not rule out neonatal HSV infection. Magnetic resonance imaging (MRI) is recommended because of the highest sensitivity among the imaging modalities. As a disadvantage, it requires sedation to avoid motion artifacts. Therefore, cranial computed tomography (CT) or ultrasonography suffice for cranial imaging in neonatal HSV infection [6]. Multifocal involvement is common. The temporal, frontal, and parietal lobes' gray and white matters and the brain stem may be involved [5]. The basal ganglia and cerebellum are other potential sites to be involved. Patchy involvement of the parenchyma and meningeal enhancement can be present. Other imaging findings in CNS HSV infection include parenchymal brain edema, cortical thinning or atrophy, encephalomalacia, hemorrhage, ventricular enlargement, and scattered calcifications [5, 33].

12.7.6 Electroencephalogram (EEG)

All newborns with suspected CNS involvement of HSV infection should undergo an EEG. The result is often abnormal in the very early stages of the disease. Focal or

multifocal periodic epileptiform discharges on EEG are characteristic even before abnormalities are seen on CT or MRI [14].

12.7.7 Evaluation of Hearing

All infants with HSV infection should undergo routine audiological screening [34].

12.8 Neonates Exposed to Herpes Simplex Virus and Hearing Loss

One of the sequelae of HSV encephalitis in infants and children is sensorineural hearing loss (SNHL) [35]. In HSV encephalitis, hearing loss (HL) is rare, and when present, it is bilateral, severe, and associated with severe neurological complications [36]. Herpes simplex encephalitis typically involves the temporal lobes. Bilateral temporal involvement may lead to cortical deafness. Kaga et al. [35] described four children with HSV encephalitis, with only mild-moderate SNHL but severe auditory agnosia due to bilateral auditory cortex lesions. Animal studies have also indicated that HSV infection may cause HL and vestibular symptoms. Following HSV-1 or HSV-2 infection, it has been shown that fibrosis of the scala tympani and vestibule, loss of outer hair cells, and atrophy of the stria vascularis and tectorial membrane occurred [36, 37]. In animal studies, viral antigens were detected in the cochlea and viral capsids in cochlear nerve fibers [36, 37]. In animal studies, changes in temporal bone structures caused by HSV infection have been reported to resemble those observed in humans who suddenly develop SNHL [37–39].

Due to the potential for HSV encephalitis to adversely affect hearing in infants and children, intrauterine and perinatal HSV infections are considered risky conditions in permanent congenital, delayed-onset, or progressive HL in childhood. However, the incidence of immediate and delayed-onset SNHL in children after exposure to HSV is unknown [34]. In addition to the fact that congenital HSV is a rare congenital infection, few studies have evaluated congenital HSV cases regarding HL. The current leading pediatric infectious diseases textbooks have no information about HL in congenital HSV infection [5, 6, 18].

The three studies in the literature evaluating audiometric findings in newborns with HSV infection included 20, 58, and 13 cases [12, 16, 40]. In the study, which included 20 symptomatic neonatal HSV cases, audiological evaluations were performed in the postnatal period, at 2–75 months, with a median of 32.5 months [40]. Half of the patients had CNS involvement, 13 had psychomotor retardation, and 11 had visual abnormalities. Sensorineural HL has been detected in two infants, although patients are severely affected in other respects.

The other study included 58 neonatal HSV cases followed up until the second month of life [12]. Among the cases with neonatal HSV infection in this study, 62.5% had HSV-1; among those, the HSV type was determined. While 60% of the

cases had localized infection, the rest had disseminated or CNS disease. Hearing loss was not detected in any of the patients.

The third study included 13 newborns with intrauterine-acquired HSV infection [16]. The presence of HSV infection was confirmed in all cases by culturing the virus in skin or brain biopsy specimens. All patients infected with HSV-2 had multisystemic involvement, and 92% had CNS abnormalities. Four of the patients died in infancy due to complications caused by HSV disease. Hearing loss was detected in three (33%) of nine living children [16].

A review described SNHL after neonatal HSV infection in five case reports following disseminated HSV-2 infections. The patients had apparent clinical sequelae, and comorbid conditions were present. There were no reported cases of delayed-onset SNHL after perinatal infection [34].

Although it has been reported that HSV-1 infection is associated with encephalitis and HL in newborns at a higher rate than HSV-2, there is not enough data to reach a definite conclusion on this issue [36, 41]. Hearing loss is associated with severe neurological complications; however, it is also rare following HSV-1 infection.

Hearing loss caused by neonatal HSV infection can be bilateral or unilateral [36].

Herpes simplex virus causes HL via neuronal damage to the cochlea and CNS [36]. However, the relationship between HSV infection and HL is not clearly known [33].

Newborns with congenital or perinatal HSV infection should undergo a screening hearing test before hospital discharge. At least one additional audiological evaluation is recommended by 24–30 months of age to detect HL early.

12.9 Treatment

All neonates with HSV should be treated, regardless of the clinical findings. Newborns with HSV disease are administered intravenous (IV) acyclovir at 60 mg/kg/day. The patients with disseminated or CNS HSV disease are treated for 21 days and those with SEM disease for 14 days [14].

Currently, acyclovir is used in the treatment of HSV encephalitis. Early treatment is associated with a better prognosis [35]. The CSF HSV-PCR test is highly sensitive for the diagnosis, but false-negative results can also be obtained, albeit rarely. Therefore, if clinical and radiologic findings suggest HSV encephalitis, acyclovir treatment should be continued [8, 42]. At the end of IV acyclovir treatment, a lumbar puncture should be repeated for CSF PCR for HSV. If CSF PCR is still positive for HSV, IV acyclovir treatment is given for one more week, and the CSF PCR for HSV is repeated at the end of the week. Parenteral acyclovir therapy should be extended at 1-week intervals until CSF PCR negativity for HSV is achieved [18]. Delayed acyclovir treatment is associated with a poorer prognosis. Before acyclovir treatment, the case fatality rate of HSV encephalitis was 70%; however, even with efficient antiviral treatment, >35% of patients still suffer from severe sequelae or death [8, 42, 43].

After completion of parenteral acyclovir treatment for acute disease, better neurodevelopmental outcomes and less recurrence of the skin lesions have been reported with oral acyclovir suppression therapy [44]. Regardless of neonatal HSV disease classification, oral acyclovir treatment should be administered for 6 months. The oral dose of acyclovir is 300 mg/m^2/dose, 3 times a day. The dose should be adjusted according to the current weight by monthly monitoring. During the treatment period, absolute neutrophil counts must be done at weeks 2 and 4, then monthly after starting suppression therapy [6, 18, 44]. There are no studies on the use of valacyclovir for more than 5 days in young infants, so this is not an appropriate alternative to suppressive therapy [6].

Infants with ocular HSV involvement should be given parenteral acyclovir with a topical ophthalmic drug (1% trifluridine, 0.1% iododeoxyuridine, or 0.15% ganciclovir) [14].

12.10 Prognosis

In utero HSV infection prognosis is poor, and 60% of these cases die in the first month of life [20]. The prognosis of HSV SEM disease is very good with early treatment; however, three-quarters of patients progress to disseminated disease if left untreated [1]. Central nervous system HSV disease has a high probability of long-term sequelae [24]. Disseminated disease has the worst prognosis among neonatal HSV disease forms with the highest mortality; however, with timely treatment, the mortality rate drops to 30% [13].

12.11 Prevention of Neonatal Herpes Simplex Virus Infection

For women with active, recurrent genital herpes, the American College of Obstetricians and Gynecologists (ACOG) recommends antiviral suppression therapy at or after 36 weeks of gestation [45]. However, neonatal HSV disease has also been reported in infants of mothers given antiviral prophylaxis [6].

In newborns born to mothers with active genital lesions at birth, the classification (primary infection, first-episode non-primary infection, and reactivation) of the mother's HSV infection should be evaluated. In this way, the risk status of the newborn can be estimated [6].

12.12 Conclusion

Herpes simplex virus transmission can occur from mother to child during the intrauterine or perinatal period. Both HSV-1 and HSV-2 can lead to neonatal HSV infection. Although skin lesions are a significant sign of HSV infection, they may not always be found. Congenital and neonatal HSV infections may cause unilateral or bilateral HL, although the frequency is not clearly known. Hearing loss in neonates

with HSV infection may develop due to neuronal damage in the CNS or cochlea. Newborns with HSV infection should undergo screening hearing tests before hospital discharge and thereafter.

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Hearing Loss in Neonatal Sepsis and Meningitis

13

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13.1 Introduction

Neonatal sepsis and meningitis are worrisome infectious diseases that can lead to serious consequences. Sepsis is defined as systemic signs of infection and isolation of a pathogen from the bloodstream [1]. An infant with signs of infection without culture confirmation from blood or other sterile sites is considered to have clinical sepsis. Meningitis usually accompanies bacteremia and shares a common cause and pathogenesis. Patients may have complications such as neuromotor and learning disabilities, seizure disorders, visual problems, hearing loss (HL), and impaired cognitive function. Here, the sequelae of neonatal sepsis and meningitis, emphasizing auditory problems, will be discussed.

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13.2 Etiology

Neonatal sepsis may develop due to bacterial, viral, fungal, or protozoal infections. Among neonates treated in the neonatal intensive care units (NICUs), 80% of confirmed infections are bacterial, causing receipt of antibiotics [2]. Bacterial pathogens, the most common causes of sepsis, differ according to the age of onset and geographical areas. Early-onset sepsis (EOS) occurs in the first 72 h [3]. However, some experts consider EOS acquired in the first week of life. *Streptococcus agalactiae* (group B *Streptococcus* [GBS]) and *Escherichia coli* are the most common pathogens of EOS in high-income countries. *Listeria monocytogenes* is also a well-known, relatively rare cause of EOS. In a recent multicenter study in the United States, GBS (29.8%) was the most common gram-positive bacterial cause of EOS [4]. *Enterococcus* and *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) were detected in 5.5% and 3.8% of patients. *Escherichia coli* accounted for 35.3% of infections, and an increased rate among the very-low-birth-weight (VLBW, <1500 g) infants was observed. Although data is scarce in low- and middle-income countries, *Klebsiella* species, *E. coli,* and *Staphylococcus aureus* constitute almost half of neonatal community-acquired infections [5]. Neonatal meningitis develops most commonly by GBS and *E. coli* [6]. *Streptococcus pneumonia, Neisseria meningitidis*, and non-typeable *Haemophilus influenzae* may rarely be detected.

Bacterial pathogens encountered in neonatal late-onset sepsis (LOS) are mainly coagulase-negative staphylococci (CONS), *Klebsiella, Enterobacter*, and other gram-negative bacilli (GNB) such as *Pseudomonas, Citrobacter*, and *Serratia* species in NICUs. Fifty percent of LOS cases in most countries are associated with CONS [7].

Candida species is the third most common cause of LOS in VLBW infants [8]. *Candida parapsilosis* has emerged as a significant cause of catheter-associated infection in neonates [9]. Herpes simplex virus (HSV) infection may present as a disseminated neonatal disease. Meningoencephalitis is seen in one-third of neonatal HSV diseases [10]. Enteroviruses are among other viral causes of meningoencephalitis in neonates [11].

13.3 Microbiology

Group B streptococcus has major virulence factors, including capsular polysaccharide, pili, and C5a peptidase [8]. Capsular polysaccharide is effective in the prevention of phagocytosis. The pili enhance adherence of GBS to the host's epithelial cells and transepithelial migration, and C5a peptidase inhibits complement activation. Among ten capsular types, serotypes Ia, Ib, II, III, and V are the most prevalent in invasive infections of infants [12].

The most crucial virulence factor of *E. coli* is the K1 capsular antigen [13]. This antigen is immunologically similar to the capsular antigen of serogroup B *N. meningitidis*. Strains of *E. coli* carrying the K1 antigen produce more severe illnesses, including meningitis than those without the K1 antigen. Bacterial proteins such as

ompA, ibeA, and ibeB are effective in endothelial invasion and promote penetration of *E. coli* into host tissues.

Polysaccharide capsules, which prevent opsonization, phagocytosis, and bacterial lysis, are also responsible for the invasiveness of other bacteria, including *Enterobacter* spp., *Klebsiella* spp., and *Serratia* spp. [14]. *Citrobacter* spp. and *Cronobacter sakazakii* can cause meningitis and brain abscesses in neonates [15].

Listeria monocytogenes is a facultative anaerobic pathogen found in soil, feces, and contaminated food and has an affinity to attacking the host's monocyte-macrophage system [8]. By listeriolysin, the bacterium escapes from the oxidative stress of phagolysosomes and can replicate intracellularly. Lecithinase, phospholipase C, and Act A provide polymerization of actin and lysis of phagosomal membranes, which permit cell-to-cell transmission. The most commonly detected *L. monocytogenes* serotypes are 1, 2, and 4, with serotype 4 being the most common in neonatal meningitis [16].

Staphylococcus epidermidis, the leading species of CONS, is a common skin colonizer. The ability to form biofilms around implantable devices and catheters makes *S. epidermidis* a significant pathogen causing LOS [17]. Biofilms protect bacteria from the host immune system and inhibit antibiotic penetration. Preterm and low-birth-weight (LBW, <2500 g) infants have an increased risk of *S. epidermidis* sepsis [7]. Other species, such as *Staphylococcus haemolyticus, Staphylococcus hominis, and Staphylococcus capitis,* have also been reported in LOS. *Staphylococcus aureus* is also responsible for healthcare-associated infections, especially in neonates with vascular catheters [8].

Candida species can colonize the skin, gastrointestinal, and genitourinary tracts. Both vertical and horizontal transmission can lead to invasive infection in neonates [18].

13.4 Epidemiology

13.4.1 Incidence

During childhood, meningitis is most common in the first month of life [19]. Forty-four percent of all deaths under the age of 5 years occur during the neonatal period, and 26% is assumed to be due to sepsis [20]. Severe infections are the second cause of neonatal deaths (35%) after birth asphyxia in low- and middle-income countries [21]. In a neonatal unit in Kenya, among infants with suspected sepsis, 17.9% had meningitis [22].

Early-onset sepsis has decreased by 80% following intrapartum antibiotic prophylaxis (IAP) in countries administered [23]. The incidence of EOS is 0.77 cases per 1000 live births in the United States [24]. Limited data show community-acquired sepsis incidence as 21/100,000 person-years for infants under 2 months to 1.571/100,000 live births in low- and middle-income countries [25]. Late-onset sepsis prevalence ranges from 14. 0 to 36.4% among infants with birth weight 401–1.500 g [26].

13.4.2 Risk Factors

Preterm birth, premature rupture of membranes, prolonged rupture of membranes (>18 h), chorioamnionitis, and maternal GBS bacteriuria during pregnancy are among the risk factors for EOS [27]. Complications during birth and fetal hypoxia may also lead to infection. In a study, 70.8% of newborns with EOS had a premature birth compared to 57.1% with LOS, and meningitis was more frequent in patients with LOS (14%) than EOS (2%) [28]. Early-onset sepsis due to *S. aureus* has been associated with invasive procedures antenatally [29].

Pregnant women are infected with *L. monocytogenes* by ingestion of contaminated food. The organism is transported to the mother's liver and transplacentally passed to the fetus [14]. The newborn may also be infected by swallowing the amniotic fluid. Seventy percent of infected neonates are preterms due to insufficient immunity to clear the organism.

Risk factors for LOS are prematurity, endotracheal intubation, catheter insertion, failure in early enteral feeding, prolonged duration of antibiotic treatment, and extended hospital stay [8]. Children with underlying respiratory and cardiovascular diseases are also predisposed to infection. Eleven to 46% of VLBW infants have a culture-proven infection during hospitalization [30]. In premature neonates, LOS due to CONS may develop following gut translocation [31].

13.4.3 Morbidity and Mortality

The mortality rate of neonatal sepsis depends on gestational age, and the causative pathogen and varies widely (5–40%) [32]. Infants with VLBW and GNB sepsis have the highest mortality rate [33]. *Pseudomonas* sepsis has a mortality rate of 52–78% compared to 10–25% for other GNB. In high-income countries, meningitis mortality is 10–20%, and 20% of patients develop moderate to severe disabilities [34]. In low- and middle-income countries, mortality is much higher (40–60%) [35, 36]. Meningitis mortality is increased in premature newborns [37]. Extremely low cerebrospinal fluid (CSF) glucose level (CSF/blood glucose <0.10) is another factor increasing mortality in meningitis [38].

13.5 Bacteria and Host Interactions

13.5.1 Host and Bacterial Factors

Neonates are vulnerable to infections due to the immaturity of the immunity system [39]. Neutrophilic chemotaxis, T helper 1 (Th 1) cell levels, and complement reactions decrease. Neutrophil functions are decreased in preterm infants. In addition, they have low concentrations of immunoglobulins (Igs), leading to increased susceptibility to invasive infections. The lectin pathway, an important component of complement activation, is less expressed in neonates, especially preterms, than in

older infants [40]. Among 47 neonates with sepsis, the cord blood concentration of H-ficolin and mannose-binding lectin were lower than control subjects [40].

Capsular polysaccharides in GBS, *H. influenzae* type b (Hib), *S. pneumonia,* and *N. meningitidis* are essential virulence factors [41]. The most common serotype causing GBS meningitis is serotype III. The cell walls of GNB contain endotoxins, and those of gram-positive cocci consist of peptidoglycan and teichoic acid. In case of infection, they cause vascular endothelium damage and breakage of the blood–brain barrier. As a result, vascular leak, thrombosis, cerebral edema, and cerebral perfusion impairment may develop.

13.5.2 Invasion and Disease Production

Early-onset sepsis may occur through the transplacental transmission of infectious agents such as *L. monocytogenes, Treponema pallidum, Mycobacterium tuberculosis*, cytomegalovirus (CMV), rubella virus, *Toxoplasma gondii*, or during labor in case of colonization of the mother with pathogenic bacteria such as GBS, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas*, or *Salmonella* species. Chorioamnionitis can induce preterm labor, a risk factor for both EOS and LOS [42].

Late infections are caused by environmental organism community-acquired or healthcare-associated. Bacteria responsible for LOS and meningitis are usually acquired after birth due to breakage of the—natural—skin and mucosal barriers with the prolonged use of catheters and invasive procedures such as endotracheal intubation. Contamination of healthcare personnel's hands has been accused of being the most common cause of postnatal infections among hospitalized infants [43]. Prolonged use of antibiotics, H2 receptor blockers, or proton pump inhibitors have also been associated with developing LOS [44, 45]. Meningitis can develop by hematogenous spread via the choroid plexus or, less often, from the contiguous spread of organisms in babies with open neural tube defects.

13.6 Clinical Manifestations

Clinical features of neonatal sepsis are nonspecific and can be similar to noninfectious problems. Patients may present with seizures, fever or hypothermia, respiratory difficulty, grunting, pallor, or cyanosis. Signs and symptoms of EOS usually appear during the first 24–48 h and show a multisystemic pattern. In LOS, although many systems can be affected, focal infections such as pneumonia, skin abscess, arthritis, osteomyelitis, and meningitis can accompany sepsis [46]. Any changes in the baby's activity and feeding difficulty should be regarded as clues for infection [27].

Listeria monocytogenes-infected babies usually have an embolic granulomatous rash and hepatosplenomegaly. Meconium staining of amniotic fluid, apnea on the first day or after 2 weeks, hypoglycemia, and metabolic acidosis may be associated with sepsis [47]. Bulging fontanelle has been reported in 30% and seizures in up to 50% of infants with meningitis [27].

13.7 Diagnosis and Laboratory Findings

Blood culture is the gold standard and should always be taken before antibiotic therapy. The sensitivity of a single blood culture is 90% in diagnosing bacteremia [27]. The blood culture is considered positive for the etiologic agent if the isolated bacteria is a known pathogen [2]. Time to positivity shows the level of bacteremia, and most true positives occur within 48 h [48]. Central line blood cultures should be taken with simultaneously peripheral blood cultures. The sensitivity of C-reactive protein (CRP) positivity (>1 mg/dL) is high (50–90%) at the time of clinical signs [27]. Decreased neutrophil count and increased immature to total leukocytes may indicate sepsis [49]. A CSF examination should be performed in suspected sepsis since blood cultures may be negative in 28–38% of neonates with bacterial meningitis [50].

13.8 Treatment

13.8.1 Empirical Treatment

Empirical antimicrobial therapy for EOS is recommended as ampicillin plus an aminoglycoside. When cefotaxime was used instead of gentamicin during the first 3 days after birth, an increased risk of death was observed [51]. Community-acquired LOS is treated with the same regimen. For meningitis, the combination of ampicillin plus an aminoglycoside, mainly gentamicin, and an expanded-spectrum cephalosporin is recommended [27]. Neonates with signs of staphylococcal infection, such as extensive skin pustules, abscesses, or omphalitis, are recommended to receive cloxacillin rather than ampicillin [20]. Vancomycin is substituted with ampicillin for LOS in neonates hospitalized since birth [27]. Ampicillin should be added if GBS, enterococci, or *Listeria* infections are suspected [52]. If the NICU is risky for multiresistant pathogens, meropenem may be used instead of cefotaxime. Although multidrug-resistant gram-negative bacterial infections are uncommon in NICUs in the United States, prevalence is increasing in older children [53]. Table 13.1 summarizes recommended empiric antibiotics and doses for neonatal sepsis and meningitis [27, 52].

13.8.2 Specific Treatment

In neonates with suspected GBS meningitis, if a repeat lumbar puncture (LP) at 24–48 h shows CSF sterilization, penicillin G or ampicillin monotherapy is given for 14 days [27]. *Listeria monocytogenes* meningitis is treated with ampicillin or penicillin plus gentamicin [52]. If the patient is improved and CSF sterilization is obtained, a 21-day course of therapy is completed with ampicillin. For meningitis with methicillin-susceptible *S. aureus* (MSSA), nafcillin or oxacillin is preferred. Vancomycin is recommended for treating MRSA meningitis, with a 14-day treatment duration [32].

Table 13.1 Recommended empiric antibiotics and doses for sepsis and meningitis in neonates

Condition	Antibiotic (Intravenous)	Dose (mg/kg/day)		Duration (days)
		0–7 days	8–28 days	
Early-onset sepsis (EOS) in term	Ampicillin[a] *plus* Gentamicin[b]	Ampicillin 200–300, divided q8h Gentamicin 5, divided q12h	Ampicillin 300, divided q6h Gentamicin 7.5, divided q8h	10
Early-onset sepsis (EOS) in preterm	Ampicillin *plus* Gentamicin	Dose and frequency change according to gestational age and birth weight Serum levels of gentamicin are required if therapy is given for >72 h, renal function is abnormal or unstable, or birth weight is <1500 g		14–21
Meningitis	Ampicillin *plus* Gentamicin *plus* An expanded-spectrum cephalosporin (e.g., ceftazidime, cefepime, or cefotaxime)[c]	Ampicillin 300, divided q8h Gentamicin [2] Ceftazidime 100–150, divided q12h	Ampicillin 300, divided q6h Gentamicin [2] Ceftazidime 50, divided q8h	14–21[d]
Late-onset sepsis (LOS) in terms (community-acquired)	Ampicillin *plus* Gentamicin *or* an expanded-spectrum cephalosporin (e.g., ceftazidime, cefepime, or cefotaxime)[c]	Same in meningitis	Same in meningitis	10–14
Late-onset sepsis (LOS) in preterm hospitalized since birth	Vancomycin[e] *plus* Gentamicin or amikacin	Vancomycin 20–30, divided q8h or q12h Amikacin 15–20, divided q12h	Vancomycin 30–45, divided q6h or q8h Amikacin 30, divided q8h	14–21
Late-onset meningitis in neonates hospitalized since birth	Vancomycin *plus* Gentamicin *plus* An expanded-spectrum cephalosporin (e.g., ceftazidime, cefepime, or cefotaxime)[c]	Same in meningitis and LOS	Same in meningitis and LOS	14–21[d]

(continued)

Table 13.1 (continued)

Condition	Antibiotic (Intravenous)	Dose (mg/kg/day)		Duration (days)
		0–7 days	8–28 days	
LOS with intestinal source suspected	Ampicillin, gentamicin, *plus* clindamycin[f] or Ampicillin, gentamicin, *plus* metronidazole[g] or Piperacillin-tazobactam *plus* gentamicin	Clindamycin 5–20, divided q6h or q8h Metronidazole Loading 15[g] Piperacillin-tazobactam 240–300 mg piperacillin, divided q6h or q8h		10–14

Adopted and modified from Refs. [27, 52]

[a]Ampicillin dose for noncentral nervous system infections: 50 mg/kg/dose every 8 h for neonates ≤2 kg and ≤34 weeks during the first week of life; 75 mg/kg/dose every 12 h between 8 and 28 days of life

[b]Gestational and postnatal ages for gentamicin dose:

<30 weeks	≤14 days	5 mg/kg per dose intravenous (IV) every 48 h (h)
	>14 days	5 mg/kg per dose IV every 36 h
30–35 weeks	≤14 days	5 mg/kg per dose IV every 36 h
	>14 days	5 mg/kg per dose IV every 24 h
≥35 weeks	≤7 days	4 mg/kg per dose IV every 24 h
	>7 days	5 mg/kg per dose IV every 24 h

[c]Meningitis/sepsis caused by the community and hospital-acquired extended-spectrum beta-lactamase (ESBL) producing and multiple drug resistant (MDR) gram-negative organisms may be seen in some newborns. If ESBL-producing or MDR gram-negative organisms are suspected, consider carbapenem, such as meropenem, until susceptibilities are known

[d]Reassess at 14–21 days end of treatment to see if prolonged therapy is indicated. In cases of ventriculitis and/or brain abscess development, extend treatment to 28–42 days

[e]Vancomycin initial loading dose: 20 mg/kg; subsequent dosing is based on gestational age and serum creatinine level

[f]Gestational age for clindamycin dose:

≤32 weeks	5 mg/kg/dose every 8 h
>32–40 weeks	7 mg/kg/dose every 8 h
>40 weeks	9 mg/kg/dose every 8 h

[g]Gestational age for metronidazole dose:

≤34 weeks	7.5 mg/kg/dose every 12 h
>34–40 weeks	7.5 mg/kg/dose every 8 h
>40 weeks	7.5 mg/kg/dose every 6 h or 10 mg/kg/dose every 8 h

13.8.3 Supportive Treatment

Newborns with sepsis are closely followed for vital signs, serum glucose, electrolytes, and liver and kidney functions. Enteral or parenteral nutrition, inotropes if shock is present, and mechanical ventilation in respiratory insufficiency are supportive treatments [54].

13.8.4 Adjunctive Treatment

Anticonvulsive therapy, fresh frozen plasma, thrombocyte, and erythrocyte suspensions are given if indicated. Steroids are used only in adrenal insufficiency [48]. A recent Cochrane review showed routine intravenous immunoglobulin (IVIG), or IgM-enriched IVIG provides no benefit in neonatal sepsis [55]. A meta-analysis evaluating pentoxifylline treatment in sepsis showed a decrease in mortality; however, the quality of evidence was low [56]. Granulocyte stimulating factor (GSF) treatment is not routinely recommended [54].

13.9 Complications and Prognosis

Neonatal meningitis and sepsis have critical impacts on a child's life. Long-term consequences include learning and neuromotor disabilities, HL, seizure disorders, and visual, speech, language, and behavioral problems [54]. A study evaluating the outcome of GBS meningitis showed that 26% of cases develop neurologic impairment, such as hypotonia, hypertonia, seizures, clonus, dysphagia, ptosis, cortical blindness, HL, and temperature instability [57]. A worse neurodevelopmental outcome, including cerebral palsy, low psychomotor developmental index, and HL, was seen in VLBW infants with a history of sepsis than in those without sepsis [58]. Klinger et al. [41] reported that 19% of term or near-term infants with meningitis develop a moderate or severe disability at 1 year of age. Seizures, coma, leukopenia, and the need for inotropes were predictors of adverse outcomes. de Louvois et al. [59] performed a questionnaire survey to identify sequelae of neonatal meningitis after 5 years. Twenty-three percent of children had a severe disability, including cerebral palsy, hydrocephalus, gross motor delay, and HL. Moderate or severe disability was commonly seen in children with a positive CSF culture, 34% in GBS, 30% in *E. coli,* and other GNB meningitides.

13.10 Hearing Loss in Neonatal Sepsis and Meningitis

Sensorineural HL (SNHL) is an important complication of meningitis. Persistent HL develops in 2.5–18% of children with a history of meningitis [60–63]. In England and Wales, among 1584 children treated for meningitis between 1985 and 1987, HL, with a rate of 25.8%, was the most common long-term disability [56].

After 11 years, a repeat study evaluating children treated for meningitis between 1997 and 1998 showed that the mortality rate decreased from 22 to 6.6% [59]. Among 166 neonatal meningitis cases, five developed SNHL (one severe, four moderate). The Joint Committee on Infant Hearing (JCIH) in the Netherlands defined chemotherapy, cholesteatoma, and meningitis as causes of acquired HL [64]. In Austria, Weichbold et al. [65] assessed the causes of postnatal HL in children. Among 23 children who passed universal neonatal hearing screening but later developed permanent HL, two had meningitis.

Of 6093 infants evaluated in a multicenter study investigating the neurodevelopmental and growth impairment among extremely low-birth-weight (ELBW, <1000 g) infants with neonatal infection, 1922 had sepsis, 279 sepsis and necrotizing enterocolitis (NEC), 193 meningitis, and 1536 clinical infections [66]. Adverse neurodevelopmental outcomes were more common in all four infection groups than uninfected infants. Among 906 infants with CONS infections, 2% developed HL. Gram-negative bacterial and fungal sepsis had a significantly higher risk for HL.

Bielecki et al. [67] evaluated 5282 neonates to identify risk factors for HL. The research defined 2 groups: the first group included babies with underlying conditions associated with hearing problems, and the other comprised infants with no risk factors but failed hearing tests twice. The highest risk was for syndromes already known to alter hearing capability (15.5%). Mechanical ventilation for more than 5 days (11.4%), gestational age under 34 weeks (16.2%), and birth weight under 1500 g (12%) were other common risk factors. Meningitis was number 9 among conditions identified to cause HL in infants (6.1%).

Bassler et al. [68] evaluated the relationship between neonatal infection and visual, hearing, or neurological impairment development among ELBW infants. Hearing loss was reported in 3.3% (12/359) of babies with sepsis and 4.8% (1/21) with meningitis. The authors concluded that bronchopulmonary dysplasia, brain injury, and severe retinopathy were the most significant factors associated with the 18-month outcome. Meningitis added a considerable risk for poor prognosis.

A multicenter study investigated risk factors for HL among 4478 neonates treated in NICU [69]. Babies who received ototoxic medications, mechanically ventilated, were LBW and had low Apgar scores failed hearing tests more commonly than well babies.

Aminoglycosides, bactericidal, are among the most common antibiotics accused of causing ototoxicity [70]. After the lysis of bacteria by aminoglycosides, several more immunogens are released, leading to an exaggeration of inflammation, which can harm the ear. Prolonged therapy with aminoglycosides is known to lead to ototoxicity. Genetic susceptibility to mitochondrial mutations also increases the risk [71]. The risk is higher if the patient has fever, hypoxia, renal dysfunction, and poor nutritional or low antioxidant status [72]. Co-administrating other drugs, such as vancomycin, loop diuretics, and neuromuscular blockers, may increase ototoxicity [73]. In mice, systemic inflammation and endotoxemia increased cochlear uptake of aminoglycosides and exacerbated ototoxicity [74].

Periventricular leukomalacia (PVL) and severe intraventricular hemorrhage (IVH) are the most common causes of adverse neurodevelopmental outcomes in

preterm babies [75]. Infection-induced inflammation leads to astrocytosis and microglial reactivity. Inflammatory cytokines interleukin (IL)-1, IL-6, and IL-8 and tumor necrosis factor-alpha (TNF-α) increase. Free radical production and oxidative injury add to the necrosis of oligodendrocyte precursors and axonal death.

The pathogenesis of HL in meningitis is multifactorial, including direct labyrinth involvement, cochlear neuroepithelial damage, eighth cranial nerve damage, and vascular insult [76]. Hearing loss following meningitis results in speech and language disabilities and the inability to participate in school activities [77]. Bedford et al. [56] identified that 9.4% of children with meningitis had speech or language delay at 5 years of follow-up.

Otoacoustic emission (OAE), brain stem auditory evoked response (BAER), and behavioral audiometry are recommended tests performed in children with meningitis [78, 79]. Children should be tested before discharge to diagnose any degree of HL with a high level of accuracy [78]. In a large cohort of 578 children with meningitis, 68% were checked for HL during routine follow-up, and 32 were found to have [80]. An additional 11 cases of HL were detected among children tested after the follow-up period had ended since they had complaints, of which ten were detected after 6 months of meningitis. The authors suggested that if all children with predicted risk factors had been evaluated during routine follow-up, all cases with HL would have been identified.

Turel et al. [81] evaluated children under 5 years of age diagnosed with bacterial meningitis at 11 hospitals in İstanbul. Sensorineural HL was detected in 7.6% of patients, and speech or language problems were the most common (14.5%) sequelae. Other affected abilities included fine and gross motor skills and social contact. Most patients whose hearing was affected also had delays in neuromotor or developmental functions. Seventy-five percent of the cases had not been referred for audiological services at discharge.

13.11 Prevention and Control

13.11.1 Prevention of Early-Onset Sepsis

All pregnant women should be searched for GBS colonization at 35–37 weeks, and those colonized should be given prophylaxis [82]. However, IAP does not prevent GBS-associated LOS [83]. Since most LOS cases are acquired after birth from the environment, hospital infection control strategies effectively reduce the incidence.

13.11.2 Isolation and Prophylactic Measures Against Nursery Outbreaks

Effective programs can prevent one-third of healthcare-associated infections [84]. Every NICU should have rules for providing good hand hygiene to prevent LOS [85]. Environmental disinfection systems and advances in cleaning practices of

medical devices aid in preventing healthcare-associated infections [86]. Removing catheters when no longer necessary is also recommended [87].

13.11.3 Breastfeeding

Breastfeeding has been shown to decrease sepsis and necrotizing enterocolitis (NEC) in premature babies [88].

13.11.4 Chemoprophylaxis and Immunoprophylaxis

Every NICU should have programs for the judicious use of antibiotics and antibiotic stewardship programs [89, 90]. Fluconazole prophylaxis given to ELBW infants decreases colonization and invasive infection due to *Candida* spp. [91]. Loss of intestinal microbial diversity is accused of a predisposing factor to sepsis [92]. In a randomized controlled trial, *Bifidobacterium* and *Lactobacillus* probiotics were given to VLBW infants for 6 weeks [93]. The incidence of NEC and mortality were significantly lower in infants who received probiotics. Enteral lactoferrin has been shown to decrease culture-confirmed LOS [94]. However, studies evaluating this subject are not adequate yet.

13.12 Conclusion

Neonates with meningitis and sepsis have an increased risk of developing HL. Permanent HL is a devastating sequela that can influence speech, cognitive, and developmental issues. Every infant with neonatal sepsis and/or meningitis should be checked and followed up routinely for hearing problems.

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Part III

Focal and Systemic Infectious Diseases

Otitis Externa in Children and Auditory Impairment

14

Seyda Belli, Cemal Cingi, and Suela Sallavaci

14.1 Introduction

Otitis externa refers to any condition in which the epidermis, dermis, or hypodermis of the external auditory meatus becomes infected. Infection may also affect the ear drum or auricle. Otitis externa may occur in various forms, such as acute diffuse, circumscribed, chronic otitis, or malignant (where necrosis is a feature). A number of conditions may be responsible, such as perichondrial inflammation, erysipelas, a fungal infection, herpes zoster of the ear, bullous and hemorrhagic forms, otitis media with a perforated tympanic membrane, eczema, cholesteatoma, or a malignant neoplasm involving the external auditory meatus [1, 2].

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14.2 Etiological and Epidemiological Features

Otitis externa occurs frequently worldwide but is more common in the tropics than in more temperate regions since the tropical climate is warmer and more humid. It is estimated to affect one in ten people during their lifetime [3]. People who swim are five times more likely to develop otitis externa [4], which explains why it is often referred to as "swimmer's ear." Bacterial infections account for at least 90% of cases [4]. The most frequently isolated pathogen is *Pseudomonas aeruginosa* (22–62% of cases), followed by *Staphylococcus aureus* (between 11 and 34%). The simultaneous isolation of multiple pathogens occurs frequently [5]. Fungal infections are infrequent reasons for acute otitis externa (10% of cases) but are more frequently seen where the infection becomes chronic. The usual fungal pathogens are from the genus *Aspergillus* (between 60 and 90%) [1, 6] or Candida (between 10 and 40%) [1]. The prolonged use of antibiotics predisposes to otomycosis. Also at risk are patients who are immunosuppressed or have diabetes mellitus [1].

14.3 Classification

Cases of otitis externa (OE) may be categorized in the following manner [7]

- Acute diffuse OE. This is the most frequently encountered form, with patients usually being swimmers.
- Acute localized OE (furuncle). This occurs when a hair follicle becomes infected.
- Chronic OE has the same features as acute diffuse OE, although it persists for at least 6 weeks.
- Eczematous/eczematoid OE is an umbrella term for a variety of skin disorders that may cause an infection of the external auditory meatus and thus provoke OE. This includes allergic dermatitis, psoriasis, systemic lupus erythematosus, and eczema.
- Malignant (i.e., necrotic) OE occurs when the site of infection extends deep into the tissues surrounding the external auditory meatus. This condition mainly affects patients with immunocompromise (such as those with diabetes mellitus or AIDS).
- Otomycosis refers to an infection of the external auditory meatus caused by fungi, such as *Candida* spp. or *Aspergillus* spp.

14.4 Signs and Symptoms: Otitis Externa and Auditory Impairment

On physical examination, the main signs to look for are pain when the tragal region is touched, or the auricle is pulled (a cardinal sign). There are a number of other potential signs or symptoms to look out for, such as [7]:

- Earache, which may be slight or severe and generally worsens over the course of one to a couple of days.

- Auditory impairment.
- Perception of fullness or pressure in the ear.
- The external auditory meatus may be reddened, swollen, and narrower than usual.
- Tinnitus.
- Pyrexia (in a few cases).
- Pruritus, particularly in chronic OE or otomycosis.
- Pain that is severe and deep in a patient with immunocompromise may signal malignant OE.
- Otorrhea, which begins as a clear fluid, after which pus is seen, accompanied by a foul odor.
- In a few cases, there may be facial or cervical cellulitis, and the lymph nodes of the same side may be swollen and tender.
- Rarely, there may be symptoms from both ears.
- The history often reveals that the patient has been involved in water-based activities, such as swimming, surfing, or canoeing.
- There may also be a history of injury to the ear, frequently as a result of cleaning the ears too energetically, inserting a cotton bud in the canal or taking water into the ears.

14.5 Signs and Symptoms: Otitis Externa and Hearing Loss

OE is typically a clinical diagnosis made on the basis of a matching history and supportive physical findings, not omitting otoscopy. Any patient with diabetes or some other source of immunocompromise and who complains of severe otalgia should be referred to an ENT specialist in case malignant OE is the diagnosis.

14.5.1 Physical Examination

On physical examination, the main signs to look for are pain when the tragal region is touched, or the auricle is pulled (a cardinal sign). The external auditory meatus may be reddened, swollen, and narrower than usual. There may be otorrhea, either clear or containing pus. Auditory impairment of conductive type may be noted. In a few cases, there may be facial or cervical cellulitis, and the lymph nodes of the same side may be swollen and tender [8].

Although it is potentially challenging to get a clear view of the ear drum on otoscopy in such cases, it may be possible to see evidence of tympanic inflammation. The drum should move normally when subjected to pneumatic otoscopy. The auricle may show signs of eczema. If there are signs of the cranial nerves being affected (such as the facial nerve or the ninth to twelfth nerves), the diagnosis cannot be uncomplicated OE [8].

Otomycosis generally causes severe pruritus but is not normally as painful as infection with bacteria. There is frequently an accompanying viscous otorrhea of gray or white color. Infections caused by *Pseudomonas* generally provoke a

green- or yellow-colored discharge of pus, whereas a fungal infection caused by *Aspergillus* resembles a fine mat of white with black spheres resting on top. When the fungal discharge is examined microscopically, spores or hyphae may be seen, or there may be indistinct areas [8].

If the ear is viewed under magnification, the presence of granulation tissue may be apparent within the meatus. Infection may extend into the adjoining soft tissues, including the parotid gland. If the infection tracks into the bone, the mastoid, temporomandibular joint, or basal skull may be invaded, resulting in involvement of CN VII and IX–XII [8].

14.5.2 Laboratory Tests

Generally speaking, the diagnosis does not call for laboratory investigations, although these may be of value where there is immunocompromise, treatment failure, or features suggestive of otomycosis. Potentially useful investigations include the following [7]:

- Gram staining and microscopy of discharge from the ear
- Serum glucose estimation
- Urinalysis

14.5.3 Imaging Investigations

In the majority of patients with suspected OE, imaging is not appropriate. Nonetheless, imaging studies may be required in specific cases, where, for example, malignant OE or mastoiditis is the putative diagnosis.

The following imaging methods may be of value

- High definition computed tomography (CT) is the investigation of choice as it reveals osseous erosion.
- Bone scan utilizing radionucleotides.
- Gallium scan.
- Magnetic resonance imaging (MRI) is less commonly employed than other methods but may be helpful as a second line investigation if there is a suspicion the infection has spread to the soft tissues [9, 10].

14.6 Treatment

The first line in treating OE is to provide analgesia, debride the external auditory meatus, provide topical treatments to counter infection and reduce swelling, and prevent factors that are complicating the situation [8].

The majority of cases resolve with over-the-counter painkillers and ear drops applied to the canal. The ear drops usually employed for this purpose are ones containing ethanoic acid (to manipulate the acidity of the meatus), antibiotics (for bacterial causes), and antifungals. Although OE of eczematous or psoriatic type is frequently responsive to topically applied steroids, such cases may recur or become persistent. There may be a need for regular debridement using suction and under microscopic guidance. If the meatus is very swollen, a wick may be placed in the canal to carry topical treatments deeper into the meatus [8].

Clinical improvement is observed within 7–10 days in 65–90% of treated cases of OE, irrespective of the agent employed [5]. A meta-analysis of randomized controlled trials, conducted by the Cochrane Collaboration, found that equal benefit occurred when either antiseptic or antibiotic medications were used. Monotherapy was as effective as combination treatments and the addition of steroids did not affect the outcome [11]. When corticosteroids were applied topically, however, it was noted that there was a reduction in erythema and ear discharge. Some of the trials included did purport to indicate varying outcomes, depending on whether a single or multiple agents were employed in treatment. The wide variety of different agents employed means that meaningful conclusions about best practice were difficult to draw [11].

In a systematic review that compared topical antibiotic agents with placebo, the active agent was associated with a 46% increase in resolution as assessed clinically, or 61% when assessed bacteriologically [12]. In cases of tympanic perforation, agents with known ototoxicity should not be used. The use of a gauze wick impregnated with medication as monotherapy appears to increase the efficacy of topically applied agents and to reduce swelling from inflammation, but no randomized trial of this method has yet been reported [11].

14.6.1 Antibiotics

Since the majority of patients with OE have a superficially located bacterial infection of the ear canal, a topically applied antibiotic solution is generally appropriate. Sometimes the antibiotic is combined with a corticosteroid. The dose of corticosteroid involved is low, but sufficient to reduce otalgia and swelling in the canal [8].

14.6.1.1 Hydrocortisone/Neomycin/Polymyxin B (Cortisporin, Cortomycin)

This agent is a combination of antibiotic and anti-inflammatory intended to be applied to the ear. It comes in solution or suspension forms. The indication is where OE is caused by a condition susceptible to treatment by corticosteroid and either a bacterial infection already exists or there is a danger of one occurring [8].

14.6.1.2 Ofloxacin Ear Drops

This antibiotic is a broad-spectrum quinolone that prevents bacterial multiplication through inhibition of DNA gyrase. It is supplied as a solution containing ofloxacin 3 mg/mL (i.e. 0.3%) [8].

14.6.1.3 Ciprofloxacin Otic (Cetraxal)

Ciprofloxacin is another agent that interferes with bacterial DNA replication through inhibition of DNA gyrase. It is classed as a fluoroquinolone. Bacterial species with sensitivity to this agent include *Pseudomonas* spp., *Streptococcus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), *S. epidermidis*, and the majority of Gram negatives. It is not effective against anaerobic bacteria. Preparations are available alone or in combination with hydrocortisone. Cetraxal is an ear drop that is supplied as 14 single-use applicators, each of which carries 0.25 mL of a 0.2% solution of the antibiotic.

Ciloxan is an eye drop that is also suitable for use in cases of OE [8].

14.6.1.4 Dexamethasone/Tobramycin (TobraDex)

Tobramycin works by disrupting the bacterial outer membrane. It prevents the bacterium from manufacturing proteins by forming a bond to the 30S and 50S subunits of the bacterial ribosome. Dexamethasone exerts an anti-inflammatory effect through preventing recruitment of polymorphonuclear leucocytes and decreasing the permeability of the vascular endothelium.

TobraDex is an eye drop that is of value in treating OE.

14.6.1.5 Gentamicin Ophthalmic (Garamycin, Gentak)

Gentamicin is classified as an aminoglycoside. It has activity against Gram negative organisms. This agent is an eye drop that is suitable for treating OE. The preparation is a mixture in which 1 mL contains both gentamicin sulphate 3 mg and betamethasone sodium phosphate 1 mg [8].

14.6.1.6 Ciprofloxacin and Dexamethasone Otic (Ciprodex)

As stated earlier, ciprofloxacin is classified as a fluoroquinolone. Its mode of action is inhibition of DNA gyrase and DNA topoisomerase. Thus, it prevents bacteria from replicating and manufacturing gene products. Bacterial species with sensitivity to this agent include *Pseudomonas* spp., *Streptococcus* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), *S. epidermidis*, and the majority of Gram negatives. It is ineffective against anaerobic bacteria. Dexamethasone exerts an anti-inflammatory effect through preventing recruitment of polymorphonuclear leucocytes and decreasing the permeability of the vascular endothelium. It also lessens otalgia [8].

Ciprodex has an indication for OE, and may be used for cases of otitis media in patients with grommets in situ.

14.6.1.7 Ciprofloxacin and Hydrocortisone Ear Drops (Cipro HC Otic)

Ciprofloxacin is classified as a fluoroquinolone. Its mode of action is inhibition of DNA gyrase and DNA topoisomerase. Thus it prevents bacteria from replicating and manufacturing gene products. Bacterial species with sensitivity to this agent include Pseudomonas spp., Streptoccus spp., methicillin-resistant *Staphylococcus aureus* (MRSA), *S. epidermidis* and the majority of Gram negatives. It is ineffective against anaerobic bacteria. Hydrocortisone exerts an anti-inflammatory effect through preventing recruitment of polymorphonuclear leucocytes and decreasing the permeability of the vascular endothelium [8].

14.6.2 Debriding and Draining the Ear Canal

The external auditory meatus is generally only debrided in cases of malignant OE or if complications occur, such as stenosis of the meatus. Debridement is frequently indicated if OE is highly severe or if there is a high level of otorrhea. This procedure is usually undertaken by an ENT specialist utilizing the operating microscope and suction equipment. For otomycosis, debridement is a key component in treatment.

Abscess formation within the external auditory meatus is unusual but may result from infection with *S. aureus*. The abscess can be treated straightforwardly by incising the lesion and draining it. Typically, an ENT surgeon uses a small bladed scalpel or needle to achieve this [8].

14.6.3 Complications

Although complications seldom occur, potential complicating factors include the following [8]

- Malignant OE, development of which heralds an emergency
- Mastoiditis
- Inflammation of the collagenous tissue in the pinna, by extension, especially in individuals whose ears have recently undergone piercing
- Osteomyelitis of the basal skull, causing osseous erosion [13]
- Invasion of the brain or spinal cord
- Cellulitis or lymphadenitis

Diabetic patients with these complications frequently also have diabetic ketoacidosis.

Herpes zoster may resemble OE at the start, with blisters erupting 1 or 2 days later. An infrequently occurring complication of herpes zoster is the Ramsay Hunt syndrome, in which patients develop a one-sided palsy of the seventh cranial nerve peripherally. Patients with herpes zoster should be informed about this potential complication and be instructed to consult a physician if symptoms develop [14].

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Necrotising (Malignant) Otitis Externa and Auditory Impairment in Children

15

Neslihan Sarı, Songül Demir, and Nuray Bayar Muluk

15.1 Introduction

Malignant otitis externa, also referred to as necrotising otitis externa (NOE), results from infection of the external auditory meatus and the temporal bone. The most frequent pathogen responsible is *Pseudomonas aeruginosa*, with elderly, diabetic individuals those most at risk of developing the condition. NOE develops from otitis externa when osteomyelitis of the temporal bone develops. The infection can track into the bone via the fissures of Santorini and the junction between the cartilage and bone [1].

It seems that the first reported case of NOE dates from 1838, when Toulmouche described its occurrence. There is a report from 1959 in which Meltzer describes osteomyelitis of the temporal bone secondary to *P. aeruginosa*. Chandler argued in 1968 for the existence of NOE as a distinct clinical entity [2]. Chandler attached the term 'malignant' to his description on account of the aggressive nature of the condition, the low response to treatment, and the large number of associated deaths in patients with the condition [3].

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Since Chandler was writing, antibiotics with activity against *P. aeruginosa* have been developed, and this has meant an improvement in the prognosis. Accordingly, some experts favour discontinuing the use of the epithet 'malignant' as it no longer accords with a realistic picture of the usual clinical situation [3]. Throughout this chapter, the term necrotising otitis externa (NOE) will be used.

15.2 Pathophysiology

Necrotic otitis externa results from infection of the external auditory meatus and temporal bone. The pathogen responsible is typically *P. aeruginosa*, and the condition frequently affects elderly, diabetic individuals. Otitis externa becomes NOE when it invades the temporal bone, setting off an osteomyelitic reaction. The path taken by the pathogen is through the fissures of Santorini and the junction between the bony and cartilaginous canal [1].

The pathogen may invade other tissues, leading to osseous erosions and distant spread via the planes of fascia and venous sinuses. It may affect the basal skull and the adjacent structures, causing damage to the cranial nerves and entering into the cranial cavity [4].

If the pathogen spreads to the temporal bone via the fissures of Santorini, it may pass through the stylomastoid foramen and jugular foramen, through which cranial nerves VII, IX, X and XI pass. Where the infection tracks through the junction of the bone and cartilage of the external auditory meatus, it passes subtemporally to the retrocondylar and parapharyngeal adipose tissues, the temporomandibular joint, and the masticator muscle [5].

The routes followed by pathogens in NOE can be classified in the following way [4]

- Anterior route. The infection tracks to the masticator, the interior of the mandibular condyle, the parotid gland, seventh cranial nerve, fossa of the temporal bone, temporomandibular joint and the stylomastoid opening.
- Medial or crossed route. The infection invades the adipose tissue surrounding the pharynx, the musculature of the nasopharynx, cranial nerves IX–XI, the sphenoid, clivus, jugular foramen and the apical portion of the petrous temporal bone.
- Intracranial. If the dura mater is thickened, the infection may track to the signoid sinus, jugular vein, internal carotid artery, jugular fossa and the dura.
- Posterior. The pathogen may spread to the bony mastoid, but no soft tissues are invaded by this route [6].

In addition to the above, infection may spread intravascularly, especially where the causative pathogen is a fungus. Nonetheless, otomycosis rarely affects the temporal bone [7].

15.3 Mortality and Morbidity

15.3.1 Cranial Nerve Palsies

Inflammation around the basal skull may directly affect the cranial nerves, or a palsy may result from toxins secreted by Pseudomonal organisms. The seventh cranial nerve is the most frequently affected in this way, with the site usually being the stylomastoid foramen. Continuing spread of the infection leads to the glossopharyngeal, vagal and accessory nerves developing a neuropathy at the site of the jugular foramen. Finally, the 12th cranial nerve is affected within its canal. If the infection spreads to the apical portion of the petrous temporal bone, the trigeminal and abducens nerves may be affected [3].

Chandler stated that a seventh cranial nerve paralysis was present in 32% of cases in 1977 [8], but this now seems to have gone down with the advent of antibiotic treatment effective against *Pseudomonas*. Franco-Vidal et al. [9] noted that only 20% of a group of 46 cases undergoing treatment had paralysis of the seventh cranial nerve. Cranial neuropathies other than facial palsy are rarer. It was previously considered that the development of a cranial nerve palsy heralded severe otitis externa and meant a poor clinical outlook, but it has now been proposed by both Soudry et al. and Mani et al. that the clinical outcome is not affected by whether a seventh nerve palsy is present or not [10, 11]. Resolution of a seventh cranial nerve palsy can be problematic, and unexpected outcomes do occur; hence, clinicians should not consider that cure has been achieved if the symptoms fully resolve. For the other cranial nerve palsies, resolution is generally more frequent than for the facial nerve [3].

15.3.2 Intracranial Extension

Intracranial spread is seldom seen without there being present a cranial neuropathy. Spread into the cranial cavity may cause meningitis, a cerebral abscess or thrombus formation in the cranial sinuses. A cranial nerve palsy suggesting the jugular foramen is affected ought to prompt a search for thrombus formation in the sigmoid sinus. A trigeminal or abducens palsy should raise suspicion of thrombus within the cavernous sinus. Spread into the cranial cavity indicates high severity of NOE and often results in death [3].

15.3.3 Comorbidities

It is virtually invariably the case that a patient with NOE is also diabetic, and there may well be other comorbidities in addition [12]. In Chandler's study, mortality occurred due to pneumonia, uraemia, myocardial infarction, cerebrovascular accidents, and hepatic failure. Cases where systemic immunodeficiency is present fare less well, as Franco-Vidal has demonstrated [9].

A Taiwanese study reported by Yang et al. using a case-control design and based on the general population across the island noted that NOE was associated with diabetes mellitus. The authors noted that the frequency of diabetes mellitus amongst patients with NOE was 54.8%, whereas diabetes only occurred in 13.9% of control subjects. For patients suffering from NOE, the adjusted odds ratio for having a pre-existing diagnosis of diabetes was 10.07 [13].

Sylvester and colleagues looked at 8300 cases where NOE was the diagnosis. These cases were sourced from the National Inpatient Sample database between the years 2002 and 2013. It was discovered that cases where the patient was an adult or older adult and diabetic were more likely to suffer from co-morbid conditions, require a longer in-patient period (5.5 days in diabetics compared to 4.0 days where diabetes was not present) and paid more for their care (on average $25,118 compared to $17,039). Despite these differences, the risk of dying as an in-patient did not differ at the level of statistical significance between diabetic and nondiabetic patients (0.6% compared to 0.5%) [14].

15.4 Aetiology

- Diabetes mellitus (present in 90% of cases) [3]:
  - The highest risk for NOE is found in those individuals with diabetes.
  - Diabetic changes in the small-calibre vessels and less effective immunity in diabetics explains this association.
  - Ear wax in diabetic patients is less acidic than normal and contains less lysozyme. This may lead to less localised bactericidal activity.
  - Diabetes mellitus types I and II both predispose equally to NOE.
  - There does not appear to be a straightforward relationship between how long or how severely raised the blood glucose level is.
- Immunodeficiency, which may be secondary to a disorder such as a lymphoproliferative condition or may be drug-related.
- AIDS [3].
  - Cases of NOE occurring in association with AIDS may differ in their pathological features from non-AIDS-associated cases.
  - The symptomatic presentation is similar to other cases, but the age at onset is lower, and the patient is not diabetic.
  - Granulation tissue may not form within the ear canal.
  - There may be a different pathogen responsible, unlike other cases, which are typically due to *P. aeruginosa*.
  - The prognosis in this group of patients is worse in general than in patients who are diabetic.
- Ear irrigation/washout. Up to half of all cases of NOE have a history of trauma secondary to ear washing out and are diabetic [3].

15.5 Epidemiology

- Although the introduction of antibiotics with activity against a broader range of micro-organisms has decreased the frequency of NOE, it is still by no means a rare disorder [1].
- Although cases occur across the entire age range, it is most frequently seen in older adults (i.e. above the age of 60 years [15].
- NOE has a male predilection [16].
- The incidence rises in locations where the climate is typically humid [17].
- NOE is seldom seen in children [18].

15.6 Signs and Symptomatology of NOE

Signs of inflammation are seen within the ear canal and the soft tissues surrounding the pinna. The degree of otalgia is greater than would be expected from the physical findings alone. The area lying between the ramus of the mandible and the tip of the mastoid is very tender to palpation. Granulation tissue is visible on the floor of the external auditory meatus at the junction between the bony and cartilaginous canal. If granulation tissue is observed at this location, the diagnosis is almost certainly NOE. There may be bare bone visible on otoscopy [3].

There are several other features in the clinical presentation to look out for, such as the following [3]

- Presence of diabetes mellitus (in 90% of cases) or a reason for the immune system to be suppressed (either due to another condition or drug-related).
- Ear ache is felt deeply and severely and does not stop. It is especially bothersome at night.
- Headaches are felt around the temples.
- Pus may be discharged from the ear, with a foul odour.
- Swallowing may be impaired, and there may be dysphonia +/− signs of a seventh cranial nerve palsy.

15.7 Complications, Including Auditory Impairment, in NOE

NOE may cause auditory impairment of conductive type. It varies in severity. If NOE is of high severity, a cranial neuropathy may be evident. A seventh cranial nerve neuropathy is the initial development, but if the condition progresses, the glossopharyngeal, vagus and accessory nerves may be affected. The basal skull develops osteomyelitis, stretching from the stylomastoid to the jugular foramen, or even further [19].

15.8 Physical Examination

- Signs of inflammation are seen within the ear canal and the soft tissues surrounding the pinna.
- The degree of otalgia is greater than would be expected from the physical findings alone.
  - The area lying between the ramus of the mandible and the tip of the mastoid is very tender to palpation.
  - Granulation tissue is visible on the floor of the external auditory meatus at the junction between the bony and cartilaginous canal. If granulation tissue is observed at this location, the diagnosis is almost certainly NOE. There may be bare bone visible on otoscopy.
- A neurological examination of the fifth to twelfth cranial nerves should be undertaken.
- Assessment of mental state is needed. Any change in mental state may potentially signify extension of infection into the cranial cavity.
- The ear drum is typically normal.
- Pyrexia is rarely noted [3].

The most effective approach to diagnosing NOE involves the use of the diagnostic criteria first proposed by Cohen and Friedman [4]. The diagnostic scheme involves major criteria, which must be present to make the diagnosis, and minor criteria, which represent features that are sometimes present.

Major Diagnostic Criteria
- Otalgia, which is frequently greater than physical examination might suggest
- Swelling
- Discharge
- Granulation tissue formation within the external auditory meatus
- Microabscess (visible during a surgical procedure)
- Imaging evidence from radioisotopic technetium scan (^{99}Tc)
- Topical treatment does not lead to resolution within 7 days

Minor Diagnostic Criteria
- Diabetes mellitus
- Cranial neuropathy
- X-ray evidence
- Debilitation
- Elderly patient

To diagnose NOE, the major diagnostic criteria must apply. The existence of minor criteria alone is insufficient to confirm the presence of NOE [20, 21].

There should be a neurological examination, focused on the cranial nerves, which are frequently involved in cases of NOE.

- The seventh cranial nerve is the most frequently involved.
- The ninth, tenth, and eleventh cranial nerves may also be affected.
- The 12th cranial nerve is not usually affected [11].

The patient's mental state must also be assessed, as any change in this may indicate that there is involvement of the intracranial cavity [22].

15.9 Diagnosis

There is generally either no leucocytosis or at most a mild leucocytosis in NOE. A left shift is an infrequent finding. However, in every case, the erythrocyte sedimentation rate (ESR) is raised. The mean value is 87 mm h^{-1} [3].

In cases where there is pre-existing diabetes mellitus, a biochemical profile is required to assess any metabolic effects of the infection. If there is no previous diagnosis of diabetes, testing should be undertaken for impairment of glucose tolerance [3].

Wherever feasible, any otic discharge should be cultured prior to starting antibiotic treatment. The pathogen occurring with the highest frequency (95% of cases) is *P. aeruginosa*. Radiological investigations are key to assessing whether osteomyelitis is present, and if so, how extensive it is and how it responds to treatment. Suitable investigations include a bone scan with Tc99m methylene diphosphonate, a gallium-67 citrate study, scans using indium-111 leucocytic labelling, computed tomography (CT) or magnetic resonance imaging (MRI) [3]. A histological specimen of the external auditory meatus should be sent for evaluation of potential malignancy or other conditions [3].

15.9.1 Imaging Investigations

Imaging plays a key role in diagnostic work-up, since it can confirm whether osteomyelitis is present and, if so, how extensive it is and how it responds to treatment [3].

15.9.2 ^{99m}Tc Methylene Diphosphonate Bone Scan

Imaging of the bone using 99mTc methylene diphosphonate works by labelling osteoblasts. Even if the osteoblasts are only 10% more active than usual, this change can be seen on the scan. The result lacks specificity, however, as the same appearances may also result from a neoplastic or dysplastic bone lesion, which both increase osteoblastic activity. Nonetheless, this investigation is helpful in appropriate situations since a positive result confirms the clinical impression [3].

This form of imaging cannot supply information about whether the lesion is responding to treatment because the osteoblastic activation continues for a considerable period after clinical resolution. It also has limitations in cases where there has

been mastoiditis or ear surgery in the past. Historically, the scan suffered from low spatial resolution, but the advent of single-photon emission computed tomography (SPECT) has somewhat improved this situation [3].

15.9.3 Gallium-67 Imaging Scan

Although imaging using a gallium-67 tracer benefits from high sensitivity, the specificity is low since this isotope is bound to any actively mitotic cell, whether in inflammation, neoplasia or osteoblastic activation. Thus, a positive scan may be difficult to interpret diagnostically, since it may represent inflammation or another lesion of the soft or osseous tissues. Its main value lies in the evaluation of response to therapy. A less active lesion on imaging indicates treatment success in this setting. The usual method is to scan the patient when NOE is first diagnosed to allow meaningful comparison with later scans as treatment progresses [3].

If the two ears are compared in a quantitative manner, so that the diseased ear is compared with the normal ear, imaging may be able to differentiate between acute otitis externa and NOE and may indicate how successful treatment has been. Once again, by using SPECT, there can be an improvement in the level of spatial resolution the scan can offer [3].

15.9.4 Imaging Utilising Indium-111 Leucocytic Labelling

Imaging that uses the indium-111 radioisotope to label leucocytes is as sensitive as the gallium-67 method but offers greater specificity in identifying inflammation. It does not appear to be superior as a nuclear medical technique for diagnosing NOE, but it is possibly superior in terms of monitoring when therapy has succeeded. Scans used for other chronic osteomyelitic lesions at other body locations suffer from a lack of reliability; thus, further investigation is needed into how reliable this technique is in cases of NOE [3].

15.9.5 CT and MR Imaging

Both CT and MRI offer benefit in locating where soft tissue inflammation occurs, identifying an abscess and assessing possible extension into the cranial cavity. CT has limited ability to highlight osteomyelitis in its initial stages, since it can only detect the lesion following 30–50% osseous destruction. MRI, on the other hand, is not the ideal method to image bone. Response of the lesion to treatment is apparent on CT and MRI as regression of soft tissue changes. The osseous tissues appear abnormal on CT for more than 1 year. MRI does not reveal these osseous changes clearly. Accordingly, neither CT nor MRI can determine whether the osteomyelitis has fully resolved.

Goh and colleagues [23] examined MR images retrospectively. They ascertained that there were differences apparent between cases of advanced malignancy of the nasopharynx and NOE. In the latter, the findings were that the lesion extends laterally, there is enhancement of the surrounding soft tissues on T2 weighted scans, the architecture does not become distorted, and the enhanced areas have the same signal as mucosa or even higher [23].

The majority of the literature is in favour of undertaking CT imaging at the initial stage of diagnosis. Benecke, however, believes that CT should only be requested where the cranial nerves are involved, the Tc99m scan indicates osteoblastosis, or the lesion does not show a clinical response to therapy. According to both Grandis et al. and Okpala et al. CT imaging should be undertaken at an early stage in management. Peleg et al. found that the size of the lesion on CT imaging performed at the beginning of treatment correlated with the clinical progression [24].

Whilst MRI and CT have the same associated sensitivity for detecting soft tissue involvement, MRI has superior sensitivity for evaluating spread into the cranial cavity [3].

15.10 Therapy

The management of NOE may involve scrupulous control of blood sugar, manual cleaning of the ear, both topical and systemic antibiotics and hyperbaric oxygen administration [25, 26]. Currently, operative intervention is indicated where there is an area to be debrided, there are sequestrated lesions in the bone or an abscess needs to be drained [3].

15.10.1 Antimicrobial Treatment

- Pharmacotherapy consists of systemic antibiotics using agents that are active against *Pseudomonas* spp. One of the fluoroquinolone agents is usually chosen if the pathogen is *P. aeruginosa*. Since ciprofloxacin is very widely used in cases of upper respiratory tract infection, drug-resistant organisms have been extensively documented [7]. This agent may be given by mouth to patients in the community provided there is no cranial neuropathy, and they do not require hospitalisation for analgesia and stabilisation of diabetes mellitus. In cases of treatment resistance, antibiotics of beta lactams which are active against *Pseudomonas* +/− an aminoglycoside can be administered intravenously [4].
- Whilst *P. aeruginosa* is the pathogen responsible in the majority of cases of NOE, there are other microbes that may cause the condition, and thus, treatment selection should be guided by identification of the pathogen.
- How long treatment goes on for is dictated by how well the lesion responds to treatment. Progress should be monitored by means of a gallium-67 scan each 4–6 weeks whilst therapy continues.

- Pharmacotherapy continues for 7 days after the last normal result from a gallium-67 scan [4].

15.10.2 Hyperbaric Oxygen Administration

- The use of hyperbaric oxygen in treating NOE is common, but multiple researchers have demonstrated that it adds no additional benefit to pharmacotherapy with or without operative intervention [26, 27].

15.10.3 Operative Interventions

- Surgical interventions are only used where pharmacotherapy alone does not result in resolution of the lesion. Operative interventions consist of debriding a particular area, excising sequestered lesions in bone and draining of abscesses. Decompression of the seventh cranial nerve is not required in cases of facial neuropathy since it has no effect upon the outcome [28, 29].

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Acute Otitis Media and Hearing Loss in Children

16

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16.1 Introduction

For children below the age of 5 years living in the United States, acute otitis media (AOM) is the most frequently occurring indication for pharmacotherapy. AOM is defined as acute inflammation of the middle ear resulting in typical signs and symptoms and having a maximum duration of 3 weeks [1–4].

Although AOM and the related otitis media with effusion (OME) each cost the American economy billions of dollars every year and have been intensively investigated, both in terms of how they can be prevented and how best treated, the incidence has not fallen significantly, and the cost keeps going up [1].

Whereas AOM by definition refers to a disorder of maximum 3-week duration with signs and symptoms consistent with an acute inflammatory process, the definition of OME stipulates that fluid be found in the middle ear, and there should be auditory impairment of conductive type but no signs or symptoms indicating an acute process. If the period for which OME exists is between 3 weeks and 3 months

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after the beginning of AOM, it is described as ‘subacute’, whereas OME lasting beyond this time is termed ‘chronic’ [2, 3].

Conventionally, AOM has been treated by antibiotic therapy, and this still remains the first line of therapy, despite concerns arising from the growing numbers of antibiotic-resistant bacterial pathogens isolated. In cases where operative interventions are required, there are three alternative techniques used: tympanocentesis, myringotomy and myringotomy with grommet placement [1].

16.2 Pathophysiology

The key triggering event for the development of AOM seems to be blockage of the auditory tube. By far, the most common cause is an upper respiratory tract infection that affects the nasopharyngeal region [1].

16.2.1 Infections by Bacteria and Viruses

Although the upper respiratory tract infection is typically caused by a virus, other pathological processes that affect the patency of the auditory tube, such as an allergic reaction or other cause of inflammation, may result in a similar pathology. Nasopharyngeal inflammation affects the medial portion of the auditory tube, provoking stasis and an inflammatory response. The middle ear pressure is changed by these events, being, in most cases, lower than the surrounding pressure, although sometimes higher.

Since stasis develops, this sets up the necessary conditions for bacterial pathogens to colonise the middle ear cavity, an area which is usually sterile. Nasopharyngeal bacteria may enter through being refluxed, aspirated or insufflated into the auditory tube.

There develops an acute inflammatory response to the presence of the pathogen. This consists of dilation of blood vessels, formation of an exudate, recruitment of white cells to the area, phagocytosis of the offending organism and localised immune responses in the middle ear cavity. This response accounts for the way AOM presents clinically [1].

16.2.2 Immunological Factors

There may be an important immunological component to how commonly AOM occurs and its eventual outcome. There has been a greater research focus on immunological factors in OME than in AOM; however, there are also demonstrable effects of the patient’s immunocompetence on AOM, too. These include the following [1]:

- The ability to synthesise immunoglobulins can ensure the middle ear is cleared of the pathogen following the initial invasion.

- Being exposed to the same pathogen before, or being vaccinated against it, may offer some protection by preventing the pathogen's presence within the nasopharynx.
- Patients whose immune systems can synthesise immunoglobulins during the acute phase may not suffer from future episodes, or, if they do occur, attacks may be less serious. However, the neutralising antibodies against *Streptococcus pneumoniae* and *Haemophilus influenzae* target bacterial polysaccharides, and these develop later than antibodies directed against bacterial proteins or glycoproteins.
- Mild immunodeficiency or immunodeficiency of brief duration may cause repeated middle ear infections.

16.3 Aetiology

16.3.1 Pathogenic Viruses

Respiratory syncytial virus (RSV) is usually found in bronchiolitis or pneumonia in young children, although it is potentially capable of producing acute respiratory infections in patients at all ages [5–7]. In northern locales, RSV typically appears in the course of epidemics occurring over winter or in the first weeks of spring; however, any newborn who appears lethargic, irritable or apnoeic should be suspected of harbouring RSV, regardless of whether a middle ear infection is present. Children who are beyond the neonatal period usually have symptoms that point more clearly to a respiratory infection and are thus more straightforward to diagnose.

It has long been recognised that RSV can cause longer term lung problems in up to 50% of cases of bronchiolitis occurring amongst infants. The usual sequela is asthma. This virus is especially liable to cause death in those born with congenital cardiac disorders, cystic fibrosis, immune deficiencies, dysplasia of the bronchi and lungs or those delivered earlier than 37-week gestation.

The only indication for use of intravenous immunoglobulin targeting RSV is in children at high risk. It is vital that clinical management of children who have otitis media at the same time as pneumonia, or systemic disorders, involves consideration of the whole picture when deciding on treatment. In certain patients, draining the ear through performing tympanocentesis or myringotomy is required, with any aspirate sent for microbiological culture and sensitivity testing. If a newborn is thought to be in sepsis or a child has immunosuppression, draining the middle ear is obligatory [1].

16.3.2 Pathogenic Bacteria

In 50% or more of paediatric cases of AOM, a bacterial pathogen is cultured from a middle ear effusion. In a further 25%, where culture is negative, DNA testing finds bacterial DNA or remnants of the bacterial cell wall. In most patients, except those

under the age of 6 weeks, four bacterial pathogens are the causative organisms, namely, *S. pneumoniae*, *H. influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*. Certain other pathogens may also be identified in AOM, such as *Staphylococcus aureus*, alpha-haemolytic *Streptococci* and *Pseudomonas aeruginosa*.

Just as with other conditions treated by antibiotics, pharmacotherapy of AOM increasingly needs to take into account the possibility of an antibiotic-resistant organism as the causative pathogen [8]. The mechanisms through which bacteria acquire resistance to specific agents will be discussed in the context of each particular pathogen known to cause AOM [1].

16.3.2.1 *Streptococcus pneumoniae*

Infections due to *S. pneumoniae* are the most common in AOM, as is the case for all invasive infections by bacteria in children, regardless of age [9]. This organism is a diplococcus, which is Gram-positive. Serotyping reveals 90 different variants, which differ in terms of their antigenic polysaccharides. The serotypes occur with different frequencies depending on the age of the patient and where he or she lives. Some 29–40% of cases where a pathogen is cultured are a result of *S. pneumoniae*, but the number of cases is actually higher, since antigenic components of *S. pneumoniae* can be identified in around 33% of culture-negative isolates [1].

Thus, *S. pneumoniae* potentially causes more than half of cases of AOM. In the United States, the majority of cases where this organism causes invasive infection of any kind can be attributed to the following serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F. In cases of AOM, the most frequently identified serotypes are 19, 23, 6, 14, 3 and 18, with frequencies of 23%, 12.5%, 12%, 10%, 8.5% and 6%, respectively. Being vaccinated with Pneumovax 23 (a polyvalent vaccine) provides immunity to around 85% of the pneumococcal variants that cause AOM [1].

Although at one time *S. pneumoniae* could generally be successfully eradicated using any of the antibiotics in frequent use, in particular penicillin G, erythromycin or the majority of sulfonamides. These antibiotics targeted the penicillin-binding protein located on the bacterial cell wall. This target has now mutated in some variants, with the result that multidrug-resistant *S. pneumoniae* (MDRSP) are no longer sensitive to beta-lactam type agents, macrolides or the sulfonamides. Indeed, up to 40% of pneumococci may now withstand treatment with antibiotics of beta-lactam, macrolide or sulfonamide type. The serotypes most likely to be insensitive to penicillin are 6B, 9V, 14, 19A, 19F and 23F [1].

16.3.2.2 Heamophilus İnfluenza

H. influenzae occupies the second rank in the list of bacterial pathogens most commonly identified in aspirated fluid from cases of AOM. It accounts for around one in five of cases in children under school age [10]. This organism may be more common in paediatric cases where otitis recurs and the child is somewhat older or in adults vaccinated against streptococci [1].

Martin et al. examined cases of AOM, which occurred from 1991 to 2014 in children over the age of 6 months but under 2 years. They ascertained that *S.*

pneumoniae was less prevalent in the nasopharynx following introduction of the pneumococcal conjugate vaccine, but the number of individuals colonised with *H. influenzae* then went up for some time before falling to the original level recorded at a time when the heptovalent pneumococcal vaccine (PCV7) was not routinely given. For this study, four different paediatric cohorts were examined. In each case, the study looked at culture of swabs obtained from the nasopharynx. The initial cohort dated to 1999–2000, at a time when PCV7 was not routinely provided. The second and third set of cultures dated from 2003–2005 and 2006–2009, respectively. At the time of the second set, 93% double vaccination levels applied, whereas by the time of the third set, this figure was 100%. The final set came from 2012 to 2014, when at least double vaccination with a triskaideka-valent conjugated vaccine (PCV13) was universal. Colonisation of the nasopharynx with *H. influenzae* was proven in 26% of the initial cohort, 41% of the second, 33% of the third and only 29% of the fourth [11].

16.3.2.3 *Moraxella catarrhalis*

Fifty years ago, the organism now called *M. catarrhalis* was not considered a pathogen causing otitis media, despite it being identified in around one in ten cases where an aspirate was cultured. The bacterium was also believed at that point to be within the Neisseria genus. In the 1970s, it was rare for *M. catarrhalis* to exhibit resistance to ampicillin and related penicillin. Since then, not only has the organism been twice reassigned to different genera (first to *Branhamella* and now to *Moraxella*), it has become virtually invariably resistant to beta-lactam antibiotics that resemble ampicillin and is recognised as a pathogen in approaching 25% of paediatric cases of AOM.

M. catarrhalis is a normal component of the bacteria flora within the upper respiratory tract. It is Gram-negative and is a diplococcus. Its ability to withstand beta-lactam arises from possession of several isoenzymes performing a lactamase function. The genes coding for these enzymes may reside on the chromosome or on plasmids. Furthermore, they may only be expressed at significant levels when an antibiotic is used. Possession of more than one lactamase by the bacterium is possible [1].

16.3.2.4 Anaerobes

Although anaerobes are found in some paediatric cases of AOM where the contents of the middle ear are cultured, it appears that they do not act as significant pathogens responsible for otitis media, especially in the acute form. It is possible that anaerobes are of greater significance where adenoiditis becomes chronic and a biofilm is secreted. It is unusual for an aspirate to yield only an anaerobe when cultured. Usually, another pathogenic species is also grown [1].

16.3.2.5 Frequently Noted Pathogenic Bacteria in Neonates

Around the time of birth, the usual pathogens, which cause sepsis or meningitis, are *Escherichia coli*, Enterococci or Group B streptococcal organisms. It is not unusual for a middle ear aspirate to yield one of these pathogens, but they likely constitute no more than one in ten of the pathogens causing AOM in newborns.

The single pathogen most frequently identified in AOM, regardless of age, is still *S. pneumoniae*. In second place come *H. influenzae* organisms lacking a capsule or the untypeable variants, which may cause invasive infections in newborn infants [1].

16.4 Risk Factors

There is evidence to confirm all of the following are risk factors for the development of middle ear infections [1]

- Premature birth and low body weight on delivery
- Extreme youth
- A first episode occurring early
- Family history
- Ethnic inheritance. Native Americans, Inuits and Australian aborigines are at increased risk
- Immunodeficiency
- Abnormal development of skull or face
- Neuromuscular disorders
- Allergic conditions
- Attending childcare facilities
- Overcrowding at home
- Socioeconomic disadvantage
- Being exposed to smoking or other air pollution
- Using a dummy
- Sleeping face down
- Seasonal—infections are more common in winter and autumn
- Not breastfed or bottle feeding continued for longer than usual

16.5 Epidemiological Aspects

Seven out of ten American children have at least one episode of AOM before they reach the age of 2 years. Researchers based in Pittsburgh who prospectively tracked a cohort of children living in the city or countryside up to the age of 2 years found that 48% of children had had a middle ear effusion by the age of 6 months, 79% by the first birthday and, by the second birthday, 91% had suffered a middle ear effusion [12].

The age at which AOM is most common in paediatric patients is between 3 and 18 months. A child who has an initial episode of AOM as a neonate is at elevated risk of recurring middle ear infections. When Megged et al. compared paediatric patients with a first episode of AOM in the neonatal period with those where the episode occurred later, they found the incidence was raised three times (30% vs 10%) [13].

16.5.1 Demographic Characteristics—Age, Sex and Ethnicity

There is an increased tendency to develop AOM between the ages of 6–11 months, and the incidence falls at the time the child reaches the age of approximately 18–20 months. Male children are at somewhat greater risk than females. The onset of AOM in some children begins after the age of 3 or 4 years. Once the permanent dentition has erupted, the number of episodes greatly decreases, albeit certain patients remain susceptible to recurrent attacks up to when they turn adult. On rare occasions, adults who are suffering with acute viral infections of the upper respiratory tract but have not had middle ear infections before present with a de novo episode of AOM [1].

There are also clear ethnic differences in the rate of AOM, with Native American or Inuit individuals prone to a highly elevated incidence of ear infections, both acute and chronic. By contrast, African American children are somewhat less prone to ear infections than their Caucasian peers [1].

16.6 Signs and Symptoms

Despite some variability in presentation at different ages, during the time when children are most likely to develop ear infections, there are several features that tend to be consistent, such as the following [1]:

- The sole sign of an infection in many newborns is irritability or difficulty feeding.
- Older children typically present with pyrexia and earache, or keep pulling at their ears.
- Auditory impairment is usually present in cases of AOM or OME in older children or adults. The ear may feel blocked prior to any demonstrable fluid in the middle ear cavity.

Adults who present with earache but neither auditory impairment nor pyrexia are likely to have otitis externa, a tooth abscess or a temporomandibular joint problem causing referred pain. It is common for dental prostheses to cause referred pain on account of their changing how occlusion occurs.

16.7 AOM and Auditory Impairment

AOM and OME is invariably accompanied by auditory impairment in an older child or adult. Prior to fluid accumulating in the middle ear patients complain of ear blockage. If a patient complains of earache but has neither loss of hearing nor pyrexia, the cause may be otitis externa, a tooth abscess or a temporomandibular joint problem causing referred pain. It is common for dental prostheses to cause referred pain on account of their changing how occlusion occurs.

In its acute stage, AOM causes auditory impairment of conductive type [14]. It has also recently been shown that auditory loss of sensorineural type also occurs in cases where AOM is acute or recurring. The loss particularly affects higher pitched sounds in the range 2–8 kHz [15, 16]. There is a paucity of research on the effects of auditory loss of high frequencies, but there does appear to be an association with difficulty hearing the difference between musical notes, problems working out where a sound is coming from, comprehending speech (particularly where background noise exists) and tinnitus [17–20]. One study that followed up a cohort of adults prone to repeated episodes of AOM as children found these adults were significantly more likely to suffer from tinnitus than controls who had not suffered from acute middle ear infections [20, 21].

Given the fact that high-frequency hearing loss is the most likely deficit in AOM, it appears useful to screen hearing when the illness is acute, to identify as soon as possible the likelihood of future auditory impairments and other complications of the acute phase, for example, suppurative infection of the labyrinth [15, 22–24]. This procedure may enable early therapeutic intervention and protect against future hearing loss. The evidence base for using hearing tests during an acute attack of AOM is slender, and further research is called for to establish exactly what changes in the auditory thresholds occur, both for conduction through air and bone [14].

16.8 Diagnosis

16.8.1 Physical Examination

A careful and complete physical examination is essential. In cases of both acute and chronic middle ear infections, the ear should be examined with the pneumatic otoscope. Patients with AOM present with an inflamed eardrum, which starts as mucosal erythema and goes on to involve a pus-filled effusion in the middle ear and a less mobile eardrum. There may be bulging of the eardrum in the posterior quadrant, whilst the superficial epithelium may look as though a scald has been sustained [1]. It is fairly common for the eardrum to become perforated during the course of AOM. This generally occurs in the posterior or lower quadrant. In some cases, rather than perforating, there is sometimes seepage of an opaque exudate with the viscosity of serum. This seepage occurs over the whole surface of the drum [1].

In cases of both acute and chronic middle ear infections, the ear should be examined with the pneumatic otoscope. The potential physical findings in cases of AOM are as follows [1]:

- The eardrum appears inflamed
- The posterior quadrant of the eardrum may bulge outwards. The superficial epithelium has the appearance of a scald
- Perforation of the eardrum, usually in the posterior or inferior quadrant

- Seepage of an opaque exudate with the viscosity of serum. This seepage occurs over the whole surface of the drum
- Earache, with or without a discharge from the ear
- Pyrexia

16.8.2 Auditory Tests

It is usually not beneficial to test hearing in children during an acute attack of AOM, since the effusion in the middle ear cavity invariably produces auditory impairment of conductive type. Tympanometry is potentially beneficial to diagnose the presence of an effusion but is rarely necessary if the clinician can utilise pneumatic otoscopy correctly [1].

If the ear has recently perforated or tympanocentesis has been performed, sending aspirate for microbiological culture and susceptibility testing may be beneficial [1].

16.8.3 Imaging Investigations

Unless complications occur, imaging investigations are not routinely required in cases of AOM. Nonetheless, CT imaging may be needed if there are suspected complications. If the complication may be intracranial, MRI may be a more suitable modality [1].

16.8.4 Operative Interventions

Tympanocentesis refers to a procedure whereby the eardrum is pierced with a needle and any effusion aspirated for laboratory analysis.

The indications for tympanocentesis in cases of AOM are as follows [1]

- Newborn infants less than 6 weeks old, who are at risk of infection by unusual pathogens or of more invasive illness
- Cases where immunosuppression or immunocompromise is present
- Cases where there is ongoing evidence of AOM, either local infection or systemic signs, in spite of appropriate antibiotic pharmacotherapy
- Cases where complications are present and culture is necessary to guide treatment

16.9 Clinical Management

16.9.1 Medication

The only pharmacotherapeutic intervention that has been shown to be effective in treating AOM is antimicrobial pharmacotherapy. Accordingly, antibiotics are the

first-line management. The choice of agent depends on the most probable pathogen, any allergies, degree of tolerability, previous treatment, cost and resistance pattern in the area where the child is living. It may also be important to consider the length of treatment [25].

The following agents are all antibiotics, which may be considered in AOM [1]

- Amoxicillin
- Co-Amoxiclav
- Erythromycin base/sulfisoxazole
- Co-trimoxazole
- Cefixime
- Cefuroxime axetil
- Cefprozil
- Cefpodoxime
- Cefdinir
- Clindamycin
- Clarithromycin
- Azithromycin
- Ceftriaxone

16.9.2 Surgical Interventions

The options for surgery in AOM involve the following techniques [1], which have a degree of overlap:

- Tympanocentesis
- Myringotomy
- Myringotomy and grommet placement

Choice of surgical intervention depends on various factors, including the individual patient, the experience of the surgeon, the resources that may be accessed and the degree of emergency involved.

16.10 Complications

The extent of the spread of infection is the basis for classifying complications in AOM. Infection may extend beyond the middle ear cavity in the following patterns [1]:

- Intratemporal. This includes cases where the eardrum perforates, and there is acute mastoid osteitis, involvement of the seventh cranial nerve, acute inflammation of the labyrinth, infection of the petrous temporal bone, acute otitis causing necrosis or chronic otitis media.

- Intracranial. This includes meningitis, encephalitis, central nervous system abscess, otitis hydrocephalus, subarachnoid abscess, subdural abscess or a thrombotic event within the sigmoid sinus.
- Systemic. Bacterial spread to the bloodstream, infected joints or bacterial endocarditis.

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Otitis Media with Effusion and Hearing Loss in Children

17

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17.1 Introduction

Otitis media with effusion (OME), a term also encompassing serous otitis media, is a condition in which fluid accumulates in the middle ear, but there are no indications of an acute infection [1]. There is also a subgroup of cases of OME where the fluid is viscous and yellow in colour and has the consistency of glue when viewed during tympanic surgery [2]. This condition is termed 'glue ear'. Although OME and glue ear are sometimes used interchangeably, glue ear in fact only occurs in a portion of cases of OME [3].

The effusion in OME does not contain pus. It is mucoid or serous. The usual presenting symptoms are auditory impairment or feeling the ear is full, whilst pyrexia or otalgia rarely occur. In paediatric cases, auditory impairment is usually no more than mild, being revealed by audiogram rather than spontaneously reported.

Serous otitis media involves the formation of a watery and clear effusion as a result of transudation caused by negative pressure developing in the middle ear space [4]. It is a subtype of OME.

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It is important for clinicians to appreciate that there are significant differences between OME and other infective conditions affecting the middle ear cavity [5]. The term 'otitis media' is a generalised term for any inflammatory condition of the middle ear. It does not indicate the particular cause or pathological mechanism involved. The pneumatised regions of the temporal bone (mastoid, perilabyrinthine and petrous apex air cells) are interconnected; hence, otitis media may lead to inflammation of these spaces, too. A range of disorders are all grouped under the umbrella term otitis media, namely, acute otitis media (AOM), recurrent acute otitis media (RAOM), OME and chronic otitis media with effusion (COME) [6].

17.2 Pathophysiology

OME may develop following AOM, as it begins to resolve and the acute phase has passed. Up to 45% of paediatric cases of AOM still have an effusion present 1 month after onset, with this number falling to 10% at the 3 month mark [6].

17.2.1 Classical Explanation

There are two principal ways in which the pathogenesis of AOM is said to occur. According to the classical theory, the auditory tube does not function correctly, which is a necessary step in pathogenesis. The auditory tube is generally credited with three functions, namely, equalising the pressure in the middle ear cavity and external auditory meatus, draining secretions and defence of the middle ear. If these functions are impaired, AOM may develop. Accordingly, several events may trigger eventual AOM, ranging from anatomical abnormality causing obstruction, to allergic inflammation, an infection of the upper respiratory tract or traumatic injury [6].

In cases where the auditory tube is dysfunctional for more than a brief period, the pressure in the middle ear cavity will fall, since nitrogen and oxygen diffuse out of this space. If there is a sizeable pressure gradient as a result, transudation develops from the mucosa, with a serous, typically sterile, fluid building up in the space. Since there is no drainage through the auditory tube, this stagnant fluid provides a suitable environment for bacterial species to grow, and AOM develops in response. However, this theory cannot be entirely correct, since it has been shown several times that cases of AOM and OME feature identical bacterial pathogens [4].

17.2.2 More Recent Explanations

More recently, it has been proposed that the initiating event in AOM is mucosal inflammation within the middle ear in response to pre-existing bacteria in the cavity. Imaging studies were used by Bluestone et al. to demonstrate reflux passing into the auditory tube in paediatric cases of recurrent otitis media [7]. Moreover, pepsin has been identified in the middle ear cavity of some 60% of paediatric OME cases [8],

albeit reflux into the auditory tube can also be observed in individuals without any evidence of disease.

Likewise, O'Reilly et al. discovered, in their study of 129 children undergoing myringotomy with grommet insertion for an indication of otitis media, that pepsin A was present in aspirates from 64 cases. The presence of pepsin A indicated that stomach contents must have been refluxed as far as the nasopharyngeal region. These researchers relate this finding to the development of AOM by suggesting reflux triggers an inflammatory response or worsens any inflammatory response that is already occurring [9].

17.2.3 Middle Ear Effusion

Whatever the causative agent is in cases of AOM, a dysfunctional auditory tube is virtually invariably present in cases of OME. In animal models, when the auditory tubes are experimentally ligated, a long-standing effusion develops in the middle ear. Even when the infection has been eradicated and inflammatory responses cease, the effusion continues to be present due to non-drainage of the middle ear. The inability to drain the effusion may be a result of various pathophysiological changes, such as non-functioning cilia, oedema within the mucosa, excessive viscosity of the fluid and, potentially, pressure changes in the middle ear [6].

Not all cases of AOM proceed to become OME. There have been proposed a variety of mechanisms to account for how an effusion develops in the cavity. One is that inflammation of the mucosal lining causes fluid to be secreted. According to this explanation, the mucosa undergoes sensitisation following the presence of bacterial pathogens, and when reflux occurs from time to time, bacterial antigens are present to trigger an inflammatory response. However, as explained earlier, the bacterial species detected in cases of OME do not differ from those present in AOM. The effusion is not completely void of pathogens, as used to be thought [6].

17.2.4 Cleft Palate

In paediatric cases of cleft palate, OME is always seen. This is explained as occurring due to the incorrect insertion of the tensor veli palatini muscle. Accordingly, when patients swallow or open their mouths wide, this muscle does not perform its usual function of opening the auditory tube. Thus, the tune is functionally blocked [10].

17.3 Frequently Occurring Pathogens

The bacterial pathogens that are most frequent in cases of AOM are *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* and then *Moraxella catarrhalis*. The same group of organisms are also the most common bacterial causes of sinusitis

and pneumonia. These three species collectively are found in 85% of cases of AOM. They occur with the following frequency [6]:

- *S. pneumoniae* is present 35% of the time, with no apparent effect of age on prevalence. The most frequently identified serotype is 19, followed by 23, 6, 14 and 3.
- Some 20% of cases are attributed to *H. influenzae*. At present, between 25 and 45% of the organisms isolated are capable of expressing a beta-lactamase, and the frequency of antibiotic insensitivity is clearly rising.
- In cases of AOM, *M. catarrhalis* is responsible for between 4 and 13%. This figure rises during the winter and autumn months. Beta-lactamase expression occurs in 70–100% of these pathogens.

The other pathogenic bacteria involved are *Streptococcus pyogenes*, *Staphylococcus aureus*, enteric bacteria-staining Gram-negative, and anaerobic species. *Pseudomonas* is the most commonly isolated bacterial genus in cases where an effusion has persisted for more than 3 months.

No pathogen is identified in 30% of aspirates obtained during tympanocentesis. A meta-analysis based on ten studies dating from 30 years ago collated data on 663 patients. In 29 cases (4.4%), a viral pathogen was identified. Data from more recent research indicate that a viral pathogen is identifiable in 15–20% of cases of AOM, co-existing with a bacterial pathogen. The viral pathogens most common in such cases are respiratory syncytial virus (RSV) and influenza virus [6].

17.4 Risk Factors

A number of risk factors for OME have been identified. These include the environment, age and dysfunction of the auditory tube [6].

17.4.1 Environment

There are a number of factors in the environment of the patient that increase the risk of OME, besides the presence of specific pathogens. Epidemiological data indicate the following are associated with raised risk: bottle feeding, being fed lying down, having a brother or sister with a middle ear infection, going to a childcare facility, being allergic to frequently encountered environmental allergens, low socioeconomic condition, presence of smokers in the household and a family history of OME in at least one parent [11, 12].

17.4.2 Age

Age is strongly associated with a heightened risk of OME. During infancy, the auditory tube in the anatomical position is virtually parallel to the ground, with the angle steadily increasing up to adulthood, when it has an angle of 45°. Furthermore, the anatomical configuration of the auditory tube in neonates permits less efficient ventilation of the middle ear than in adults [6, 13].

The results of several Danish studies on paediatric cases show that, up to the age of 1 year, in 24% of ears assessed, a type B (flat) or type C (indicating negative pressure) was found on tympanometry. Auditory function became more normal in springtime or the summer months, but winter witnessed declining function. The peak occurrence of a type B pattern was between the ages of 2 and 4 years. Thereafter, this type of tympanogram is more rarely seen, as could be anticipated from the lower frequency of OME in children after the age of 6 years [6].

It is vital that OME affecting one ear in an adult is identified without delay as the most dangerous underlying diagnosis is a neoplasm of the nasopharynx [6].

17.4.3 Disrupted Auditory Tube Function

OME is also more common in cases where the nasopharyngeal ostium cannot remain patent. This situation frequently affects individuals with cleft palate or Down Syndrome, as well as other conditions involving the palatal region. It has been proposed that the reason patients with cystic fibrosis are more prone to OME is because the clearance of accumulated mucus by ciliary action is impaired in cystic fibrosis, where mucus is abnormally viscid [6].

17.4.4 Diet

Research undertaken by Choi et al. concluded that eating a diet overly rich in fats does increase the risk of paediatric OME, although several other aspects of diet examined did not affect the risk, namely, body mass index and classification, dietary protein, water or sodium, and the times at which carbohydrates were consumed [14].

17.4.5 Other Factors

Kaya and colleagues disagree with the findings of the research by Choi et al. These authors state that OME is indeed linked to the patient's being overweight or obese, based on a sample of 60 paediatric cases of OME and 86 healthy controls, with an age range of 2–10 years. They examined data linking body mass and height, noting that there was an association between excess body weight (including obesity) and higher frequency of OME. They speculate that being overweight or obese

potentially increases the risk of OME, or, conversely, that OME is a risk factor for obesity [15].

Walker and colleagues noted specific characteristics of paediatric cases of OME occurring prior to school age [16]. These patients typically have a blocked nose, snore frequently or invariably, spend an above average length of time in childcare facilities each week, have coryzal illnesses frequently, tend to have siblings in whom grommet placement has already occurred, were born following prolonged labour and began drinking bovine milk relatively early. Being of Asian extraction and having older siblings, in contrast, had an association with less likelihood of developing OME [16].

17.5 Epidemiological Features

Acute otitis media occurs once or more in the majority of children, that is, in 84–93%. Moreover, around four in five children experience OME at least once by the time they are 10 years old. The cross-sectional prevalence of auditory impairment secondary to OME of at least 3-month duration is 5% in children aged between 2 and 4 years. The peak prevalence of OME occurs up to the third birthday and falls rapidly after the sixth birthday [6].

17.6 OME and Auditory Impairment

The aims in managing cases of OME are to remove the effusion from the middle ear cavity and normalise the pressure gradient, to restore auditory function. The first-line treatment consists of either watchful waiting or grommet insertion, which may sometimes be accompanied by removal of the adenoids. Myringotomy without grommet placement is not an effective option for treating OME. Initial results from balloon dilatation of the auditory tube have been encouraging, but the method needs further quantification of its benefits and risks before it can be generally recommended [3].

The method chosen and the timing of any intervention may be decided by considering whether there are other co-existent problems that may worsen the effect of conductive-type auditory impairment, such as speech and language disorders or learning disability. It is also important to consider how severely impaired hearing is, how long the effusion has been present and if the lesion is one- or two-sided [1, 2]. The season in which OME occurs also influences the outcome, with summer and autumn episodes less likely to resolve without intervention [1, 17, 18]. With these factors taken into consideration, the two options of observing and intervening only when required, or performing myringotomy with grommet insertion, remain valid for most cases.

Hearing aids, whether external or implanted, are appropriate only in paediatric cases of persistent OME where the insertion of grommets is unfeasible or where it brings no benefit, such as in cases of aural atresia or abnormally functioning ossicles [3].

Children in whom there is a risk of problems with speech and language development, or learning are a special category within OME clinical management. This group encompasses children with pre-existing auditory impairment, inherited disorders (Down Syndrome, 22q11.2 deletion disorder) or neurodevelopmental conditions (such as autism), abnormal craniofacial development (such as cleft palate) and those with visual problems not corrected by appliances, since these children are especially reliant on hearing to compensate for their lack of vision [1, 2, 19].

Thus, assessment of hearing should be carried out on children with OME falling in the 'at risk' category [1]. The conductive-type auditory impairment found in OME has a disproportionately negative effect on disabled patients. The modality used to assess auditory function should be selected according to how old the child is and how much he or she has the ability and willingness to co-operate. Where auditory loss is large, operative intervention is indicated. Patients in whom language development is delayed need to be assessed by a speech and language pathologist.

There is consensus amongst various professional bodies that children diagnosed with OME and who have a speech and language or learning disability require surgical consultation at an early stage, namely, no later than 3 months after diagnosis [1, 19]. In the majority of trials where the outcomes of OME were examined, whether immediate or longer term, such cases have been purposely excluded [20]. Thus, there is a lack of definite evidence to quantify the extent to which these individuals suffer more severe consequences. Practical experience, however, suggests that conductive auditory impairment can only worsen the prognosis where a pre-existing linguistic or intellectual disability is present [21].

Children without pre-existing linguistic or intellectual disabilities. For paediatric patients without these risk factors, the usual practice is to assess auditory function only where OME is persistent and the duration exceeds 3 months [1, 19]. The advantage of this delay is that the auditory impairment has often already spontaneously remitted by this point [2]. There may be an additional need for speech and language pathology appraisal of a case, especially if the auditory impairment is evident at a threshold of 21 dB or more.

Managing patients who do not fall into the special risk category depends on judgements about how the eardrum and middle ear cavity appear, the results of auditory testing (including audiometric and tympanometric evaluation), how long an effusion has been present, whether one ear or both is affected, and the wishes of parents or other carers [3].

Structural changes affecting the ear drum or middle ear. The following are signs that an urgent referral for surgical intervention is required: atelectasis of the tympanic membrane (i.e. retraction); partial collapse of the drum/retraction pocket, a perforated eardrum, discharge from the ear, and cholesteatoma [1]. In these cases, surgical intervention may be needed for another indication, besides OME.

The threshold for hearing is 40 dB or higher. Children with OME-induced auditory impairment raising the threshold for hearing to 40 dB or above should receive a referral for surgical assessment.

Despite the paucity of evidence about longer-term outcomes in paediatric patients with this degree of impairment, if the loss becomes longstanding, there may be negative effects on the development of speech and language and scholastic achievement. Thus, an ENT assessment is warranted [22–24].

A systematic review has examined the benefits of grommet insertion on auditory perception. The trials reviewed all involved paediatric patients with OME. The procedure seems to offer limited benefit, and by 6–9 months post-surgery, any benefit appears minimal. This is the normal time frame for the condition to resolve spontaneously [20]. No benefit in terms of speech or language acquisition, nor intellectual development, was proven, albeit the evidence base consulted was slender. There is a lack of published evidence regarding paediatric patients in whom a pre-existing deficit of speech, linguistic performance, psychological development or intellect is present [3].

Hearing threshold located between 21 and 39 dB. In children without pre-existing disability who experience auditory impairment sufficient to raise the hearing threshold to between 21 and 39 dB as a result of OME, a more conservative approach is suitable. Since the degree of auditory impairment is mild, decisions may be taken on the basis of a risk-benefit discussion with parents or carers about watchful waiting or grommet insertion [1, 2]. The majority of patients in this situation do not require surgical intervention, and watchful waiting is adequate management. The general recommendation is to rebook the patient and arrange further hearing tests after between 3 and 6 months [3].

The extent to which benefit outweighs the risks of surgery can usually be decided by considering how the child would be affected by having a mild auditory impairment lasting 6–9 months. This is the period for which grommet insertion has been shown to be beneficial. Nonetheless, even when various studies conducted in this area, including some RCTs and other studies using controls, have been systematically reviewed, the evidence base supporting the benefits on speech and linguistic performance of grommet insertion for children with mild auditory deficits appears weak [20, 25–27]. Grommet insertion is potentially justified in children with OME affecting one or both ears, which has persisted for at least 3 months (i.e. it qualifies as chronic), and impacts scholastic achievement and creates challenging behaviour or lowers the quality of life [19].

A number of factors need to be taken into consideration when deciding, such as the following [1, 2, 19, 28]

- Is language abnormal or delayed, if the child is very young? Is scholastic achievement impacted by an older child's acting out-of-character?
- Is OME chronic (has lasted at least 3 months) and affecting both ears? Research employing an observational design has determined that OME affecting both ears tends to cause a higher degree of severity in auditory impairment and to resolve more slowly than unilateral cases. After 6 months only around 25% of cases remit spontaneously, whilst this figure is 30% at 1 year [1, 2, 29].
- Is OME of at least 3 months' duration (i.e. chronic), whether affecting one or both ears, whilst also being the most probable cause of any of the following

issues: difficulty balancing (from vestibular involvement), scholastic underachievement, challenging behaviours, otalgia, and a poorer quality of life than usual, from the point of view of parents or carers? This change in life quality may be manifested as insomnia or acting out-of-character [30–32].
- An extended period for which OME persists, such as OME affecting one ear which persists for at least 6 months, or which has been present for a minimum of 6 months in the preceding year, makes the lesion less likely to resolve spontaneously [33] and entails greater likelihood that the eardrum will be structurally damaged [24].

If there is no auditory impairment present (in other words, any loss of hearing occurs at a level of 20 dB or less), and speech, language and development are all on target, the patient may be followed-up by watchful waiting. Since auditory testing usually occurs 3 months after the onset of OME, this means watchful waiting lasts for 6 months in total [1, 2].

17.7 Clinical Work-Up

Probably, the diagnostic test most value in assessing a case of OME is tympanometry. Some 43% of tympanometric tests in patients with OME are of type B, with 47% of type C, showing the middle ear pressure is lowered. The effusion may be aspirated by performing tympanocentesis, which may be satisfactorily performed in clinic, even if the patient is very young. Performing tympanocentesis allows culture of the aspirate and is therapeutic in its own right [34].

However, to obtain the gold standard diagnostic evidence to show OME, myringotomy is needed. This procedure benefits from a greater degree of exposure of the lesion and allows more effective suctioning than is possible through tympanocentesis [35].

Imaging using computed tomography (CT) plays a significant role in excluding potential complications of otitis media, such as mastoiditis, thrombus formation in the sigmoid sinus or where the lesion may erode into the bone and spread intracranially. It is also valuable if there is an atypical cause, such as cholesteatoma. CT is especially beneficial in cases of OME affecting one side only and in which a suspected mass may be present in the nasopharynx or auditory tube [6].

Magnetic resonance imaging (MRI) has particular value in cases where a mass lesion within the soft tissues is potentially aggravating a middle ear effusion. MRI is especially good at defining the boundary between different soft tissues and can show how far a mass, in the nasopharynx, for example, has invaded into the cranial cavity. MRI can also easily reveal particular vascular complications, for example, thrombosis within the venous sinuses. For these purposes, the augmented MRI techniques, such as magnetic resonance venography (MRV) and magnetic resonance arteriography (MRA) are helpful. In all cases where the lesion extends into the cranial cavity, nonetheless, CT is necessary to define the osseous anatomy and determine the path the lesion has taken, whether via the nasopharynx or the temporal bone [6].

17.8 Management

Pharmacotherapy for OME involves the use of antibiotics, corticosteroids, antihistamines, decongestant and mucolytic agents. This approach to treatment has, however, been criticised on the grounds of limited evidence for clinical benefit in the longer term, plus the cost and side effect burden involved. In particular, the International Federation of Otorhinolaryngological Societies Congress in 2017 looked at each class of agent and recommend against their use on the grounds outlined above [7].

In chronic OME, the treatment modality enjoying the broadest acceptance is surgery, for the effectiveness of which there is clear evidence. Surgical options include myringotomy (+/− grommet insertion), removal of the adenoids or a procedure involving all three. As first-line therapy for OME, tonsillectomy has *not* been demonstrated to offer significant advantages [6].

17.8.1 Grommets

Possible indications: Before deciding to treat OME by grommet insertion, there should be a discussion of the benefits and risks involving the patient, parents or carers, GP and ENT specialist.

The following are possible situations where grommet placement is indicated [1, 2, 19]

- OME in a child who has risk factors for speech or language delay or learning disability. This applies regardless of the degree of auditory impairment. It is recommended such cases are seen by an ENT specialist within 3 months.
- Alteration to the eardrum, such as a retraction pocket.
- Chronic auditory impairment as a result of OME resulting in an auditory threshold of 40 dB or above.
- OME in both ears that has persisted for at least 3 months, or in one ear for at least 6 months, or OME which has recurred within a year, resulting in a total duration lasting at least 6 months within a year.

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Recurrent Otitis Media and Hearing Loss in Children

18

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18.1 Introduction

When acute otitis media (AOM) recurs frequently, clinical management calls for systemic antimicrobial pharmacotherapy. However, given the rising prevalence of resistant pathogens, caution is advisable. Antibiotics may be administered prophylactically to prevent the recurrence of AOM. In cases where recurrent AOM leads to discharge passing out of grommets, ear drops may be used topically. Meanwhile, conjugated vaccines against *Streptococcus pneumoniae* appear to somewhat reduce the incidence of all types of otitis media [1].

The definition of recurrent AOM in paediatric patients is three acute attacks within the space of 6 months, or four attacks in the space of 1 year. The bacteriological features of recurrent AOM are more complicated than in its sporadic form; however, there are three pathogens that predominate in this disorder, namely *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. As children grow and approach their third or fourth birthday, recurrent AOM tends to remit

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without intervention. However, recurrent AOM does put families under great pressure, and therefore, carers or parents frequently request prophylactic treatment. The most frequently utilised treatment to provide both therapeutic benefit and prophylaxis is the insertion of grommets [1, 2].

18.2 Prevalence

The frequency with which recurrent AOM (rAOM) is diagnosed differs between generalists and specialists. General practitioners diagnosed rAOM in 27% of paediatric patients, whilst the rate amongst ENT practitioners was lower, 14%. Indeed, when diagnosis was based upon the findings of tympanocentesis, this rate dropped even further, to a mere 6%. There is, however, no recommendation that tympanocentesis be performed as a routine diagnostic measure in children with suspected otitis media [3, 4].

18.3 Risk Factors

In paediatric patients where AOM is the only type of infection to which they are prone, there is low suspicion of severe immunodeficiency. However, if rAOM is just one infection amongst several or there are other infections from which the patient takes an unusually long time to recover, there should be a clinical suspicion of immunodeficiency caused by reduced gamma immunoglobulins, defective granulocytic activity, abnormal cell-mediated immune responses or human immunodeficiency virus [5].

Another group that are prone to recurrence of AOM are children with cleft palates, such as those with abnormal craniofacial development occurring in association with a submucous cleft palate, as occurs in micrognathia and glossoptosis. These abnormalities may be part of the Pierre Robin sequence or related disorders [3].

The age at which the first attack of AOM occurs also has an effect on proneness to recurrence. Children who have an initial attack prior to age 6 months are prone to recurrence, and the severity is greater than usual [6, 7]. One potential mechanism by which this occurs is that an early attach creates abnormality of the auditory tube, predisposing to future infection. Another possibility is that episodes occur early in children with abnormal anatomy or genetic risk factors. Both mechanisms may also be operative simultaneously [8].

The family history is also of importance, since being related to an individual prone to recurrent or severe AOM is associated with a raised risk of both sporadic and recurrent AOM [3].

Age also plays a role in how beneficial more active interventions, such as prophylactically prescribed antimicrobials or grommet placement are in rAOM. This increased benefit occurs because AOM is more frequent in children before their second birthday, with attacks becoming rarer as age increases in the majority of cases [3].

One study looked at the frequency of AOM in children at different ages following introduction of the pneumococcal vaccine. Children aged from 6 to 11 months were twofold to threefold more prone to AOM than those aged 25–35 months. Compared to the latter group, children between the ages of 12 and 23 months are around twice as likely to suffer an episode of AOM [9].

A recent study, by Calatayud-Sáez et al. consider diet to be a risk factor for the recurrent otitis media. They stipulate that the mucosa covering the entire ENT area is in a pro-inflammatory and hyper-reactive state, as a repercussion of the modifications produced by a deficient diet. A total of 42 boys and 48 girls, between 1 and 5 years of age, have received traditional Mediterranean diet for 1 year. The study concluded that healthy food significantly reduces occurrence of acute otitis media and may contribute to the treatment of patients diagnosed with recurrent acute otitis media [10].

Seasonality There are variations in the frequency of infections by particular pathogens at different times of year. Having been infected on several occasions prior to the end of November (i.e. before winter in Europe and North America) puts a child at increased risk for the rest of the winter. Conversely, recurrent attacks by the end of May (i.e. prior to summer above the equator) entails a lower risk for the rest of the warmer months [3].

Siblings If patients have a sibling below the age of 5 years or attend childcare, they have a raised risk of recurrent middle ear infections [11–14].

Premature Birth Prematurity slightly raises the risk for AOM and is a more potent predictor of AOM in the first few years of life than having a lower body mass than average at birth [15].

Overall Level of Development, Especially Linguistic Children with irreversible deafness, delay in speaking or using language (whether definitely diagnosed or thought probable), delayed development, autistic spectrum disorder or irreversible loss of sight all have a heightened likelihood of problems with speech and language or intellectual development if AOM recurs [16]. This should be borne in mind when planning whether to actively intervene.

18.4 Prevention

18.4.1 Socioeconomic Status, Breastfeeding and Use of Tobacco by the Parents

There are numerous accounts in the literature linking otitis media with socioeconomic status and deprivation, in a variety of populations [17–21]. The findings relate to otitis media in all its form, rather than specifically to rAOM. It is unclear exactly how greatly young children coming from deprived households with insufficient access to healthcare and where the parents lack educations are at risk of

rAOM. One study examined a population from the Philippines where otitis media was especially prevalent [22]. This study concluded that genetic influences were stronger on risk than environmental influences. In particular, possession of a specific genotype raised the risk more than living in deprivation. Meanwhile, a Danish study [23] has identified epidemiological features indicating a heightened risk of middle ear infections prior to the age of 6 months. Early otitis media is known to predict the development of recurrence in AOM [24, 25].

Having at least one parent who smokes is also a recognised risk factor for developing respiratory disorders, including URTI and AOM. A study from Norway [26] showed that mothers who smoked whilst pregnant had children with a heightened likelihood of developing middle ear infections when very young (RR 1.34) as well as a somewhat less raised likelihood of suffering rAOM (RR 1.24).

18.4.2 Genetics

It has long been recognised by clinicians treating rAOM that there is often a definite family history of AOM. Clinically, a positive family history may be used to anticipate the likely prognosis of children with the condition, particularly the risk of AOM becoming recurrent. It has also been shown by research that genetic factors play a major role in middle ear infections [27–29]. Knockout mice in which the toll-like receptor 4 has been silenced are particularly prone to developing otitis media [30, 31]. This association has now also been demonstrated in humans, from clinical studies [32].

18.4.3 Vaccination

Whilst there has been a slight reduction in the incidence of AOM following the introduction of conjugate vaccination against *S. pneumoniae* and the use of the influenza vaccine, a larger effect seems to have occurred in terms of prevention of recurrence in middle ear infections and the number of procedures undertaken to insert grommets [33].

18.4.4 The Conjugated Vaccine Against Pneumococcus (PCV)

Routine Anti-Pneumococcal Vaccination In healthcare systems with routine anti-pneumococcal vaccination, the recommendation is for the vaccine to be administered at age 2 months, then 4, 6, and 12–15 months. This is the case in the United States. The World Health Organisation has published suggested vaccination schedules for elsewhere in the world [34, 35]. Not only does the vaccine protect against invasive infections by *S. pneumoniae*, it also somewhat reduces the frequency of AOM, lowers the number of clinic attendances required, diminishes the incidence of complications, and results in lower numbers of procedures to insert grommets [8].

Anti-Streptococcal Polysaccharide Vaccine For paediatric patients aged over 2 years and prone to recurrence of AOM, it is recommended that they be vaccinated with the 23-valent polysaccharide vaccine against *S. pneumoniae* (PPSV23). This is in addition to the earlier vaccination with PCV13. The aim is to provide immunity against the highest number of different serotypes of *S. pneumoniae*. There should be an interval between these two vaccines of a minimum 8 weeks [35].

Anti-Influenza Vaccination There is a recommendation to administer yearly anti-influenza vaccination to every child aged at least 6 months living in the United States. In healthcare systems where this approach is not adopted, it may be beneficial to administer anti-influenza vaccines yearly to any child whose initial episode of AOM was prior to the age of 6 months, or who has experienced rAOM in the previous winter [36].

18.5 Diagnosis

Otalgia is a common feature of upper respiratory tract infections (URTI) in children. These are virtually invariably the result of viral infection. Erythema of the eardrum is frequently noted, but is not pathognomonic of AOM. Unaided otoscopy is often insufficient to diagnose AOM. A fuller picture can be obtained by pneumatic otoscopy, which tests how mobile the eardrum is. Tympanometry can also confirm whether fluid has built up in the middle ear cavity. The external auditory meatus in infants is both floppy and narrow, with the result that the meatus must first be cleared of cerumen before the eardrum can be visualised. Clinicians know well from experience that cleaning the canal in a distressed baby is highly challenging. Paediatric patients in whom rAOM has been diagnosed or where this is the likely diagnosis frequently attend specialist otorhinolaryngological clinics. In such cases, the initial task is to confirm if the putative diagnosis is correct [1].

In case of nasal obstruction and in case of unilateral otitis media, nasal endoscopy must be undergone, in order to assess the adenoid tissue dimensions [37].

Tonal audiometry is also recommended to be performed for the differential diagnosis (transmission or sensorineural hearing loss). Inner ear damage association should be considered if a hearing loss greater than 50 dB is found [38].

18.6 Treatment

In the majority of children with AOM, penicillin or amoxicillin/co-amoxiclav is adequate for treatment. Recent research into the ideal treatment duration for co-amoxiclav compared a 5 day and 10 day course. It concluded that 10 days was preferable [9]. This study did not comment on subgroups of patients with recurrent AOM, and indeed, the evidence base in general for how long antimicrobial treatment should continue in middle ear infections is generally deficient.

Children in whom grommets have been placed frequently have ear discharge during attacks of AOM. Some studies [39, 40] have shown that ear drops containing steroid plus antimicrobial are usually adequate to treat AOM in such patients, and systemic treatment is therefore not required.

Over the years, many studies have been performed regarding the use of corticoids (intranasal or systemic), for their anti-inflammatory effect on the Eustachian tube impairment [41, 42]. Recently, according to Francis et al., who developed a prospective, double-blind, randomized clinical trial using a cohort of 389 patients with ages between 2 and 8 years, the use of systemic corticoids did not show a significant hearing gain [43].

The easiest, cheapest, and no side effects treatment method is considered to be the Politzer manoeuvre. Its role is to relieve the dysfunction of the Eustachian tube, by blowing air up the nostril [44]. Even though the tonal audiometry and tympanometry results after using Politzer manoeuvre were not statistically improved, patients considered a significant symptoms improvement [45].

Deciding Whether to Use Watchful Waiting or More Active Management After assessing the risks versus benefits in the individual patient, on some occasions, watchful waiting will be preferable, whilst on other occasions, a more interventional approach will be called for [3].

A more conservative approach, including watchful waiting, is often appropriate for paediatric patients above the age of two, provided there is no immunodeficiency, given that the frequency of AOM precipitously falls after the age of 2 years [46].

A more active approach to management may involve prescription of antimicrobials prophylactically and insertion of grommets. These interventions potentially make attacks less frequent or at least delay them. A more aggressive approach to managing the case is needed in children where the following features are present [3]:

- The child is under the age of 2 years. At this stage in life, hearing is especially vital for normal linguistic development. Children whose first episode occurs very early warrant more aggressive management.
- There are several risk factors present, and the risk cannot otherwise be reduced. For example, the attacks are in the peak season, and the child attends a crowded nursery.
- There are co-morbid conditions with the potential to increase the risk of rAOM, such as cleft palate, immotility of the cilia, deficient expression of immunoglobulins in general or of a particular class of antibody and craniofacial anomalies (such as occur in Down Syndrome), or the auditory tube is prone to dysfunction.
- There is a suspicion or an actual diagnosis of linguistic developmental delay or any condition causing developmental delay. AOM may result in conductive-type auditory impairment that persists long after the acute episode has resolved, and therefore, AOM can cause disproportionate delay if not aggressively managed.

- The tympanic membrane keeps rupturing, which may be a sign of underlying chronic suppurative middle ear infection [47].
- The attacks are severe in nature, resulting in moderate or severe otalgia, otalgia that lasts for more than 2 days or the temperature becomes 39 °C or greater [34].

Factors to Consider in Deciding on Prophylactic Antimicrobials or Grommet Insertion The decision to prescribe prophylactically or to insert grommets depends on several factors, such as the prevalence of antibiotic resistance in the specific locale, linguistic competence of the child, anaesthetic or surgical hazards, age of the child and the priorities and wishes of the child's family. If a child continues to suffer from attacks of AOM despite ongoing prophylactic treatment, or is allergic to several antibiotic agents, meaning more interventions are needed, grommet insertion may be a reasonable strategy to adopt [3].

18.6.1 Insertion of Grommets/Ventilatory Tubes

Ventilatory tube insertion may be appropriate in a child who has experienced at least three separate attacks of AOM in the space of 6 months, for which there is clearly documented evidence, or at least four in the space of a year. However, the decision to go ahead with this surgical intervention needs to take into account what risks and advantages are involved [3].

The insertion of grommets is recommended in paediatric patients where a more aggressive management approach is needed and in cases where

- Antimicrobial prophylaxis has not prevented rAOM.
- The parents do not wish the child to receive antimicrobials prophylactically.
- The child is allergic to more than one antimicrobial agent [3].

Potential Advantages of Grommet Insertion The procedure may make attacks less common and milder in children prone to rAOM, although there is a lack of confirmatory evidence for this claim. Paediatric patients with ventilatory tubes in situ who develop AOM have a discharge from the middle ear into the external meatus. Since the discharge is infected and can drain away, otalgia may be lessened, and any further attacks may be milder. Furthermore, grommets may make management easier, since topical otic medications can be utilised. The subject of ear discharge through grommets has been discussed earlier [3].

Accompanying Removal of the Adenoids or Adenoids Plus Tonsils The sole indication for performing a simultaneous adenoidectomy when inserting ventilatory tubes is where the nasal cavity is blocked by the adenoids to at least a moderate degree [48].

Adenoid +/− tonsil removal seems to lack efficacy as an initial treatment for paediatric cases of rAOM [49–52]. Two RCTs were run concurrently, investigating

outcomes in children aged between 3 and 15 years and prone to recurrent middle ear infections. The trial subjects had not previously had grommets inserted. These trials ascertained no benefit on AOM from either adenoidectomy or adenotonsillectomy, regardless of the presence or absence of adenomegaly or tonsillomegaly [49].

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Mastoiditis and Hearing Loss in Children

19

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19.1 Introduction

Mastoiditis refers to inflammation within the mastoid air cells of the temporal bone [1]. Since the mastoid air cells are in communication with the middle ear cavity and are adjacent to it, mastoiditis is present in nearly every case of acute otitis media, both in children and adults, and in the majority of cases of chronic otitis media. Typically, it is the middle ear-related symptoms that are most prominent, namely pyrexia, otalgia and auditory impairment of conductive type, and mastoiditis is not distinct from this clinical picture. In a number of cases, the infective process extends beyond the mucosal lining of the middle ear cavity to affect the bone (osteitis) or periosteum (periosteitis) of the mastoid region. The infection may directly invade the bone by eroding cortical bone or spread haematogenously through the mastoid emissary vein. Where this spread occurs, the diagnosis of acute (surgical) mastoiditis may be made. This condition is considered a complication of middle ear infection affecting the temporal bone [2].

Three categories of mastoiditis are recognised, namely acute, subacute and chronic. Acute mastoiditis comprises two different conditions—incipient

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mastoiditis and coalescent mastoiditis. In the former, which may also be termed ‘acute mastoiditis with periosteitis’, pus collects in the spaces of the mastoid cells. In the latter, also referred to as acute mastoid osteitis, the osseous septa, which divide the air cells from each other, appear effaced. Abscesses may form in the space and track into adjacent regions. In subacute mastoiditis, there is a long-standing infection affecting the middle ear and mastoid. Although the osseous septa are destroyed by this process, the degree of inflammation is low, and the condition may also be referred to as masked mastoiditis [2]. Meanwhile, chronic mastoiditis refers to a persistent purulent inflammatory process of the mastoid cells, with a duration from months to years. This condition is usually found in association with chronic suppurative otitis media (CSOM) and is strongly linked to cholesteatoma [2].

19.2 Definitions

Mastoiditis refers to purulent infective inflammation of the mastoid air cells.

- **Acute mastoiditis** refers to purulent infective inflammation of the mastoid air cells, which lasts for a maximum of 1 month. These cases can be further classified depending on the pathological features [3, 4]:
- **Incipient mastoiditis** (i.e. with periosteitis) refers to a condition wherein there is pus within the mastoid spaces but the osseous septa remain intact. If imagery reveals the presence of fluid within the mastoid cells, this finding lacks diagnostic specificity, as it may also be noted in paediatric cases of acute otitis media (AOM) or otitis media with effusion (OME). To make the diagnosis, there must be appropriate clinical signs, such as tenderness behind the ear and redness, and the pinna should be swollen and protruded.
- **Coalescent mastoiditis** (synonymous with acute mastoid osteitis) features osseous septal damage. Although appearances confirming the septa have been destroyed do allow the diagnosis to be made, in the majority of paediatric cases, imaging is not needed diagnostically. This condition may be complicated by abscess formation, and purulent infection may track into nearby structures. The most frequent site of abscess formation is subperiosteal [3].
- **Subacute mastoiditis** (sometimes termed ‘masked’) features destruction of the osseous septa separating the mastoid cells but as a result of a long-standing inflammatory process of low intensity [5]. This condition is found either in children where OME persists or where there are repeated attacks of acute otitis media without effective pharmacotherapeutic intervention.
- **Chronic mastoiditis** involves an infection that persists from months to years and results in the formation of pus within the mastoid spaces.

Complicated mastoiditis is where the inflammation within the mastoid is complicated by further pathology within or outside the cranial cavity [3].

19.3 Pathophysiological Mechanism

Acute mastoiditis usually develops as a complication of acute otitis media (AOM), due to the contiguity of the middle ear cavity and mastoid spaces [6]. Thus, inflammation that affects the mucosal lining of the middle ear can readily expand into the mastoid. In most cases, resolution of mastoiditis occurs in conjunction with resolution of otitis media. If there is persistence of otitis media, pus builds up within the mastoid [7].

The inflammation and swelling of the antral mucosa mean that pathogenic infection cannot drain away from the mastoid and air cannot easily reach the space via the middle ear cavity. Inflammation may cause erosion of the antrum and allow the infection to spread into several adjacent structures, which creates a high degree of morbidity and may even endanger the patient's life [2].

There are five distinct stages to which mastoiditis may progress. The stages consist of the following [2]:

- Stage 1. The mucosal surfaces of the air spaces become hyperaemic.
- Stage 2. There is a transudated or exudated fluid, which may be purulent, present in the spaces.
- Stage 3. Osseous necrosis results from destruction of the septal blood supply.
- Stage 4. The walls of the mastoid cells break down and cavities develop filled with abscesses.
- Stage 5. The inflammation spreads to adjoining regions.

If an acute infective process within the mastoid cells persists, there may develop osteitis in which the bone loses mass. This results in loss of the osseous trabecular framework within the mastoid spaces and coalescence of the spaces. This is the reason for the label 'coalescent mastoiditis'.

In essence, coalescent mastoiditis is a collection of pus (empyema) within the temporal bone. If the condition continues, drainage will either occur via the antrum, in which case the empyema resolves, or a pathological drainage may occur, complicating mastoiditis. The latter refers to drainage to the mastoid surface, apex of the petrous temporal bone or into the cranial cavity. When coalescent mastoiditis does not resolve, there may be involvement of the adjacent structures, including those within the temporal bone, such as the seventh cranial nerve, the labyrinthine complex or the venous sinuses [2].

19.4 Aetiology

19.4.1 Acute Mastoiditis

Since acute mastoiditis develops from acute otitis media, it is no surprise to find that the pathogens responsible are generally the same, namely *Streptococcus pneumoniae*, *Haemophilus influenzae* and Streptococcal organisms in Group A, i.e.

Streptococcus pyogenes [8]. These microbes are all capable of invasion and are those most frequently identified in paediatric cases of acute mastoiditis.

The pneumococcal serotypes identified with the highest frequency in this condition are 19 (which accounts for above 50% of cases), followed by 23 and 3 [9]. As rollout of the pneumoccal conjugated vaccine continues, this pattern may alter. It is unusual to identify *Pseudomonas aeruginosa*, Gram-negative bacilli of aerobic type or anaerobic bacteria, at least in acute cases. Recently, however, it has been reported that acute mastoiditis secondary to *Fusobacterium necrophorum* is becoming more common, with studies reporting its isolation in 8.5% of cases [10, 11]. If there is a history of recurrent episodes of AOM with recent antimicrobial pharmacotherapy and perforation of the eardrum, *P. aeruginosa* may be detected. Otherwise, it seldom occurs. In first-world countries, *Mycobacterium tuberculosis* seldom produces inflammation in the mastoid.

At the moment, many of the cases of acute mastoiditis secondary to *S. pneumoniae* are infected with multi-drug-resistant strains (MDRSP). Choice of pharmacotherapy needs to be guided by the following frequencies of drug-resistant MDRSP: to penicillin (35–40%), to macrolides (30–35%) and to ceftriaxone (15%). These frequencies may differ depending on the particular local prevalence [2].

19.4.2 Chronic Mastoiditis

Chronic mastoiditis typically develops from chronic suppurative otitis media and is seldom caused by ineffective pharmacotherapy. In the majority of cases, the pathogens identified in chronic mastoiditis are the same as those responsible for chronic suppurative otitis media. Thus, the likely pathogens are *P. aeruginosa*, Enterobacteriaceae, *Staphylococcus aureus* (including methicillin-resistant strains) and anaerobes [12]. In more than 50% of cases, there is more than one pathogen isolated, typically an aerobe plus an anaerobe [2].

The most frequently identified anaerobes are Peptostreptococcus, Gram-negative anaerobes with a bacillary morphology (such as pigment-bearing *Prevotella*, Porphyromonas and Bacteroides spp.), as well as organisms from the Fusobacterium genus [13, 14]. Recently published research highlights the growing prevalence of mastoiditis secondary to Fusobacterium necrophorum within the preceding 20 years [15].

The ability to express a beta-lactamase is possessed by more than 50% of Gram-negative bacteria with a bacillary morphology, or members of the genus Fusobacterium [16].

S. pneumoniae or *H. influenzae* are seldom detected in cases of chronic mastoiditis. If *P. aeruginosa* is cultured, it may represent a contaminant introduced from the ear canal at the time of sampling, as these bacteria are colonisers of the external auditory meatus. A number of rarer pathogenic organisms are sometimes detected, namely Blastomyces [17], *M. tuberculosis*, other Mycobacterial species not responsible for tuberculosis and *Mycobacterium bovis* [18, 19].

19.5 Prognosis

Complete resolution of acute mastoiditis is the usual outcome provided there is no involvement of the seventh cranial nerve or vestibule, nor extension into the cranial cavity.

In the majority of cases, there will be no cosmetic defect caused by surgery on the affected ear provided the incision is carefully positioned and flaps are created, which apply posterior traction to the pinna when sutured into place.

Unless the ossicles are damaged, resolution of any conductive-type auditory impairment may be anticipated. Hearing should be re-tested when ear discharge is no longer present and the ear has recovered [11].

Mastoiditis of at least stage 3 is regarded as a complication of a middle ear infection. When mastoiditis extends beyond the mastoid to involve other structures, it is considered complicated. There are several ways in which this can occur, for example:

- The inflammation extends into the sigmoid sinus, which then triggers thrombus formation
- If the infection tracks into the occipital bone, osteomyelitis or a Citelli abscess may develop
- The infection may extend superiorly, reaching the posterior cranial fossa, subdural cavity and the meningeal coverings of the brain
- If the infection tracks forward, it involves the root of the zygomatic bone
- In a lateral direction, an abscess may develop in the subperiosteum
- Where the infection extends inferiorly, a Bezold's abscess may be formed
- Involvement of the petrous apex occurs if infection tracks medially
- The seventh cranial nerve and the labyrinth may be involved if the infection tracks infratemporally

19.6 Diagnosis

19.6.1 History Taking and Auditory Impairment

Auditory impairment may be noted, as is the case with any condition affecting the middle ear. There is no evidence from the history for recurrent middle ear infections in above 80% of cases [2].

There may be specific signs indicating acute or chronic mastoiditis. Acute mastoiditis frequently causes pyrexia and is typically seen either during an episode of acute otitis media or shortly thereafter. The clinical features vary depending on how old the patient is and what stage acute mastoiditis has reached. Chronic mastoiditis frequently results from incomplete antimicrobial pharmacotherapy for AOM and may not come to the attention of a physician. An ear discharge that has been occurring for more than 3 weeks is strong evidence that a chronic infection has taken hold in the mastoid.

Pyrexia may be noted in 76% of cases [20], and the temperature is potentially very elevated. Constant pyrexia is a potential feature of acute mastoiditis and probably originates from the middle ear inflammation. Even where sufficient doses of the correct antibiotic are being administered, pyrexia frequently does not stop in an acute infection of the mastoid. If the pyrexia is spiking, there should be a suspicion of thrombophlebitis in the signoid sinus.

Around two-thirds of patients (67%) complain of pain [20]. The pain is felt deep within or posterior to the ear and usually becomes more intense in the evening. Pain that does not remit is a clue to underlying mastoid involvement. However, assessing this symptom may be problematic if the patient is very young. Patients may present with systemic features, such as feeling lethargic or generally unwell, becoming irritable, not feeding properly or with diarrhoea [2].

19.6.2 Physical Examination

There are some signs indicative of acute mastoiditis, in particular [20]

- The ear drum may bulge and appear reddened.
- The ear drum perforates in 37% of cases, and ear discharge occurs in 50%.
- The skin overlying the mastoid is reddened, painful to touch and swollen.
- There is an area of fluctuance behind the pinna.
- The pinna typically protrudes inferolaterally in patients under the age of 2 years and superolaterally in children over this age.
- The posterosuperior wall of the external auditory meatus sags in some 71% of cases [20].

In cases of chronic mastoiditis, there may be features indicating the presence of a complication, as where there is spread to adjacent structures, such as the periosteal layer or an infratemporal structure, like the seventh cranial nerve. The following appearances may be observed [2]:

- The eardrum may have normal appearances or appear inflamed.
- There may be no external indications suggestive of mastoiditis.

When the neurological system is examined, there are generally no localising signs. In cases that have become complicated, however, an abnormality in the cranial nerves may be noted. Potential findings are as follows [2]:

- Sixth cranial nerve palsy
- Seventh cranial nerve palsy
- Pain in the distribution of the ophthalmic branch of the fifth cranial nerve

In all cases of mastoid inflammation (whether acute or chronic), the periosteum may be coarsened, there may be abscess formation in the subperiosteum, a middle

ear infection is present and the central portion of the eardrum may protrude forward in such a way that it resembles a teat.

To note coarsening of the periosteum, the normal side should first be compared. The pinna may be protruded inferolaterally in children below the age of 2 years or superolaterally if the child is above that age. An abscess within the subperiosteum pushes the pinna sideways and causes loss of the skin crease behind the ear. In cases where a crease can still be seen, the abscess must be located laterally to the periosteal layer [2].

19.6.3 Tests

Any aspirate obtained from the interior of the mastoid at operation, or fluid aspirated when performing myringotomy, requires laboratory investigation. The aspirate should be cultured aerobically and anaerobically, as well as for fungal pathogens and Mycobacteria. Gram stain should be undertaken, as well as acid alcohol staining.

If there is an existing perforation of the eardrum, the external auditory meatus should be cleaned and any fluid freshly appearing aspirated for testing. The fluid sampled should originate in the middle ear cavity rather than the external auditory meatus [2].

Venous blood should be sent for microbiological culture. A full blood count and erythrocyte sedimentation rate should be obtained, which can assist in evaluating how effectively antibiotics suppress the infection [2].

19.6.4 Computerised Tomography (CT)

It is routine practice to image the temporal bone using CT in cases of mastoiditis [21]. Imaging in this modality possesses between 87 and 100% sensitivity to detect mastoiditis. One danger is that CT may lead to overdiagnosis of mastoiditis, since AOM invariably also affects the mastoid. If there are suspicions that the infection has entered the cranial cavity or other complications have occurred, CT should be undertaken without delay [2].

The imaging appearances that support a diagnosis of mastoiditis are blurring or obliteration of the edges of the mastoid cavity and cortex, accompanied by blunting or loss of the outline of the septa which usually separate the mastoid air cells, that is, coalescent mastoiditis. If the air cells have a cloudy appearance, a bone scan using technetium-99 can clarify whether destruction of bone is occurring. Both the middle ear cavity and the mastoid frequently have a clouded appearance in the initial stages of an infection, and it is common to note cloudiness of the mastoid cells in cases where AOM is the only diagnosis. Thus, a bone scan helps achieve diagnostic clarity [2].

19.6.5 Magnetic Resonance Imaging (MRI)

The main use for MRI in cases of mastoiditis is where there is a clinical or radiological suspicion of extension of infection into the cranial cavity. Generally, however, MRI is not the preferred modality for imaging the mastoid.

MRI is, however, the most usual investigation to assess lesions where there are contiguous soft tissue elements, especially within the cranial cavity. It can identify build-up of fluid outside the brain parenchyma and give warning of vascular complications. Furthermore, MRI is beneficial when planning operative interventions [2].

19.7 Treatment

19.7.1 Tympanocentesis and Myringotomy

Prior to commencing antimicrobial pharmacotherapy, tympanocentesis and myringotomy may be undertaken. It is essential that microbiological culture of any aspirate from the middle ear cavity be performed before prescribing. The most guaranteed way to obtain the middle ear fluid is by means of an operating microscope and suction traps, which have been developed with this purpose in mind. However, the procedure may also be undertaken using an otoscope, spinal needle and syringe [2].

19.7.1.1 Acute Mastoiditis

Medical treatment options in mastoiditis include antibiotics administered by the intravenous route. The agent chosen depends on the results of laboratory testing of any fluid obtained from the middle ear cavity at operation. The principal purpose of myringotomy and tympanocentesis is to procure a sample for microbiological analysis and to provide symptomatic relief in patients with AOM. The holes created typically seal themselves in the space of days. Once a sample has been obtained, whether through tympanocentesis or whilst grommets are being inserted +/− mastoidectomy, treatment may be initiated and adjusted if needed following the results of microbiological analysis. If pyrexia ceases and there is a reduction in oedema within 2–3 days, antimicrobial treatment may be administered by mouth, as guided by the results of laboratory testing [2].

Agents employed in the treatment of acute mastoiditis include vancomycin in combination with one of ceftriaxone or cefepime (which possesses anti-pseudomonal activity), or a penicillin and beta-lactamase inhibitor in combination (e.g. ampicillin-sulbactam, piperacillin-tazobactam) or a carbapenem. Aztreonam in combination with vancomycin may be employed in cases where the patient may react with anaphylaxis to the use of a beta-lactam agent [2].

In all cases of mastoiditis, antibiotics must be administered intravenously. Nonetheless, antibiotic treatment is generally inadequate as monotherapy, especially as the condition develops, since there may be problems delivering pharmaceutical agents at the necessary concentration within the osseous tissues [22].

19.7.1.2 Empirical Treatment

When deciding on the initial antibiotic agent and before culture results are known, bear in mind if the child has been subject to recurrence in attacks of AOM and what agents have been administered to the patient recently [3].

In a case where AOM is not recurrent and no antimicrobial therapy has been administered within the preceding 6 months, a reasonable option is vancomycin alone, given intravenously at a dose of 15 mg kg^{-1} at 6-h intervals, the maximum single dose not to exceed 1 g. A second option is linezolid, also intravenously administered, at a dose of 10 mg kg^{-1} 8-h if the children is under the age of 12 years, or 12-h for older children. The linezolid dose given each time must not exceed 600 mg. These regimes may be changed when culture is complete. The pathogens most likely to be responsible are *S. pneumoniae* (some strains of which are insensitive to multiple agents), *S. pyogenes* and *S. aureus* (which also may be insensitive to methicillin) [3].

In paediatric patients where episodes of AOM have been recurrent or an antimicrobial agent has been prescribed within the preceding 6 months, it is recommended to use agents in combination. One rational empirical approach is combining either vancomycin or linezolid with an anti-pseudomonal agent initially, then adjusting treatment if required once the results of microbiological analysis are known [3].

It may be necessary to add in further antibiotics in cases where a complication is present, such as a cerebral abscess, or where the initial gram staining points towards a less usual pathogen [3].

Treatment According to Pathogen. Once the microbiological analysis has shown the pathogen responsible and its sensitivity, the choice of antibiotic may need to be revised. Frequently occurring pathogens include the following [3]:

- *S. pneumoniae*
- *S. pyogenes*
- *S. aureus* (including strains insensitive to methicillin)

It is usually necessary in treating a patient with acute mastoiditis to drain any purulent discharge from the middle ear space and mastoid cells. Antibiotic treatment is generally inadequate as monotherapy, especially as the condition develops, since there may be problems delivering pharmaceutical agents at the necessary concentration within the osseous tissues [22]. Draining the lesion also helps to arrest further pathological development and may stop the condition becoming complicated [23]. Whilst it has been reported in the literature that acute mastoiditis responded fully to antibiotics without the need to undertake tympanocentesis or myringotomy [24], it is generally advisable to obtain a sample of fluid from the middle ear if antibiotic treatment is to avoid being blind.

There is considerable variation between clinics in terms of the optimal approach used to drain the lesion. Potential methods available are tympanocentesis, myringotomy, myringotomy with grommet insertion or mastoidectomy. The approach taken may depend on what stage mastoiditis has reached (e.g. with periosteal involvement or coalescent) and whether a complication is present and of what kind [4, 25, 26].

19.7.1.3 Mastoidectomy

This operation results in excision of the cortical bone of the mastoid and removal of the mastoid air spaces. There are two types. The simple type (which may be referred to as cortical, complete or canal-wall-up) involves preservation of the posterior portion of the external meatus. The radical procedure (which may be termed canal-wall-down) does not permit preservation of the posterior section of the meatus.

The simple procedure aims to clear away any infected material from the mastoid, allowing opening of the antral entrance and letting any remaining fluid drain to the outside [4]. The radical procedure is confined to cases where a simple mastoidectomy fails to relieve the problem and the patient still has an ear discharge and otalgia [4].

19.7.2 Chronic Mastoiditis

The approach to treating chronic mastoiditis resembles that taken in chronic suppurative middle ear infections, namely application of antibiotics topically. In cases of treatment failure, the ear needs to be regularly cleaned and antibiotics administered systemically. The initial agent given is one that targets both aerobes and anaerobes. More than 50% of Gram-negative anaerobes (such as pigment-bearing Prevotella, Porphyromonas, Bacteroides and Fusobacterium species) are no longer penicillin-sensitive, since they express a beta-lactamase. The agents that are still effective against anaerobes are clindamycin, cefoxitin, metronidazole, chloramphenicol, co-amoxiclav and piperacillin-tazobactam [2].

The surgical options encompass mastoidectomy, grommet insertion or tympanoplasty, depending on the specific indication. An important factor to consider is whether there is osteitis or periosteitis present. Any child with a chronic middle ear infection needs referral to an ENT specialist.

19.8 Complications

The following complications may arise from extracranial extension of mastoid inflammation [27]

- Seventh cranial nerve palsy.
- Auditory impairment, which may be of conductive or sensorineural type.
- Abscess formation within the subperiosteum.
- Osteomyelitis of the cranium, or an erosive process of the bone.
- Formation of a Bezold abscess. This lesion is located deeply within the cervical soft tissues.
- Inflammation of the labyrinth.
- Post-anginal septicaemia.
- Gradenigo syndrome, which consists of the following three features: sixth cranial nerve palsy, deep prosopalgia originating from the fifth cranial nerve and suppurative otitis media. Gradenigo syndrome arises because of inflammation of the petrous temporal bone.

The following complications may arise from intracranial extension of mastoid inflammation

- Extension of infection to the meninges. Abscess formation within the epidural space, the temporal lobe or elsewhere in the brain. Empyema formation under the dura mater. Abscess formation in the subperiosteum.
- Thrombus formation within the sinuses of the dura mater.

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Labyrinthitis in Children and Hearing Loss

20

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20.1 Introduction

Labyrinthitis refers to inflammation occurring in the labyrinth/inner ear. The clinical presentation involves symptoms of disordered balance and auditory impairment, which may vary in severity. It may be uni- or bilateral. Labyrinthitis may be triggered by bacterial or viral pathogens and occurs in the context of a local or systemic infection. Another potential cause is autoimmunity. Interruption to the blood supply of the labyrinth may cause symptoms that closely resemble labyrinthitis [1].

20.2 Aetiology

To appreciate the pathophysiological mechanism of labyrinthitis, it is vital to know the anatomy of the labyrinth and adjoining structures, namely the middle ear cavity, mastoid and subarachnoid space. The inner ear consists of an external bony framework that protects the fragile arrangement of membranes constituting the sense organs that allow for auditory perception and equilibrioception [1].

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The organs of perception consist of the utricle, saccule, semicircular canals and cochlea. Inflammation within the labyrinth results from invasion by pathogenic microbes or mediators of inflammation into the labyrinthine membranes. This then causes injury to the vestibular and auditory organs [1].

The inner ear is contained by the petrous temporal bone and lies next to the mastoid air cells. The communication with the middle ear cavity is via the round and oval windows. The internal acoustic meatus and canaliculus provide communication with the brain and the leptomeningeal space. Bacterial pathogens may invade the membranous labyrinth by this route or via a defect in the osseous labyrinth, which may have been present since birth or formed later. Viral pathogens reach the inner ear either via the bloodstream or through the canaliculus and internal acoustic meatus [1].

20.2.1 Causative Viral and Bacterial Pathogens

There is a lack of direct experimental confirmation that viruses cause labyrinthitis. Nonetheless, epidemiological data point towards several viral pathogens as likely causes of labyrinthitis. Viral labyrinthitis frequently follows an infection of the upper respiratory tract and may occur in outbreaks. On histopathological examination, the axons are degenerated within the vestibular nerve, and this implies that vestibular neuritis results from a virus [2].

Bacterial pathogens implicated in cases of labyrinthitis are identical with those causing meningitis and ear infections. If cholesteatoma is present, the pathogen involved is frequently a Gram-negative bacterium [1].

There are a number of viruses that may be responsible for labyrinthitis, namely [1]

- Cytomegalovirus
- Mumps virus
- Varicella-zoster virus
- Rubeola virus
- Influenza virus
- Parainfluenza virus
- Rubella virus
- Herpes simplex virus 1
- Adenovirus
- Coxsackievirus
- Respiratory syncytial virus

There are also a number of bacteria that may be responsible for labyrinthitis, namely [1]

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Neisseria meningitidis*

- *Streptococcus* species
- *Staphylococcus* species
- *Proteus* species
- *Bacteroides* species
- *Escherichia coli*
- *Mycobacterium tuberculosis*

20.3 Classification

20.3.1 Viral Labyrinthitis

Both congenital and acquired deafness may result from a viral infection. The most well-documented viruses responsible for congenital deafness are rubella and cytomegalovirus. If deafness occurs after birth, it is typically caused by mumps or measles. Viruses also appear likely to cause sudden sensorineural hearing loss (SNHL) in idiopathic cases. Molecules expressed in inflammation have been shown experimentally to feature significantly in the pathological mechanism by which cytomegalovirus causes deafness [3].

Herpes zoster oticus, also termed Ramsay-Hunt syndrome, is a distinctive subtype of labyrinthitis occurring secondary to a viral infection. In this syndrome, varicella-zoster virus, which has persisted from an earlier primary episode of infection, becomes active once more. It appears that the vestibulocochlear nerve is not the only region affected, since the spiral and vestibular ganglia are also affected [4]. This viral reactivation causes paralysis of facial muscles, the eruption of vesicles and, in around a quarter of cases, symptoms affecting hearing and balance [5].

20.3.1.1 Vestibular Neuritis

There are several synonyms used for vestibular neuritis, namely vestibular neuronitis, labyrinthitis, neurolabyrinthitis and acute peripheral vestibulopathy [6]. This condition resolves spontaneously and entirely in the majority of cases. However, patients with this condition may suffer briefly from limitations caused by the unpleasant symptoms. Patients complain of vertigo, feeling they are about to vomit or actual vomiting and difficulty in walking [7].

There is an overlap between the presentation of vestibular neuritis and other conditions with a graver prognosis, especially ischaemic events affecting the brain. It is vital that these more serious conditions are not misdiagnosed as vestibular neuritis, since failure to recognise them may lead to excessive morbidity or patient death [7].

The clinical picture of vestibular neuritis is a condition that occurs suddenly, without warning and affects the peripheral vestibular nerve. The patient suffers sudden vertigo, which is severe and accompanied by nausea, vomiting and difficulty walking without falling. Although vertigo in adults is often attributable to vestibular neuritis, this is not so for children. Patients demonstrate a preference for lying motionless on the opposite side from the lesion. Auditory impairment does not

result from vestibular neuritis. The aetiology has been hypothesised to involve a post-viral inflammatory response or an infection of the vestibular nerve caused by mumps, measles, Epstein-Barr virus or herpesvirus. One problem with this hypothesis is that under 50% of cases are found in patients where a recent infection with a virus has occurred. The duration of symptoms is between weeks and months [8].

Labyrinthitis is a subtype of vestibular neuritis, which appears as acute deafness accompanied by vertigo. The aetiology is infection affecting the inner ear due to a pathogenic virus or bacterium. Labyrinthitis may be seen in isolation or following a middle ear infection or meningitis. Auditory impairment in some cases does not recover [8].

Pathophysiology

Although vestibular neuritis is typically described as inflammation, which involves the vestibular division of the vestibulocochlear nerve [6], there is little evidence available to confirm this is what actually occurs in patients. Indeed, below 50% of cases can be linked to a viral infection before symptoms began [9–12]. A study that used magnetic resonance imaging scans as evidence found that 20 out of 29 cases diagnosed as vestibular neuritis exhibited enhanced lesions consistent with the putative pathogenetic mechanism [13].

Clinical Presentation

Symptoms of vestibular neuritis include an abruptly beginning vertigo of high severity that leaves patients unstable when walking and is accompanied by nausea and vomiting. It is an acute syndrome that occurs without warning and affects peripheral balance [7].

On physical examination, a picture of acutely disturbed balance is noted, namely [7]

- Unprovoked vestibular nystagmus that occurs to one side, in a horizontal direction, or horizontal plus rotary nystagmus. If the gaze is fixed, nystagmus disappears. The direction of nystagmus is not affected by where the patient is looking. The rapid phase of nystagmus is towards the unaffected ear.
- Positivity of head impulse testing. The physician turns the head swiftly in the direction of the affected ear, and the patient cannot keep their gaze fixed on one spot. A cases series found positivity of the test in 82% of cases [14]. Positivity of this test correlated with symptoms that endured for longer than average. Although positivity of the sign does correlate with vestibular neuritis, it may also occur with other conditions affecting the central nervous system [15].
- Patients can walk, albeit they are highly unstable. Any swaying or tendency to fall is on the side of the lesion, hence also in the direction of the rapid phase of nystagmus [7].
- There should be no other signs or symptoms indicating a nervous system disorder. Thus, the patient should not be dysarthric; unable to swallow; have weakness of the limbs, perceptual deficits and drooping of the face; or exhibit limb dysmetria. Although some patients do have double vision in a vertical direction or skew deviation, this finding should make the clinician suspect a cerebrovascular accident [7].

Diagnosis

Diagnosis is clinical, with no test that can rule vestibular neuritis out or in. The patient should present with features of an abrupt onset vestibular syndrome. The findings on physical examination have been discussed in the preceding section.

Where physical examination suggests features that are not consistent with a peripheral syndrome, imaging of the central nervous system is warranted. This applies where the patient is at an elevated likelihood of suffering a cerebrovascular accident, focal neurology is present or a new onset headache occurs with vertigo [10, 16]. Thus, the diagnosis is most likely in a young individual whose examination reveals a peripheral nervous disorder, exhibits nystagmus, has no other features of a nervous system lesion, and describes vertigo that begins suddenly and persists [10].

The ideal investigation is magnetic resonance imaging (MRI) with diffusion weighting (DWI) or MR angiography. Diffusion-weighted MRI is able to identify infarcted brain in the posterior fossa within 24 h of the triggering event. MR angiography is excellent for detecting vascular lesions within the posterior circulation, such as stenotic or occluded vessels. It is more than 95% sensitive and specific for this purpose [17]. Diffusion-weighted MRI may not at first reveal a cerebrovascular accident in the brain stem or cerebellum, if it is small and the investigation may need to be performed again 3 days after symptoms began, should a central lesion still seem likely. This second study should have perfusion-weighted sequences where feasible [18, 19].

If MRI is not an option (e.g. in a patient with a metal implanted device), CT may be used, with slices placed close to each other. If CT is performed within 60 min of infarction, the appearances do not reveal any abnormality. If there has been bleeding into the parenchyma or a degree of swelling sufficient to cause fourth ventricular compression, this abnormality is generally visible from an early stage. In a case where a scan of the CNS is called for, if MRI will be delayed, CT imaging should be undertaken without delay [7].

Therapy

There are several therapeutic options in cases of vestibular neuritis, such as direct treatment of the disorder using steroids and antiviral medication, treatment aiming to mitigate symptoms and vestibular rehabilitation therapy. There is limited trial evidence to confirm the efficacy of such approaches in vestibular neuritis [7].

Direct Treatment of Vestibular Neuritis Steroids administered during the acute phase of labyrinthitis have proven benefit in restoring peripheral balance, according to the results of a single trial. Nonetheless, several studies have since failed to replicate this finding. These more recent studies, however, suffered from several weaknesses [7].

Although the evidence base does not permit a definite conclusion on the clinical efficacy of steroids in acute vestibular neuritis of presumed viral aetiology, this approach appears defensible, provided the treatment is not contraindicated. Similarly, if there is a heightened risk of side effects, withholding this treatment also seems appropriate [7].

Palliative Treatment It is common to employ palliative methods to lessen vertigo, nausea and vomiting within the initial days after the onset of vestibular neuritis. Palliative agents suitable for this purpose are antiemetics and antihistamines. It is usually best not to supply oral agents, due to vomiting. Start at a minimal dose and increase until the desired effect is achieved [7].

Vestibular Rehabilitation Based on the scores used to measure symptomatic severity and functional balance in cases where peripheral damage to the vestibular system has occurred on one side, vestibular rehabilitation may be considered beneficial [20]. There is considerable clinical experience, too, showing that this treatment results in significant benefit.

20.3.2 Bacterial Labyrinthitis

Bacterial labyrinthitis may be a complication of infection of the meninges or middle ear and occurs by two mechanisms: in suppurative cases, the pathogens themselves enter the inner ear; in serous cases, it is the entry of toxins synthesised by the bacterium or inflammatory signalling molecules that trigger the condition. The most frequently occurring complication of a middle ear infection is actually labyrinthitis, which may represent 32% of all complications, whether intra- or extracranial, according to a single study [21].

Whilst bacterial labyrinthitis is seldom seen since antibiotics have become widely available, deafness is still often the outcome following meningitis [21]. Up to 20% of paediatric cases of meningitis feature symptoms related to balance and hearing [22]. In cases of meningitis, the symptoms are usually bilateral, in contrast to ear infections, which usually only affect one side [1].

20.3.2.1 Suppurative Labyrinthitis

Bacterial infection can track into the membranous labyrinth via the internal acoustic meatus or cochlear aqueduct from the cerebrospinal fluid when meningitis is present. For bacteria causing otitis media or mastoiditis to reach the inner ear, there is usually dehiscence of the horizontal semicircular canal [23]. This crack in the bone typically occurs because of encroachment by cholesteatoma. Suppurative infection of the labyrinth occurring as a complication of middle ear infection is rare now that efficient antimicrobial treatments are available. Indeed, when seen, it is virtually invariably accompanied by cholesteatoma. Bacterial labyrinthitis frequently causes almost complete deafness, vertigo of high severity, ataxia, nausea and vomiting [1].

20.3.3 Serous Labyrinthitis

In cases of serous labyrinthitis, there are no actual pathogens within the inner ear. Instead, bacteriotoxins, inflammatory signalling molecules or complement proteins traverse the round window, setting up an inflammatory reaction in the labyrinth

[24]. Serous labyrinthitis occurs in association with acute or chronic otitis media. It is considered amongst the most frequent ways a middle ear infection may be complicated.

Bacteriotoxins or mediators of inflammation enter the tympanic duct and are deposited at a point slightly medial to the round window. When these molecules diffuse into the endolymph at the base of the cochlea, auditory impairment results. This impairment is of sensorineural type and affects high-pitched sounds to a mild or moderate degree [1].

If an effusion exists within the middle ear cavity, audiometry will show auditory impairment of mixed type. Problems with balance are possible, but not as frequent. The therapeutic goal in such cases is to eradicate any pathogen and drain the effusion. Auditory impairment is generally temporary but may become chronic if the ear infection is not treated [1].

20.3.4 Autoimmune Labyrinthitis

Rarely autoimmune labyrinthitis occurs, resulting in auditory impairment of sensorineural type. It may be localised to the labyrinth or be part of a systemic autoimmune condition, such as granulomatosis with polyangiitis or polyarteritis nodosa [25, 26].

20.4 Prognosis

Although vertigo, nausea and vomiting symptoms in cases of labyrinthitis cease within days or weeks, regardless of cause, the extent to which auditory impairment resolves is less predictable [1].

Suppurative labyrinthitis virtually invariably causes permanent, almost complete deafness. However, where deafness is secondary to viral infection, the auditory impairment may resolve. Derangement of balance and position-related vertigo may persist for some weeks after the acute infective episode has ended [1].

20.4.1 Morbidity and Mortality

There is no association between labyrinthitis and mortality unless the condition is secondary to meningitis or severe septicaemia. However, labyrinthitis does cause considerable morbidity, particularly when its cause is bacterial [1].

Bacterial labyrinthitis (irrespective of the pathogen involved) is responsible for one in three cases of acquired deafness.

It is estimated that between 10 and 20% of children with meningitis will suffer permanent auditory impairment [22, 27]. According to one study, the risk of vertigo in cases of meningitis resulting from infection with *Streptococcus pneumoniae* is 23% [28].

Around 6% of cases of Ramsay-Hunt syndrome who have deafness at presentation go on to have permanent auditory loss of sensorineural type [23]. Pneumococcal infection seems to be the most common reason for deafness to occur following meningitis [29].

20.5 Diagnosis

20.5.1 History

A detailed patient account encompassing symptomatology, past medical history and drug history is vital for a diagnosis of labyrinthitis in a case presenting with vertigo or acquired deafness. The following symptoms should be carefully enquired about [1]:

- Vertigo—onset and length it persists. Whether its intensity varies when moving the body or head and its general character
- Deafness. One or two-sided, severity, length of time present and other features
- Feeling the ear is full
- Tinnitus
- Ear discharge
- Earache
- Nausea or vomiting
- Pyrexia
- Paresis of facial muscles or asymmetrical expression
- Nuchal pain or rigidity
- Symptoms suggestive of an upper respiratory tract either before or currently
- Alteration in vision

Items to take particular note of when obtaining the patient's past medical history include the following [1]

- Vertigo and auditory problems
- Infective episodes
- Contact with sick individuals
- Otological operations
- Blood pressure problems (hyper- or hypo-tension)
- Diabetes mellitus
- Cerebrovascular accident
- Migraine
- Traumatic injury to the head or neck
- History of auditory impairment or otological disorder in a family member

It is also important to check the patient's drug history, in particular exposure to [1]

- Aminoglycosides or other agents of known ototoxicity
- Beta-blockers or other blood pressure medications

- Sedatives, such as benzodiazepines
- Epilepsy drugs
- Alcohol
- Illicit substances

20.5.1.1 Physical Examination

The patient's head and neck should be thoroughly examined, paying particular attention to examining the ears, eyes and cranial nerves. An abbreviated examination of the nervous system is likewise called for. If meningitis is suspected, look for signs that may confirm the diagnosis [1].

The ears should be examined in the following manner [1]

- Examine the external ear, looking for evidence of mastoiditis, cellulitis and previous otological procedures.
- Inspection of the external auditory meatus may reveal otitis externa, ear discharge or vesicles.
- When evaluating the eardrum and middle ear, look for a perforated membrane, cholesteatoma, middle ear effusion or an acute middle ear infection.

The eyes should be examined in the following manner [1]

- Check the eyes' range of movement and how the pupils respond.
- Use the ophthalmoscope to check for papilloedema.
- Check for nystagmus and how it is provoked (spontaneously, provoked by looking in one direction, related to position). If tolerated, undertake the Dix-Hallpike manoeuvre.
- If vision is impaired, seek an ophthalmological opinion.

The nervous system should be examined in the following manner [1]

- Test each of the cranial nerves.
- Evaluation of balance uses Romberg testing and hell-to-toe walking.

20.5.2 Audiographic Assessment

Every patient with suspected labyrinthitis should have an audiogram performed. Assessment of patients who are markedly unwell or suffer severe vertigo can be undertaken when their condition stabilises and testing is bearable. There are clues to the type of labyrinthitis revealed by the audiogram. Inflammation of the inner ear secondary to a middle ear infection will probably produce an audiogram showing impairment of mixed type. A viral cause usually results in audiometric evidence for sensorineural deafness. If audiometry cannot be undertaken in a particular patient, alternative investigations of value are otoacoustic emissions testing and auditory brain stem responses [1].

Labyrinthitis of viral origin produces sensorineural pattern auditory impairment on the side of the lesion, with higher-pitched sounds usually, but not invariably, affected and of mild or moderate severity.

Suppurative labyrinthitis secondary to a bacterial infection causes deafness on the affected sound that is of severe or profound degree. Where meningitis occurs, both ears are frequently deaf. Serous labyrinthitis secondary to a bacterial infection affects one ear and causes impairment in the ability to perceive higher frequencies. An effusion may result auditory impairment of conductive type on the affected ear [1].

20.5.3 Imaging Studies

20.5.3.1 Computed Tomography (CT)

If meningitis is suspected, CT may be advisable prior to performing a lumbar puncture. This investigation is also beneficial in excluding a diagnosis of mastoiditis. Scanning of the temporal bone helps treatment planning for cases where labyrinthitis occurs in conjunction with cholesteatoma.

CT without the use of a contrast agent is the most helpful method to image fibrosis and calcification within the membranous labyrinth in cases where labyrinthitis has become chronic or is of the ossificans type [1].

20.5.3.2 Magnetic Resonance Imaging (MRI)

MRI is a helpful investigation where there are certain competing diagnoses to explain vertigo and deafness, such as acoustic neuroma, cerebrovascular accident, cerebral abscess or epidural haematoma.

T1-weighting on MRI exhibit enhancement of the cochlea, vestibule and semicircular canals after injection of contrast if the diagnosis is labyrinthitis, whether acute or subacute [30]. These appearances have high specificity and match the results of the history and examination. MRI with contrast is being steadily refined, and this may become the ideal investigation in labyrinthitis in the future [31]. Tumours within the cochlea can be differentiated from other conditions affecting the labyrinth, such as inflammation, on the basis of how intensely they enhance with gadolinium-based contrast [32].

20.6 Therapy

20.6.1 Viral Labyrinthitis

Viral labyrinthitis patients should be advised to rest in bed and maintain adequate hydration. The majority of these cases do not require hospital admission. They should, nonetheless, be warned that if fresh symptoms appear, such as double vision, unclear speech, problems walking, paresis or paraesthesia, they should urgently seek medical attention. If patients are severely nauseous or vomit frequently, intravenous hydration and antiemetic agents may be beneficial [1].

20.6.2 Bacterial Labyrinthitis

The choice of antimicrobial therapy is guided by the results of bacteriological culture and susceptibility tests. Therapeutic aims in suppurative labyrinthitis are eradication of the pathogen, support for the patient, drainage of any effusion in the middle ear or mastoid and ensuring the infection remains contained [1].

20.6.3 Surgical Interventions

For patients where labyrinthitis is secondary to a middle ear infection, myringotomy should be carried out and any effusion drained. Grommets may need to be inserted. Aspirated fluid should be sent to the laboratory for microscopy, culture and susceptibility testing.

In cases of mastoiditis or cholesteatoma, a mastoidectomy is indicated, which drains and debrides the area [1].

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Bacterial Meningitis in Children and Hearing Loss

21

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21.1 Introduction

Acute bacterial meningitis (ABM) is inflammation of the meninges caused by bacteria or bacterial products. It is still one of the primary concerns for pediatricians due to high morbidity and mortality in childhood [1, 2]. The World Health Organization (WHO) estimates 170,000 deaths due to ABM annually [2]. Despite appropriate and immediate antibiotic treatment, significant morbidities such as neuropsychological deficits, particularly hearing loss (HL), can occur.

Haemophilus influenzae type b (Hib) was one of the most common microorganisms as the cause of ABM worldwide before the introduction of the conjugate Hib vaccine into routine infant immunization globally. *Streptococcus pneumoniae* became the most common causative pathogen in global invasive bacterial vaccine-preventable disease surveillance by WHO between 2014 and 2019 [2]. The highest attributable mortality rate was also determined in patients with *S. pneumoniae*

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meningitis. The pneumococcal conjugate vaccine (PCV)-7 has been available since 2000, followed by PCV-13 in 2010. Furthermore, a dramatic decline occurred in ABM incidence after implementing conjugate Hib and pneumococcal vaccines into infant immunization programs in many countries [3–10].

The United Kingdom (UK) licensed the first meningococcal conjugate vaccine in 1999 [10]. In the following years, remarkable progress has been observed with meningococcal vaccines worldwide, including in the meningitis belt of Africa [11]. Today, a few quadrivalent meningococcal conjugate vaccines in which the capsular polysaccharides from *Neisseria meningitidis* serogroups A, C, W, and Y are conjugated to different carrier proteins are available, mainly in middle- and high-income countries [12]. *Neisseria meningitidis* serogroup B (MenB) has also been the leading cause of invasive meningococcal disease (IMD) in several European countries [13]. Two meningococcal vaccines developed against serogroup B are widely available in several countries, and one of them has been in use for infants and young children [12]. Various meningococcal serogroup C conjugate vaccine formulations have also been available in Europe, Canada, and other countries [12].

Acute bacterial meningitis still contributes to morbidities such as neuropsychological deficits and mortality. Meanwhile, ABM is still one of the significant causes of HL during childhood. Therefore, it is crucial to implement vaccines against *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* into national immunization programs worldwide to develop herd immunity and reduce ABM incidence.

21.2 Etiology and Epidemiology

The causative microorganisms of ABM vary according to the patient's age, immunization status, socioeconomical factors, geographic region, and underlying conditions such as immunodeficiency. In the neonatal period, the most common etiologic pathogens are *Streptococcus agalactiae* (group B *Streptococcus*; GBS), contributing to about half of the cases (50%), and *Escherichia coli* (20%) [13]. Screening and intrapartum antibiotic prophylaxis (IAP) have been implemented for pregnant women with high-risk factors for GBS in several countries [14]. Other strategies, including mother GBS vaccination, have also been studied to reduce bacterial translocation in mouse models [15]. A recent study using whole-genome sequencing showed that *S. agalactiae* serotype 1b sequence type 10 (ST10) carried a higher risk for neonatal meningitis [16]. The remaining rare pathogens are *Klebsiella* spp., *Enterococcus* spp., *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus pyogenes* (group A *Streptococcus*; GAS), and nontypeable *H. influenzae*. Gram-negative pathogens, including *E. coli* and *Klebsiella*, have been more common in low- and middle-income countries [17, 18]. A 7-year retrospective study from Ethiopia showed that *Klebsiella pneumoniae* and *E. coli* contributed nearly 60% of the causative pathogens, and *S. agalactiae* was the third most common [18].

Streptococcus pneumoniae (PCV and non-PCV serotypes), *N. meningitidis*, rarely non-typeable *H. influenzae*, and other rare bacterial pathogens are the leading causes of ABM beyond the neonatal period [2]. After implementing the PCV-7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), a shift toward non-PCV serotypes was observed. Following this shift, a 13-valent (additional serotypes 1, 3, 5, 6A, 7F, 19A) PCV (PCV-13) was implemented in 2010. However, despite the administration of PCV13, breakthrough cases were reported most frequently due to 3, 19A, and 19F [19]. Pediatric meningitis surveillance in Southern and East African countries from 2008 to 2017 evaluated pathogens by using the polymerase chain reaction (PCR) test, which determined a pathogen in 10% of 11,626 samples; *S. pneumoniae* (7%) was the most common, followed by *H. influenzae* (2%) and *N. meningitidis* (1.5%) [20].

In high-income countries, *S. pneumoniae and H. influenzae* meningitis have been dramatically reduced through conjugate vaccines; *N. meningitidis* has become the most common pathogen in some. The highest incidence of invasive meningococcal disease (IMD) has been observed in the African meningitis belt [21]. Of 13 *N. meningitis* serogroups, six serogroups (A, B, C, W, X, Y, and Z) predominantly cause IMD and show geographic and temporal variation [22]. *Neisseria meningitis* serogroup B has been the most common cause of IMD in the United States of America (USA) and European countries. Six college outbreaks were observed in the USA due to MenB between 2014 and 2016; a nearly four-fold increased risk was determined for college students versus non-college students [23]. Therefore, college students have been included in the risk group for MenB infection. Meningococcus serogroup A (MenA) was predominant before the MenA conjugate vaccine was developed for the African meningitis belt countries [24].

The global incidence of ABM declined after implementing Hib, PCV, and meningococcal vaccines into infant immunization programs, while deaths decreased by 21.0% from 1990 to 2016 [9]. The incidence of ABM significantly decreased in the USA, Greenland, European, high-income West Asian, and Latin American countries [25]. Invasive pneumococcal diseases, in general, also declined; however, the decrease was not as remarkable as the infections caused by Hib due in part to an increase in the incidence of non-PCV13 serotypes [19, 25]. Sub-Saharan African countries in the meningitis belt still battle with ABM that meningococci cause seasonal meningitis outbreaks every 8–12 years [26, 27].

The median age of patients with bacterial meningitis rose to 30–40 years from <5 years, while the highest incidence of ABM is still in the neonatal period (81 per 100,000 population) [1, 13]. The leading causative pathogens of ABM are transmitted via respiratory droplets, and isolation procedures can alter transmission rates. A recent prospective analysis of the effect of coronavirus disease 2019 (COVID-19) containment measures showed a dramatic decline in invasive diseases due to *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* in 26 countries in early 2020 (January 1 to May 31, 2020) [28]. However, pandemic restriction implementations did not alter the incidence of S. agalactiae infections.

21.3 Pathogenesis and Predisposing Risk Factors

Acute bacterial meningitis can occur from hematogenous spread, direct invasion from adjacent sites, or rarely secondary to epidural and subdural spaces. Bacterial entry induces the blood–brain barrier (BBB) to lead to a robust inflammatory response, including releasing cytokines, mainly tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1-β), and IL-6, and polymorphonuclear leukocyte (PMN) transendothelial migration across the BBB [29, 30]. Several factors, such as capsule, cell-wall anchored proteins, neuraminidase A of *S. pneumoniae* and capsule, type IV pili, and outer membrane proteins of *N. meningitidis*, are thought to contribute to leptomeningeal bacterial invasion by these pathogens [31].

Acute bacterial meningitis develops most commonly by two main routes of bacteria invading the central nervous system (CNS): (1) hematogenous, which can result from (a) nasopharyngeal colonization followed by bacterial translocation to the bloodstream and CNS invasion, (b) another localized source causing bacteremia such as translocation of enteric bacteria to the bloodstream and then CNS invasion, (c) transplacentally; (2) direct entry from adjacent sites (sinusitis, mastoiditis), trauma, or surgery resulting in cerebrospinal fluid (CSF) leak or via medical devices (CSF shunts, cochlear implants), via dermoid sinus tracts and meningomyelocele [1, 30].

Well-described predisposing risk factors for specific pathogens are as follows [1, 32]:

Streptococcus pneumoniae: Splenectomy or with a hyposplenic state, chronic kidney or liver disease, human immunodeficiency virus (HIV) infection, hypogammaglobulinemia, anatomic defects resulting CSF leak (surgery or fracture), presence of a cochlear implant.

Neisseria meningitidis: Complement system deficiencies, a recent visit to an endemic country (African meningitis belt countries).

Haemophilus influenzae: Hypogammaglobulinemia, splenectomy, or with a hyposplenic state.

21.4 Clinical Manifestations

Clinical manifestations are nonspecific in the neonatal period, including poor feeding, vomiting, hypothermia, hyperthermia, abdominal distension, respiratory distress, bulging fontanel, and lethargy [1, 30]. Fever and seizure are the most frequent manifestations in neonates [30].

Beyond the neonatal period, the classic triad of bacterial meningitis includes fever, neck stiffness, and altered mental status (e.g., confusion, lethargy, and irritability). However, the classic triad occurs in 40–50% of the patients [30]. Other symptoms may include headache, photophobia, nausea, and vomiting. Meningeal irritation signs include neck stiffness, Kerning, and Brudzinski signs, which may be present in 60–80% of the children with ABM [1]. Neck stiffness is the most common meningeal sign, particularly in younger children.

Other presentations may be seizure, petechiae, and purpura, particularly in meningococcal meningitis, increased intracranial pressure signs including hypertension, bradycardia, respiratory depression, focal neurologic deficits, and other systemic findings [1, 14].

21.5 Diagnosis

Acute bacterial meningitis requires prompt diagnosis and optimal treatment within 1 h of presentation. Antibiotics should be initiated immediately, even if a lumbar puncture (LP) cannot be performed due to sepsis symptoms, including hypotension, bradycardia, and respiratory failure [33]. However, blood cultures should be obtained before antibiotics are administered to increase the likelihood that the causative pathogen will be isolated to guide subsequent antibiotic treatment and help determine the need for antibiotic prophylaxis for patient contacts. The history should include the type and duration of symptoms, presence of predisposing risk factors (immunodeficiency, anatomic defect, medical devices, and trauma), travel or contact history, immunization history, and recent antibiotic use [1].

Cerebrospinal fluid culture is essential in the diagnosis of bacterial meningitis and should be obtained via LP in children with suspicion of this diagnosis unless there is a contraindication to do so. Neuroimaging should be performed before LP in the presence of the focal neurologic deficit, papilledema, and altered level of consciousness in the neurological examination. Lumbar puncture is contraindicated in cases with a mass lesion due to the risk of cerebral herniation and in patients with coagulopathy, severe thrombocytopenia, cardiopulmonary compromise, and local site infection where the LP would be performed [1, 14, 32, 34, 35].

Cerebrospinal fluid evaluation should include macroscopic and Gram stain examination, cell count and differential, glucose and protein concentration, culture, antimicrobial susceptibility testing of isolated microorganisms, and possibly PCR [1, 34]. Cerebrospinal fluid findings in ABM include pleocytosis with a predominance of neutrophils, elevated CSF protein, decreased CSF glucose, and a positive Gram stain [32, 34, 35]. Typically, CSF is clear in appearance and shows <6 white blood cells/mm^3 with no neutrophils, glucose level >45 mg/dL, and protein level <45 mg/dL. In ABM, the appearance of CSF is usually cloudy. The typical CSF white blood cell count (WBC) is >1000 cells/mm^3 with a predominance of neutrophils (80–95%); however, it can be lower in the early phase of ABM. The CSF glucose level is typically low, usually <60% of a concomitantly measured blood glucose level and usually <40 mg/dL; protein level can be high as 100–500 mg/dL [32, 34]. A traumatic LP can impact the CSF cell count and protein measurements due to bloody CSF; the first drawn tube carries the highest risk for red blood cells (RBCs) from a traumatic LP and contamination of non-CSF bacteria.

A bacterium can be determined via Gram staining in nearly 80% of the patients if an antibiotic has not already been administered. A positive Gram stain may help guide antibiotherapy. The characteristic morphologic features of the common pathogens are as follows: Gram-positive diplococci suggest *S. pneumoniae*,

gram-negative diplococci suggest *N. meningitidis*, and small pleomorphic gram-negative coccobacilli suggest Hib, gram-positive cocci or coccobacilli indicate GBS, and gram-positive rods and coccobacilli suggest *L. monocytogenes* [31, 34, 35]. Acute bacterial meningitis is confirmed with the isolation of bacteria from CSF. However, prior administration of antimicrobial agents may alter CSF biochemical parameters and cell count, while CSF culture may be negative [34]. The PCR test may identify the causative pathogen in pretreated children with suspected bacterial meningitis [36]. Latex agglutination and immunochromatographic antigen tests have little value in diagnosing ABM and are unavailable in many centers [32].

Neuroimaging should not be performed routinely before LP and should be reserved for patients with severely altered mental status (Glasgow Coma Scale score <10), papilledema, focal neurologic deficit (excluding cranial nerve palsies), CSF shunt in place, history of hydrocephalus, recent CNS trauma or neurosurgery, severely immunocompromised status, and new-onset seizure [32]. Neuroimaging is typically recommended for the evaluation of the complications of ABM, such as hydrocephalus, subdural effusion, empyema, infarction, parenchymal abscess, and ventriculitis in patients with persistent fever (>5 days), new-onset fever or seizures occurring after 48–72 h despite appropriate treatment [37].

21.6 Management

Empiric antibiotic therapy should be administered, even if LP cannot be performed in which case blood cultures should be obtained prior to antibiotic administration [32, 34, 35]. Appropriate respiratory and hemodynamic support should be based on disease severity. Patients are initially managed optimally in a pediatric intensive care unit.

The empiric antibiotic treatment differs for neonates and older children. While choosing empiric treatment, the local rate of decreased susceptibility to penicillin and third-generation cephalosporins of *S. pneumoniae* should be considered. Table 21.1 summarizes the empiric therapy for community-acquired ABM in children [32].

Antibiotic treatment should be optimized for antibiotic susceptibility testing when the culture identifies a causative pathogen. Reduced susceptibility to penicillin and third-generation cephalosporins of *S. pneumoniae* are concerns worldwide. Penicillin G or ampicillin should not be initiated empirically and should be reserved for susceptible pneumococcal or meningococcal meningitis (penicillin minimum inhibitory concentration [MIC] ≤0.06 μg/mL). Cefotaxime or ceftriaxone can be used for penicillin–nonsusceptible pneumococci (penicillin MIC >0.06 μg/mL). If a pneumococcal isolate is nonsusceptible to cefotaxime or ceftriaxone (MIC ≥1 μg/mL), vancomycin should be continued along with a third-generation cephalosporin. Most *N. meningitidis* strains are susceptible to penicillin; third-generation cephalosporins would be preferred in the rare instance when an isolate has reduced susceptibility to penicillin (MIC ≥0.06 μg/mL) [38]. Table 21.2 summarizes the definitive treatment and durations for bacterial pathogens causing community-acquired ABM in children.

Table 21.1 Empiric antimicrobial treatment for community-acquired acute bacterial meningitis in children[a]

Age	*Streptococcus pneumoniae* susceptible to penicillin	Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	Dosage
<1 month old	–	Amoxicillin/ampicillin/ penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside	Age <1 week: ampicillin/ amoxicillin 50 mg/kg q8h; cefotaxime 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/ kg q6h; cefotaxime 50 mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h
1 month to 18 years	Cefotaxime or ceftriaxone	Cefotaxime or ceftriaxone plus vancomycin ± rifampicin	Vancomycin 10–15 mg/kg q6h; rifampicin 10 mg/kg q12h; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h

q6h every 6 h, *q8h* every 8 h, *q12h* every 12 h
[a] Adapted and modified from Refs. [34, 39, 40]

Table 21.2 Definitive therapy and duration for community-acquired acute bacterial meningitis in children[a]

Organism	Standard treatment	Alternatives	Dosage	Duration
Streptococcus pneumoniae				
Penicillin susceptible (MIC ≤0.06 μg/mL)	Penicillin or amoxicillin/ ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	Penicillin G 300,000 units/kg/ day in four to six divided doses; ampicillin 50 mg/ kg q6h; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/ kg q12h	10–14 days
Penicillin nonsusceptible (MIC >0.1 μg/ mL), third-generation cephalosporin susceptible (MIC <2 mg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, moxifloxacin[b]	Cefotaxime 75 mg/ kg q6h; ceftriaxone 50 mg/kg q12h	10–14 days
Cephalosporin nonsusceptible (MIC ≥1 μg/mL)	Cefotaxime/ ceftriaxone plus vancomycin plus/minus rifampicin	Vancomycin plus moxifloxacin	Vancomycin 15 mg/kg q6h; rifampicin 10 mg/ kg q12h; cefotaxime 75 mg/ kg q6h; ceftriaxone 50 mg/kg q12h	10–14 days

(continued)

Table 21.2 (continued)

Organism	Standard treatment	Alternatives	Dosage	Duration
Neisseria meningitidis				
Penicillin susceptible (MIC ≤0.06 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	Penicillin G 300,000 units/kg/day in four to six divided doses; ampicillin 50 mg/kg q6h	7 days
Penicillin reduced susceptibility (MIC ≥0.06 μg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, or chloramphenicol	Cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h	7 days
Listeria monocytogenes	Amoxicillin or ampicillin, penicillin G plus gentamicin	Trimethoprim–sulfamethoxazole[c], meropenem plus gentamicin, linezolid	Penicillin G 300,000 units/kg/day in four to six divided doses; ampicillin 50 mg/kg q6h	21–28 days
Haemophilus influenzae				
Beta-lactamase negative	Amoxicillin or ampicillin	Ceftriaxone, cefotaxime, or chloramphenicol	Ampicillin 50 mg/kg q6h	7–10 days
Beta-lactamase positive	Ceftriaxone or cefotaxime	Cefepime, ciprofloxacin, chloramphenicol	Cefotaxime 75 mg/kg q6h; ceftriaxone 50 mg/kg q12h	7–10 days
Beta-lactamase-negative ampicillin resistant	Ceftriaxone or cefotaxime, plus meropenem[d]	Ciprofloxacin	Cefotaxime 75 mg/kg q6h; ceftriaxone 50 mg/kg q12h, meropenem 40 mg/kg q8h	7–10 days
Group B *Streptococcus*	Penicillin G or ampicillin	–	Penicillin G 450,000–500,000 units/kg/day in four divided doses; ampicillin 50 mg/kg q6h	14–21 days

MIC minimum inhibitory concentration, *q6h* every 6 h, *q8h* every 8 h, *q12h* every 12 h

[a] Adapted and modified from Refs. [14, 32]

[b] Might consider if serious allergy to ceftriaxone/cefotaxime and would not use alone but in combination with vancomycin considering the paucity of data on moxifloxacin treatment of pneumococcal meningitis

[c] Alternatives are considered only if the patient cannot be desensitized to penicillin

[d] Only a few case reports on the treatment of this infection, so very little information is available on which to base a recommendation of meropenem, along with ceftriaxone or cefotaxime

21.7 Hearing Loss in Children with Acute Bacterial Meningitis

Acute bacterial meningitis can cause short-term complications, including seizures, focal neurological deficits, brain abscesses, and long-term permanent sequelae, particularly HL, cognitive impairment, hydrocephalus, and epilepsy. Sensorineural HL (SNHL) is a significant long-term sequela, and hearing should be tested before discharge or within 1 month [34]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommended administering dexamethasone in all suspected ABM cases [32]; the American Academy of Pediatrics (AAP) advises dexamethasone use for children 6 weeks and older in Hib meningitis [39]. However, dexamethasone is not routinely recommended for *S. pneumoniae*-caused ABM; the AAP advises weighing the potential benefits and risks [40]. Dexamethasone should be discontinued if a pathogen other than these pathogens grew in the CSF culture [35]. A recent study from Denmark that evaluated all children with ABM during 1998–2016 showed that nearly every one of four children developed neurological sequelae; HL was the most common (15%) [41]. Hearing loss occurs more frequently following pneumococcal meningitis (22–30%) than meningococcal meningitis (1–8%) [35].

Once bacteria invade the meninges and disrupt the blood–brain barrier (BBB), through the hematogenous spread, direct extension from paranasal and dental infections, skull base fracture causing CSF leak, or direct implementation, immune activation is triggered by different pathogen-associated molecular patterns (PAMPs) [35, 42]. Toll-like receptors (TLRs) 2, 4, 5, and 9 first recognize bacteria and Nod-like receptors (NLRs), which lead to the activation of intracellular signaling pathway factors such as nuclear factor-kappa B (NF-κB) [35, 42]. Nuclear factor-kappa B is a transcriptional activator of the genes that encode the pro-inflammatory cytokines and adhesion molecules such as TNF-α, IL-1, IL-8, and the intercellular adhesion molecule 1 (ICAM-1). Tumor necrosis factor-alpha and IL-1β are released as inactive precursors, transforming into active forms by proteases (caspase 1 [Casp]). They are significant inducers of NF-κB and the key molecules resulting in meningeal inflammation [42]. Tumor necrosis factor-alpha and IL-1β activate proteolytic enzymes (matrix metalloproteinase [MMP]-8, MMP-9) and oxidants (peroxynitrite); chemokines and adhesion molecules subsequently trigger leukocyte accumulation and activation of proteolytic enzymes and oxidants [35, 43]. Matrix metalloproteinase-8 and MMP-9 cause extracellular matrix degradation and tissue destruction; nitric oxide, superoxide, and peroxynitrite cause oxidant-induced deoxyribonucleic acid (DNA) strand breakage and energy depletion lipid peroxidation that leads to loss of membrane integrity [43]. These host inflammatory responses result in vasculitis, focal ischemia, increased intracranial pressure, transmigrating leukocytes, glial cells and astrocyte stimulation, cortical necrosis, and hippocampal neuronal loss stemming [35, 42].

The chemokines and adhesion molecules trigger massive leukocyte accumulation into the subarachnoid space. Tumor necrosis factor-alpha and IL-1β, together with activated leukocytes, contribute to the release of oxidants, leading to the blood labyrinth barrier breakage and cochlea cytotoxicity. Another contributing

mechanism is the occlusion of the inner ear's blood vessels due to septic emboli and thrombus, leading to cochlear hypoxia, ischemia, and neural damage [35].

Hearing loss may develop early after infection, whereas late-onset HL can also occur. Early detection is crucial because patients can develop cochlea ossification, and a cochlea implant should be placed before obliteration. Furthermore, early diagnosis is essential to minimize the development of speech and language delay, balance disturbances, and behavioral disorders. Audiology assessment is recommended for children diagnosed with confirmed ABM before discharge or within 1 month [35, 39, 40, 44].

Unilateral or bilateral SNHL occurs in around 10% of children with ABM. Bilateral severe or profound HL has been mainly observed in children after *S. pneumoniae* meningitis (14–32%), followed by *N. meningitidis* (4–23%) and *H. influenzae* (20%) [33]. A 20-year invasive pneumococcal disease (IPD) surveillance, which included 83 children with meningitis, reported that 14% developed HL of the 51 patients who underwent auditory assessment [45]. At the time of discharge, 31% of 161 pediatric survivors of pneumococcal meningitis had SNHL among patients seen at eight USA children's hospitals between 2007 and 2013 [46]. A 1-year follow-up analysis of IMD conducted in Israel determined that 7% of the children developed HL, while half of the cases were severe [47].

In a study from Bangladesh, short-term follow-up (30–40 days) determined that 33% of the children had HL, while long-term follow-up (6–24 months) showed that only 18% were permanent, which demonstrated that HL developed after pneumococcal meningitis could be reversible [48]. Roine et al. [49] also showed that HL could be reversible and frequently improves in children with initially severe HL. The decrease in HL in a long-term period was attributed to recovered patients and reversible HL. In contrast, some patients with normal ears or moderate impairment became severely impaired.

The risk factors for HL after ABM were reported as underlying comorbidity, late (illness >24 h before intervention) admission, the severity of meningitis (mechanical ventilation requirement, presence of septic shock signs), raised intracranial pressure at admission, low glucose, and high protein in CSF [50].

21.7.1 Adjunctive Therapy to Prevent Hearing Loss in Children with Acute Bacterial Meningitis

Adjunctive therapies are recommended for reducing short- and long-term neurological sequelae of ABM. These therapies targeted five main areas: (1) non-bacteriolytic antibiotic use such as rifampin and daptomycin to modulate bacterial killing and the release of bacterial products, (2) initiation of the inflammatory response via host recognition of bacteria or its products, (3) adjuvant dexamethasone to modulate the uncontrolled inflammatory response, (4) host inflammatory and neurotoxic mediators inhibition, and (5) modulation of the apoptotic pathways [35].

Experimental animal models of bacterial meningitis were conducted to evaluate TNF-α, matrix metalloproteinases, nitric oxide and antioxidants, neuroprotective factors (melatonin and brain-derived neurotrophic factor), and other

anti-inflammatory therapies (triptans) because of the significant role of host uncontrolled inflammatory response in neuronal damage; however, not yet proved and not in clinical use [35]. In combination with cipemastat (Trocade®), a metalloproteinase inhibitor, daptomycin, reduced neuroinflammation and brain damage in the pneumococcal meningitis rat model [51]. G-protein cannabinoid receptor type 2 (CB2) agonists are another potential candidate that downregulates pro-inflammatory processes but did not alter brain damage in experimental pneumococcal meningitis [52].

Bacterial meningitis causes apoptotic damage to the hippocampus. Vitamin B12 lessened hippocampal damage by deactivating pro-inflammatory genes in an experimental model of *S. pneumoniae* meningitis in infant rats [53].

21.7.1.1 Adjuvant Dexamethasone Therapy

In experimental models, corticosteroids reduced inflammatory response and improved outcomes. However, dexamethasone use in children is still controversial. A meta-analysis evaluated dexamethasone adjuvant therapy in ABM included 2029 patients from five trials of all ages and showed that dexamethasone use in ABM did not alter mortality, severe neurological sequelae, or severe bilateral deafness; meanwhile, a nearly 5% decrease was observed in HL in survivors [54].

A recent meta-analysis of adjunctive dexamethasone use in ABM reported that dexamethasone significantly reduces HL compared to standard antibiotics and severe neurological sequelae; in contrast, the mortality did not decrease [55].

The most recent Cochrane meta-analysis demonstrated that HL was reduced by corticosteroid treatment in children with *H. influenzae* meningitis [56]. In contrast, corticosteroids did not significantly reduce HL in ABM cases caused by pathogens other than *H. influenzae*. Corticosteroids were shown to decrease severe HL, any HL, and short-term neurological sequelae, mainly in high-income countries but not in low-income countries.

Meningeal inflammation in the initial phase of the disease affects neuronal damage; the late presentation may lead to missing the opportunity for corticosteroids. A recent large study from Taiwan enrolled 8083 ABM episodes and found that steroid-administered children significantly had a more extended hospital stay, higher hospital costs, and mortality [57]. However, the study did not evaluate the subgroups according to pathogens. A recent study showed an association between delayed cerebral injury and steroid use in adults, and this association was attributed to effects on cerebral blood vessels leading to vasospasm [58].

Dexamethasone should be used before or simultaneously as the first dose of the antibiotic(s). However, another concern is the reduced penetration of vancomycin into the CSF by reducing meningeal inflammation with dexamethasone, leading to treatment failures [54, 55].

21.7.1.2 Adjuvant Glycerol Therapy

Meningeal inflammation leads to increased vasogenic and cytotoxic brain edema, decreasing cerebral perfusion. From this point, hyperosmotic agents have been studied to reduce neurological damage by reducing intracranial pressure. Glycerol is a cheap and widely available hyperosmotic agent [35].

A prospective, randomized, double-blind study comparing adjuvant dexamethasone or glycerol with placebo under 16 years in Latin America demonstrated that severe neurological sequelae were less frequently observed in glycerol and dexamethasone plus glycerol received patients than in the placebo group; however, a significant difference was not observed for HL [59]. The same author group evaluated hearing impairment degrees in dexamethasone and dexamethasone plus glycerol administered patients and found no significant difference from placebo at any threshold levels (40, 60, and 80 decibels [dB]) [60]. A smaller study evaluated glycerol and acetaminophen as adjunctive therapies in ABM contrasty and found no effects on neurological sequelae and deafness; however, the study group primarily consisted of pneumococcal meningitis [61]. A double-blind, randomized controlled trial in Malawian adult patients demonstrated an increased risk of death with glycerol in adults with bacterial meningitis in Malawi's high HIV seroprevalence setting [62]. The most recent Cochrane meta-analysis evaluating five studies with 922 participants on glycerol use in ABM showed a significant decrease in HL [63]. The comparison of glycerol and placebo showed no significant impact on death, while decreased neurological disability was determined.

21.8 Conclusion

Acute bacterial meningitis still causes significant morbidity and mortality in children, particularly in low-income and sub-Saharan African meningitis belt countries. Hearing loss may develop early after infection, but late-onset HL can also occur. Reversible SNHL has been determined in the follow-up of children with pneumococcal meningitis. Early detection is crucial because patients can develop cochlea ossification, and a cochlear implant should be placed before obliteration. Children with ABM should be evaluated for HL in the hospital or within 1 month of discharge. Dexamethasone may be used in ABM caused by Hib but is not routinely recommended for pneumococcal meningitis and should be discontinued if another microorganism is detected in the CSF. Glycerol is cheap and widely available; however, the studies on glycerol used to prevent neurological sequela in patients with ABM are limited and controversial.

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Recurrent Meningitis, Congenital Defects, and Hearing Loss

22

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22.1 Introduction

Recurrent meningitis (RM) is defined as two or more episodes of meningitis weeks to months apart with full recovery between events. This is in contrast to recrudescence or relapse of meningitis, which represents the persistence of the initial infection due to treatment failure [1]. Recurrent meningitis is rare in children, but a thorough examination is often necessary to identify the underlying cause. Recurrences can occur with bacterial, viral, and noninfectious causes of meningitis, but most cases are bacterial [2]. Known etiologies of RM also include cranial anatomical defects, such as skull fractures, chronic parameningeal infections, recurrent benign lymphocytic meningitis, antibody or complement deficiency, and hyposplenism [1].

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22.2 Etiology and Epidemiology

Bacterial meningitis mostly occurs when bacteria reach the choroid plexus via the blood and invade the cerebrospinal fluid (CSF). The main predisposing conditions associated with RM are congenital and acquired anatomical defects, immunodeficiencies, and chronic parameningeal infections. Epidermoid, dermoid, and neuroenteric cysts, heterotopic brain tissue, dermal sinus tracts, Mondini dysplasia, and other congenital inner ear malformations (IEMs) and asplenia are among the significant congenital anatomical defects. Head injury and neoplasia are the most commonly acquired predisposing anatomical conditions [3–7]. Congenital immunodeficiencies include complement, immunoglobulin (Ig), subclass, and interleukin-1 receptor-associated kinase 4 (IRAK-4) deficiencies. Human immunodeficiency virus (HIV) infection is an example of acquired immunodeficiency.

Streptococcus pneumoniae is the most common cause of recurrent bacterial meningitis (RBM) in patients with underlying structural defects or immune deficiencies. The second most common cause is *Neisseria meningitidis*, primarily associated with complement deficiency. *Haemophilus influenzae* type b (Hib) associated with RBM has become very rare with the widespread use of the conjugate Hib vaccine. The intracranial spread of bacteria usually causes recurrent pneumococcal meningitis due to the direct association of CSF with an extracranial source. Patients with dermal sinus have a greater risk for recurrent *Staphylococcus aureus* meningitis. Also, a connection between the subarachnoid space and the intestine increases the likelihood of RBM with gram-negative bacteria such as *Escherichia coli*. Oral streptococci, enterococci, *Proteus* spp., *Klebsiella* spp., and group B streptococcus were rarely reported as causes of RBM [2].

In a study evaluating cases with a diagnosis of RBM, *S. pneumoniae* was reported as the causative agent in 310 (56.6%) of 548 culture-proven meningitis cases. In the same study, *N. meningitidis* was the second most common cause, and complement deficiency was found in 123 (92%) of 134 patients with meningococcal meningitis attacks. In patients with other culture-proven meningitis, *H. influenzae* (6.9%), *E. coli* (4.2%), *S. aureus* (2.4%), *Salmonella* spp. (1.8%), *Proteus* spp. (0.9%), *enterococci* (0.5%), *Klebsiella pneumoniae* (0.4%), and *streptococci* (group A, group B, group D, and viridans streptococci [1.8%]) were detected [1].

In the study of Driel et al. [8], the characteristics of recurrent bacterial and fungal meningitis and the distribution of causative organisms in the Netherlands were evaluated. Data for patients with bacterial meningitis were prospectively collected nationwide from 1988 to 2005. Of the 19,163 episodes, 450 attacks of bacterial meningitis were detected. Two hundred and two patients (1.1% of all patients) experienced 11 episodes of bacterial meningitis during the study period. Of these patients, 169 (84% of patients with RBM) had two, 25 (12%) had three, 5 (3%) had four, two (1%) had five, and one had seven episodes. Of the 202 patients, 178 (88%) had experienced a second episode of bacterial meningitis ≥28 weeks after the previous episode, whereas 24 patients (12%) had experienced another episode <28 weeks after an earlier episode. The authors found that RBM occurred more often in male patients than female patients. In an adult study, 34 (4.8%) recurrent episodes were

Table 22.1 Predisposing conditions and congenital temporal bone anomalies associated with recurrent bacterial meningitis

Mondini dysplasia
Stapedial anomalies
Klippel–Feil syndrome
Pendred syndrome
Petromastoid fistula
Widened cochlear aqueduct
Hyrtl fissure

found in 696 patients with bacterial meningitis, and the annual incidence of RM was 0.12 cases per 100,000 individuals [9].

Tebruegge and Curtis [1] identified 363 cases of RM reported in 144 articles between 1998 and 2007. Of these cases, 214 (59%) were due to anatomical problems, 132 (36%) were immunodeficiency, and 17 (5%) were related to parameningeal infections. Regarding gender distribution, there was a slight elevation in males compared to females (1.2:1) [1].

Recurrent bacterial meningitis has been estimated to occur in 4–9% of all patients with community-acquired bacterial meningitis [1, 9]. Risk factors associated with RM are, in part, age-dependent. The most common risk factors are congenital anatomical defects in children, whereas remote head trauma or CSF leakage in adults [10].

Various congenital defects in the skull's bone structure in patients may cause CSF leakage, which may cause RM. Adriani et al. [9] defined head trauma, CSF leakage, and immunodeficiency as predisposing causes in 26 of 34 episodes in their study. The congenital anomalies in the temporal bone are noted in Table 22.1. Inner ear anomalies in the temporal bone were detected in 21% of patients with idiopathic sensorineural hearing loss (SNHL) [11].

Mondini dysplasia and other congenital IEMs cause most RBM cases (55 out of 363 cases) [1]. Because of the existing cranial and spinal anatomical defects, it may be easier for pathogenic organisms to enter the subdural and subarachnoid spaces. The predisposition to develop bacterial meningitis in Mondini is due to the connection between the CSF spaces and the middle ear, connected to the nasopharynx through the Eustachian tube. The organisms that cause meningitis are usually those that colonize the nasopharynx.

22.3 Pathogenesis

Recurrent bacterial meningitis results from defects or imperfections of host defense mechanisms, allowing bacteria to reach the central nervous system (CNS) or a defect in the external covering of the leptomeninges and skull. Various cranial and spinal anatomical defects may facilitate the migration of pathogenic organisms into the intradural and subarachnoid spaces. These pathological entry pathways are in the anterior cranial base (frontal, ethmoid, and sphenoid bones) and temporal bone in the skull. Congenital neural tube defects are most common in the lumbosacral

region and may also occur in the cervical and thoracic spine. Encephalocele and glioma are risk factors for RM [12–14].

An otorhinolaryngologic cause was found in up to 33% of RM [15]. Congenital inner ear abnormalities provide connections between the middle ear cavity and CSF. Anatomical abnormalities of the middle and inner ear mainly include oval window fistula, round window fistula, nasal defect, Hyrtl fissure, the roof defect of the Eustachian tube, and a defect in the middle wall of the epitympanum anterior to the semicircular canals. In these patients, CSF rhinorrhea may be indistinguishable from normal nasal discharge, or a middle ear effusion may mistakenly be diagnosed as otitis media. Also, CSF may be swallowed by flowing through the Eustachian tube.

Children with RM are generally evaluated with computed tomography (CT) because intracranial anomalies and anterior cranial fossa defects are considered the cause. The vestibulocochlear system may be overlooked if the CT sections are not very thin or the bone window settings need to be corrected. Unilateral hearing loss (HL) diagnosis is also problematic in young children without otological symptoms [16].

Mondini dysplasia occurs in the first trimester of pregnancy. It is thought to result from a developmental loss in the seventh week of the embryonic period. Hearing loss, vestibular anomalies, and a tendency to CNS infections may occur. In Mondini dysplasia, CSF mostly passes into the middle ear because of the defective oval window. Mondini dysplasia may be associated with Klippel–Feil syndrome, Pendred syndrome, DiGeorge syndrome, CHARGE syndrome, and trisomies [17, 18]. In patients with HL and RM, Mondini dysplasia should be considered. Hearing loss in these patients is sensorineural and occurs due to the anomalies of the organ of Corti and contact with the subarachnoid space due to increased pressure in the perilymphatic area. Mild -to-severe SNHL may occur. When any child presents with RM and HL, an audiometric evaluation should be performed, and temporal bone should be evaluated with high-resolution CT (HRCT).

Congenital perilymph fistula is a fistulous connection between the intracranial subarachnoid space and the middle ear cavity via the inner ear. This connection leads to the drainage of CSF into the middle ear as an underlying abnormality for meningitis. While it is symptomatic in most patients in childhood, it may sometimes present in adulthood [19]. Most patients with congenital IEMs have unilateral HL with varying degrees of severity; however, hearing rarely may be normal. Anandi et al. [20] reported that RM developed in a quarter of 20 patients with congenital IEMs.

22.4 Clinical Manifestations

Detailed physical examination is critical in patients with RM. In most patients, the presenting symptoms are similar to acute bacterial meningitis. However, the RM episode can also begin insidiously and mimic aseptic meningitis. Patients usually do not have signs and symptoms suggesting CSF leakage. The presence of a congenital or acquired CSF leak should be questioned in case of anosmia, HL, and otitis media

with effusion. There may be intermittent CSF rhinorrhea or otorrhea, and symptoms may increase during meningitis. Rhinorrhea is often unilateral. Clear nasal discharge increases with the Valsalva maneuver and when the patient leans forward [21]. Valsalva maneuver, coughing, or sneezing may increase CSF rhinorrhea. A craniospinal examination should be performed carefully for dimples, fistulas, tufts of hair, nevus, or hemangiomas. In an adult study, symptoms were most commonly reported as headache, nausea, neck stiffness, and fever [9].

22.5 Recurrent Meningitis, Congenital Defects, and Hearing Loss

Without hearing rehabilitation, HL can cause detrimental effects on speech, language, developmental, educational, and cognitive outcomes in children. Sensorineural HL results from damage, disease, or other disorders affecting the inner ear (e.g., the cochlea) and the auditory nerve. Sensorineural HL is the most widely reported neurological sequela of bacterial meningitis [22, 23]. Hearing loss may result from the spreading bacterial products and inflammatory mediators through the meninges and CSF. Bacteria reach the cochlea through the cochlear aqueduct and induce severe labyrinthitis. As a result, the blood–labyrinth barrier breaks, leading to meningitis-associated HL [24].

A retrospective study evaluated many children with bacterial meningitis and found an SNHL incidence during the initial hospitalization of 30.6% [25]. In this study, the incidence of at least a unilateral severe SNHL was 21.6% among all patients with bacterial meningitis, and permanent SNHL was seen in 5–35% of patients. In a prospective multicenter study in the United States of America (USA), among 151 children surviving pneumococcal meningitis, 32% had unilateral or bilateral HL at discharge [26]. Hearing loss may occur in approximately 20–30% of previously healthy children after meningitis due to *S. pneumoniae* and in 5–10% of patients after meningitis caused by Hib or *N. meningitidis* [27]. Hearing loss is a less common complication in patients after meningococcal meningitis in high-income countries. In a large nationwide cohort study in the Netherlands among 578 children who survived bacterial meningitis, HL occurred in 20 of 495 children (4%) after meningococcal meningitis [28]. The severity of the disease, and to a lesser extent, late admission for treatment, reflected by a history of seizure(s), has been determined to predict profound HL in a cohort of children with bacterial meningitis [29].

Furthermore, low CSF glucose levels as an indicator of bacterial density and inflammation in CSF were also shown to predict HL in childhood meningitis [25]. In a meta-analysis investigating the global and regional risk of disabling sequelae, cognitive deficit and HL were the most common combination of multiple impairments [30]. Patients should have a hearing test before or 1 month after discharge because early rehabilitation may lessen long-term adverse outcomes. Hearing monitoring in patients with meningitis is also vital as HL may indicate fibrosis and subsequent ossification of the cochlear duct, and urgent cochlear implantation may be needed before ossification makes insertion of a cochlear implant impossible [31].

Recurrent bacterial meningitis accounts for 1–6% of meningitis cases acquired in the community [9]. Recurrent bacterial meningitis warrants prompt investigation and treatment of the underlying cause.

Permanent unilateral hearing impairment (UHI) affects about 1 in 1000 newborns [32]. Unilateral hearing impairment is highly correlated with congenital IEMs. It is possible to predict that patients with UHI are at risk of concomitant CSF leakage and meningitis in their follow-up [33]. Congenital IEMs are an important cause of RM [34].

The organisms are believed to reach the CNS through a defect caused by IEM [35]. The percentage of IEM is up to 66.7% in UHI cases, whereas IEM is detected in approximately 20% of patients with bilateral SNHL [33]. About 15% of RM, especially in children, is related to IEM [1]. Among IEM, those at risk for CSF leak account for about 18.8% of children with UHI [33]. Most IEMs are associated with incomplete segmentation of the cochlea. Mondini dysplasia involves one-and-a-half cochlear helices instead of the usual two-and-a-half helices. Congenital IEMs have been recognized more recently due to advanced imaging methods [35]. Park et al. [36] showed that the average age for identifying IEMs is 25.7 months. Stein et al. [37] reported the same result.

In conclusion, IEM should be suspected in patients with UHI or speech delay. It should be kept in mind that HL in children with RM may be caused by this anomaly, not by previous meningitis attacks.

22.6 Diagnosis

Patients diagnosed with RM should be questioned regarding cranial injuries, family history of recurrent infection, CSF leakage from the nose or ear, and splenectomy. Most patients with Mondini dysplasia and other IEMs with CSF leak experience their first episode of meningitis in infancy or early childhood. Inner ear malformations should be investigated in children with a history of HL and meningitis or a family history of ear anomalies.

In recurrent attacks, CSF culture may be sterile. Early diagnosis of patients is vital to prevent episodes.

The underlying etiological cause can be estimated according to the type of bacteria detected in the patient's CSF culture or polymerase chain reaction (PCR) test. Repeated isolation of bacteria can guide in terms of the underlying condition. In the presence of IEMs or Mondini dysplasia, *S. pneumoniae, N. meningitidis*, or *H. influenzae* are the most commonly encountered causative agents. *Streptococcus pneumoniae*, *H. influenzae*, oral streptococci, or anaerobic bacteria of the oropharyngeal flora are common causative agents of meningitis in patients with middle ear anomalies, head trauma, or congenital CSF leakage. *Neisseria meningitidis* is mostly associated with complement deficiencies in patients with RM.

A fluid examination should be planned in case of rhinorrhea or otorrhea. The presence of glucose and protein in the fluid can be evaluated with a strip. It should be noted that the glucose test may have false-positive and false-negative results.

Beta (β)-2-transferrin and β-trace protein (βTP) testing can be used to distinguish whether CSF is present or not [38].

Chronic ear or sinus infections should also be considered an underlying trigger in a patient with RM. Also, CSF leakage should be investigated. The mainstays are a complete and detailed record of the patient's history and a detailed physical examination. A history of head trauma may be overlooked, and a long time could be elapsed after head trauma [39]. When RM is associated with episodes of otitis media, the history and physical examination should be directed toward an autogenic source. Otoscopic and audiological evaluations should be performed to investigate the possible otological source of RM. The probability of developing SNHL after meningitis is between 7% and 22% [28].

A translabyrinthine fistula should also be suspected in a child with RM and congenital SNHL, in which CSF leaks are often intermittent and easily overlooked. Diagnosing congenital fistulas in infants and young children can be challenging, and good history may not be given.

Although it is difficult to make recommendations, current evidence suggests that the initial investigation of RBM should be done with contrast-enhanced CT imaging of the temporal bones (2 mm in thin section) and anterior skull base, including the paranasal sinuses. High-resolution CT may also be recommended. The sensitivity and specificity for HRCT are 44–100% and 45–100%, respectively [40–44].

Magnetic resonance (MR) imaging, also helpful in diagnosis, shows the brain parenchyma and soft tissues well. Magnetic resonance imaging detects anatomical details and has no radiation risk. It is a sensitive and accurate non-invasive technique for detecting CSF leakage, even in patients not exposed to leakage at the assessment time.

A cisternography technique may be needed to detect CSF leakage. Computed tomography cisternography (CTC) is based on showing the contrast medium passing through the fistula defect or detecting its presence in the paranasal sinuses. This technique is one of the reliable approaches for accurately locating CSF leaks. The sensitivity of CTC ranges from 33% to 100%, the specificity is 94%, and the accuracy ranges from 33% to 63% [45]. Computed tomography cisternography is a valid option for CSF leak localization, although its ideal indications and accuracy are only partially clear [45, 46].

Studies show that MR cisternography has a higher sensitivity to detect CSF fistulas than CTC [47]. Radionuclide cisternography may also be helpful in some cases where CT and MR imaging fails to detect CSF leaks.

When the cause has not been identified at the time of diagnosis in a pediatric patient with RM, the following protocol is recommended:

1. Audiological evaluation: Audiogram or brainstem auditory evoked potential test.
2. Contrast-enhanced CT scan of the head with coronal images of the sinuses and thin sections of the temporal bone.
3. Spinal ultrasound or MR imaging unless otherwise stated.
4. Immunological studies, including complete blood count, total immunoglobulin (Ig) levels, Ig G subclasses, and total hemolytic complement levels.

22.7 Treatment

Regardless of the etiology of RM, treatment should be planned, as in acute bacterial meningitis. Especially the choice of empirical antibiotic therapy for RBM due to head injury, congenital anomalies, or complement deficiency should be similar to the initial meningitis episode. Antibiotics should be started immediately after the initial meningitis work-up. Antibiotics should also target these agents in patients with a dermal sinus or a history of previous staphylococcal or gram-negative bacterial meningitis. Rarely, in the presence of infections with multidrug-resistant organisms, intraventricular therapy can be needed when intravenous treatment is unresponsive [48].

The duration of treatment for RM for sporadic cases should be the same as in bacterial meningitis cases having normal conditions; the benefit of extended treatment duration has yet to be demonstrated [2]. Sterilization duration of CSF may be prolonged in infections with gram-negative bacilli associated with dermoid or epidermoid cysts because squamous collections may behave like foreign bodies. Therefore, sterility of CSF should be documented by lumbar puncture [2]. A careful examination and diagnostic evaluation, including exploratory surgery, is essential if a CSF fistula is suspected.

Spontaneous CSF otorrhea associated with cochlear abnormalities is challenging to correct surgically. Tympanostomy with a comprehensive middle ear examination is recommended to determine the leak site. The oval window is the most common leakage site in Mondini deformity. Still, it has also been reported from the round window, hypotympanum, and other preexisting anatomical fissures [49]. Cerebrospinal fluid leakage through the oval window can be treated by stapedectomy and obliterating the vestibule using fat, muscle, fascia, and cartilage [50]. In the case of otorrhea, filling the middle ear with fat is insufficient, as it cannot permanently close the fistula. Even packing with muscle or fascia alone may be insufficient, and additional vestibule grafting may be required.

A lumboperitoneal shunt procedure can be used in conjunction with primary surgery as an adjunctive procedure to help close the defect successfully. Repeated surgical procedures may be required in most patients before the fistula is permanently closed.

Cochlear implantation may be an option for patients with Mondini deformity and can help hear restoration [51]. Since CSF leakage (perilymph leakage) may occur during cochlear implant insertion, the implant should only be considered in cases of bilateral HL [52]. Surgical procedures for treating small perilymph fistulas in patients presenting with HL or vertigo usually involve simple closure of the defect after scarring the margins and simple packing of both oval and round windows [53]. However, more precise procedures are needed to prevent recurrence in patients with RM due to congenital perilymph fistula. A review of 21 reported cases of RM and congenital perilymph fistula identified a surgical failure rate of 37.5% in patients with simple fistula closure [54]. The definitive treatment of congenital perilymph fistula is vestibular obliteration. One argument against vestibular obliteration is preserving residual hearing in the affected ear. However, HL in the affected ear is

usually severe in most children. Rupa et al. [53] recommended vestibular obliteration in these children initially and concluded that a single operation is sufficient with this technique in children with congenital perilymph fistula to prevent subsequent meningitis episodes.

22.8 Prevention and Prophylaxis

Parents of children with IEMs should be educated about the possibility of RM due to a middle ear infection. Contact sports, diving, and prolonged Valsalva maneuvers may increase inner or middle ear pressure. Suspicious infections in these patients should be treated aggressively and promptly, and patients with cavity anomalies should undergo exploratory tympanotomy. Efforts should be made to identify and close CSF leaks, as continued leakage increases the risk of postoperative meningitis [55].

Prophylactic antimicrobial agents are not recommended in patients with basilar skull fractures and CSF leaks; however, pneumococcal vaccination is recommended [56]. Repairing the leak is recommended in patients with basilar skull fractures and a prolonged (>7 days) CSF leakage. A review of 51 patients with posttraumatic CSF leaks that did not improve within 24 h showed that the meningitis risk was reduced from 21% to 10% with prophylactic agents [57]. However, in a study conducted on patients with traumatic pneumocephalus, ceftriaxone did not reduce the risk of bacterial meningitis [58]. In a meta-analysis examining 208 participants from four randomized studies, no significant difference was found between the groups in terms of meningitis frequency, all-cause and meningitis-related mortality, and the need for surgical correction between the antimicrobial prophylaxis and control groups [59]. The main risk factor for developing posttraumatic meningitis is CSF leakage, which is often not noticed [60]. Most leaks resolve spontaneously within 7 days, but surgery is required if they do not [56].

The most crucial prevention point is vaccinating patients with RM and congenital or acquired anatomical skull or ear defects. Vaccination of children within this high-risk group should be routinely recommended against pneumococci, meningococci, and Hib, although meningitis can occur in patients with CSF leaks despite being vaccinated.

Streptococcus pneumoniae is the most common cause of bacterial meningitis in children with CSF leakage after head trauma; it is reasonable to try to prevent this organism-associated infection with the vaccine.

In patients 2–5 years old whose vaccinations have not been completed:

- If there are three doses of 13-valent pneumococcal conjugate vaccine (PCV13), one dose of PCV13 (at least 8 weeks after any previous dose of PCV13).
- If there are less than three doses of PCV13, two doses of PCV13 (applied 8 weeks after the last dose and 8 weeks apart).
- If there is no history of 23-valent pneumococcal polysaccharide vaccine (PPSV23), one dose of PPSV23 (at least 8 weeks after any previous dose of PCV13) should be administered.

In patients 6–18 years old:

- If there is no history of PCV13 or PPSV23, one dose of PCV13 and one dose of PPSV23 after at least 8 weeks.
- If there is any PCV13 but no PPSV23, one dose of PPSV23 at least 8 weeks after the last dose of PCV13.
- If PPSV23 is present, but PCV13 is absent, one dose of PCV13 at least 8 weeks after the last dose of PPSV23.
- When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during the same visit [61–63].

Vaccination with an age-appropriate meningococcal conjugate vaccine (MCV-ACWY) against meningococcal serogroups A, C, W, and Y, and meningococcal B vaccine is recommended for children at high risk for meningococcal disease (e.g., asplenia, and complement, factor D, and factor H deficiencies). In MCVs, capsular polysaccharides of *N. meningitidis* A, C, W, and Y serogroups are conjugated to the diphtheria toxin mutant CRM197 (ACWY-CRM), the tetanus toxoid (ACWY-TT), and the diphtheria toxin (ACWY-D). The minimum age is 2 months for MCV-ACWY-CRM and MCV-ACWY-TT and 9 months for MCV-ACWY-D [63].

Serogroup B meningococcal vaccines have also been approved in children (≥2 months old) at high risk for meningococcal disease. Adolescents and other risk groups should also be vaccinated to reduce nasopharyngeal colonization and provide immunity [64].

22.9 Conclusion

Recurrent meningitis in children is a rare but life-threatening phenomenon and increases the likelihood of repeated hospitalization of the child, with multiple and invasive risks. A detailed history and physical examination should form the basis of the evaluation. The patient should be questioned in detail about hearing impairment, speech delay, head trauma, rhino/ear discharge, recurrent infections, and family history of immunodeficiency. Physical examination should be done very carefully to evaluate for head and midline abnormalities. It generally poses a diagnostic challenge. An organized approach and early diagnosis of any underlying abnormality are essential and may be vital to preventing further attacks and improving the outcome for the affected patient. Vaccination of patients also plays a crucial role in preventing recurrence.

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Focal Suppurative Infections of the Central Nervous System in Children and Hearing Loss

23

Taylan Çelik, Mustafa Hacımustafaoğlu, and Dennis Chua

23.1 Introduction

Cerebral sinus thrombosis (CST) is a severe cerebrovascular disease that can cause adverse outcomes such as hearing loss (HL), although it is rare in children. Today, it is being diagnosed more frequently due to the widespread use of neuroimaging, more prolonged survival of children with a tendency to thrombosis, and increased clinical awareness. It should be kept in mind when symptoms (after exclusion of acute bacterial meningitis) such as unresponsive to treatment or headache and vomiting develop in infections such as recurrent and/or complicated acute bacterial rhinosinusitis, otitis media, and mastoiditis, especially in children with a tendency to thrombosis. In such patients, it is important to evaluate the brain imaging for CST in order not to miss the diagnosis.

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23.2 Septic Dural Sinus Thrombosis

23.2.1 Dural Venous Sinuses: Dural Sinus, Cerebral Sinus, and Cranial Sinus

The dural venous sinuses, the main venous drainage systems of the central nervous system (CNS), are the venous channels located in the cranium, on the inner surface of the bone, and between the endosteal and meningeal layers of the dura mater [1]. The cerebral venous system consists mainly of a network of superficial cortical, medullary, and deep cerebral veins that drain into the dural sinuses [2]. Cerebral venous return generally drains into the nearest venous sinuses, followed by drainage into the internal jugular vein through the transverse (lateral) and sigmoid sinuses (Figs. 23.1 and 23.2). In addition, they provide normal physiological drainage of cerebrospinal fluid (CSF), such as absorption and discharge into the dural sinuses through arachnoid villi that penetrate the dura from the subarachnoid area and reach the dural sinuses (Fig. 23.3).

Central nervous system venous circulation shows some differences from venous circulation in other body systems; veins usually do not run parallel to the arteries, cerebral veins are very thin due to the absence of muscular layers, and they do not have venous valves. In addition, there is an extensive collateral system in the cortical, deep veins, and sinuses, which contributes to the continuation of venous drainage by alternative routes when the primary pathway is disabled. There may also be significant individual differences in the cerebral venous drainage system. Therefore, it is helpful to consider these factors in the clinical and radiological evaluation of a patient with septic venous sinus thrombosis.

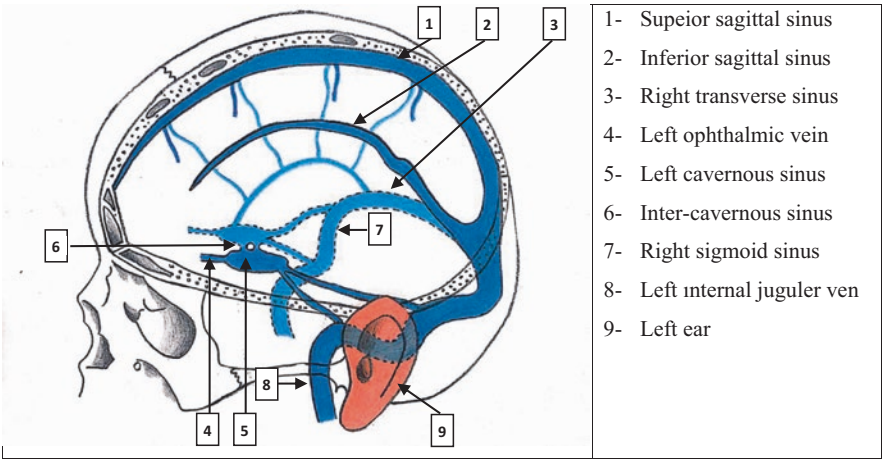

Fig. 23.1 Brain major dural sinus systems. (Courtesy Taylan Çelik, MD)

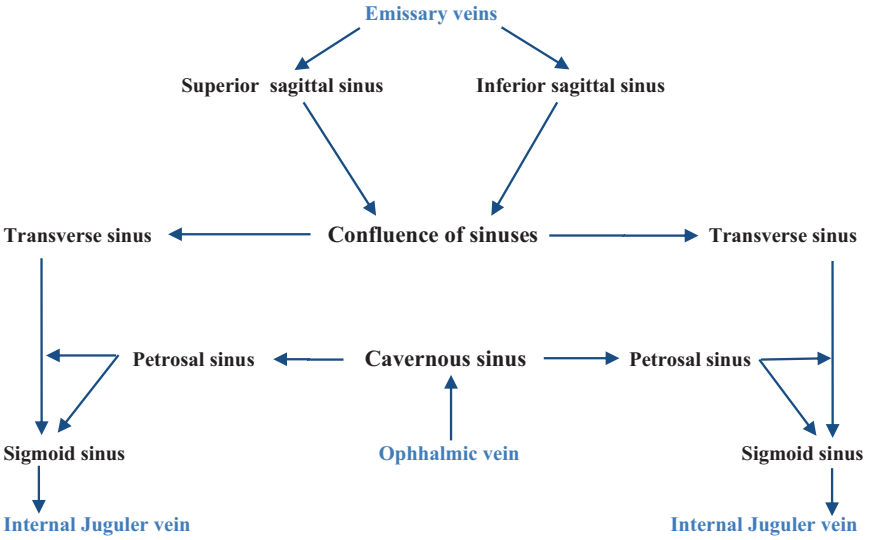

Fig. 23.2 Cerebral venous flow chart

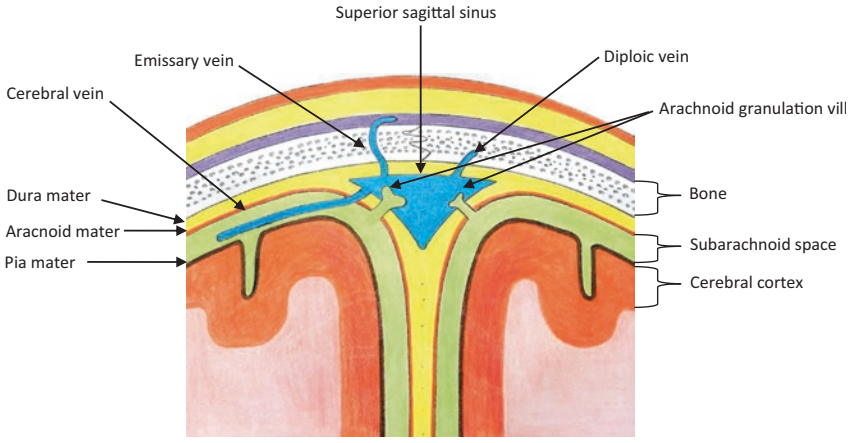

Fig. 23.3 Schematic view of the arachnoid membrane, arachnoid granulation, dura mater, and cerebral venous sinus relationship in the brain; arachnoid granulations originating from the arachnoid membrane reach the venous sinuses pass the dura from appropriate places and provide cerebrospinal fluid drainage. (Courtesy Taylan Çelik, MD)

23.2.2 Cerebral Sinus Thrombosis

Cerebral sinus thrombosis describes a set of disorders that include thrombosis of the cerebral venous system; it can be septic or aseptic. In Europe and North America, the incidence is estimated at 0.6 per 100,000 per year in childhood, with male

predominance (60–70%) and neonates accounting for 30–50% of the cases [1, 2]. Cerebral sinus thrombosis can be divided into three main sections: cavernous sinus thrombosis (CavST), lateral (transverse) sinus thrombosis (LST), and superior sagittal sinus thrombosis (very rare).

This chapter will give general information about the cerebral dural sinuses (cavernous, lateral, and sagittal) and their thromboses, followed by the clinical, laboratory, and treatment approaches of septic CST, especially in children, and its evaluations in terms of hearing loss.

23.2.2.1 Risk Factors

In general, CST occurs in previously healthy children, most commonly in the presence of or after mastoiditis (characterized by postauricular pain, swelling, erythema, or tenderness) and head/neck infections such as sinusitis, dehydration, and iron deficiency anemia. Other risk factors predisposing children to CST are inflammatory bowel disease, congenital heart diseases, cancer, autoimmune disorders, chronic kidney disease, nephrotic syndrome, systemic lupus erythematosus, and other chronic diseases [2, 3]. Local stasis that may occur in cerebral blood flow and conditions that may cause it (such as head trauma, CNS tumors, and intracranial surgery) may predispose to CST and/or aggravate the existing CST condition [3]. In addition, hereditary causes of thrombophilia such as antithrombin deficiency, protein C and protein S deficiency, factor V Leiden mutation, and homocysteinemia resulting from methylenetetrahydrofolate reductase (MTHFR) gene mutation are prothrombotic genetic conditions. Acquired nephrotic syndrome and antiphospholipid antibodies are other causes that may be risk factors in etiology, which tend to cause thrombosis in general, and are also the risk factors for CST, although not detected in every patient. Approximately 10–20% of children with CST may develop a recurrent thrombotic venous event in the future, of which at least half develop as systemic rather than cerebral venous thrombosis [3].

23.2.2.2 Pathophysiology

There is no valve mechanism in the cerebral veins and sinuses. Thrombosis in the venous system causes outflow obstruction, congestion, subsequent capillary hydrostatic pressure increase, fluid leakage into the interstitium, and edema. The increase in hydrostatic capillary pressure above a certain level and the presence of edema may lead to a decrease in arterial blood flow/supply and local ischemia in the brain tissue and subsequently to neurological findings. These physiopathological and clinical findings may cause different clinical findings to be more pronounced in different regions, depending on neighboring structures [3]. When these physiopathological changes affect the cochlear system, it may cause hypoxia due to insufficiency of venous circulation in the cochlear system, and then, sensorineural HL (SNHL) may develop. Sensorineural HL (unilateral or bilateral) may arise as thrombosis reaches the cochlear or labyrinthine veins [4].

23.2.2.3 Clinical Findings

In CST, since thrombosis causes cerebral ischemia, the most common complaints that bring the patient to the clinician are severe headache, vomiting, and confusion that progresses over days. In addition, some different complaints according to the anatomical region may develop [1, 2]. For example, in CavST, proptosis, chemosis, oculomotor nerve (cranial nerve [CN]-III), trochlear nerve (CN-IV), trigeminal nerve (CN-V), and abducens nerve (CN-VI), involvement findings and LST, otitis signs, unilateral CN-V, and CN-VI findings may develop. However, since the cerebral venous sinuses are interconnected, and there is no valve mechanism in the sinuses, some similar clinical findings can be shared in common. Mental status changes vary in patients; sometimes, only irritability and sleepiness may occur, or progression to stupor and coma may be seen [2]. In septic CST, in addition to the neurological findings secondary to thrombosis, findings of adjacent region infection such as sinusitis, persistent and/or inadequately treated acute otitis media (AOM), and mastoiditis also accompany the clinical picture. Hearing loss in septic CST may be of the sensorineural type due to the underlying chronic/persistent otitis (conductive type) or acute cochlear dysfunction, and the CN-VII is affected [5–7]. Most (about 95%) of these are unilateral. Acute HL is defined as HL that develops suddenly within days [5, 8].

23.2.3 Septic Cerebral Sinus Thrombosis

Septic CST is not common. In addition, widespread symptoms and signs, which can also be seen in other diseases, may lead to misinterpretation of clinical signs [1]. Therefore, overlooked cases may lead to an underestimation of the incidence. In this respect, it is beneficial for the physician to interpret the clinical findings and physical examination rationally.

Septic CST may show some differences according to the regions where it is involved. Here, the most common septic CavST, septic LST, and septic sagittal sinus thrombosis will be discussed briefly.

23.3 Septic Cavernous Sinus Thrombosis

23.3.1 Anatomy

The cavernous sinuses are located just lateral to the base of the sella turcica and the sphenoid paranasal sinuses. They are nearly located at the center of the dural sinuses. These irregularly shaped sinuses have multiple trabeculae that act as strainers to trap bacteria; this feature explains why cavernous sinuses have a higher risk of infection than other dural sinuses. The cavernous sinuses are connected by the sella turcica and two intercavernous sinuses that run in front and behind the pituitary gland and sella turcica (Figs. 23.1 and 23.4). Therefore, especially if treatment is

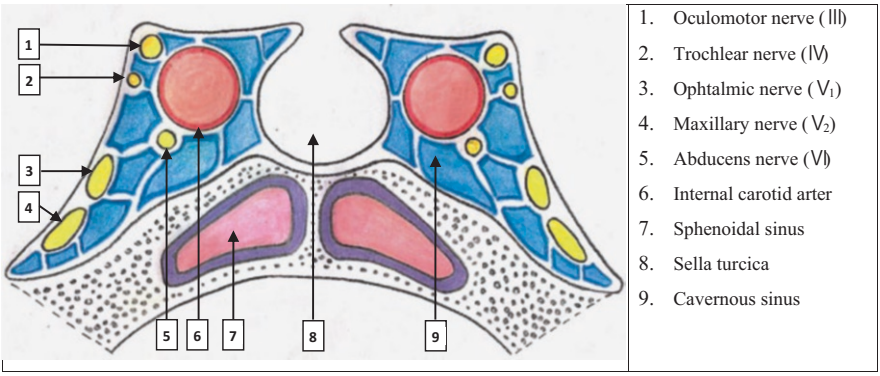

Fig. 23.4 Cavernous sinus anatomy and adjacent structures (coronal section). (Courtesy Taylan Çelik, MD)

delayed, the event may spread to the other side via venous connections; then, bilateral infection may develop, and clinical findings may be bilateral [1].

Some cranial nerves, including CN-III, CN-IV, ophthalmic (CNV1), and maxillary branches (V2) of CNV, can be counted and are located lateral to the cavernous sinuses. The cranial nerve VI is located more medially in the cavernous sinus and adjacent to the cavernous segment of the internal carotid artery (ICA) (Fig. 23.3) [1]. In CavST, in addition to the general symptoms, there may be varying degrees of involvement of these nerves, and narrowing of the ICA may be detected in radiological images. Septic CavST is more common in sphenoid sinusitis due to its proximity to the sphenoid sinus (Fig. 23.4). In addition, in facial infections, especially around the nose (danger triangle), the venous circulation primarily drains into the cavernous and other venous sinuses may increase the risk (Fig. 23.5).

23.3.2 Microbiology

The organisms associated with septic CavST differ by the site of primary infection [1, 9]; *Staphylococcus aureus* accounts for 70% of all infections and is usually associated with facial infection or sphenoid sinusitis. Community-acquired methicillin-resistant *S. aureus* (MRSA) has been reported with increasing frequency. Streptococci (including *Streptococcus pneumoniae*, *Streptococcus milleri*, and viridans group streptococci) are less common. However, in some studies, the most common (60%) microorganism was reported to be *Streptococcus anginosus* [9]. Anaerobes, *Bacteroides* spp., and *Fusobacterium* spp. are less common and are primarily associated with concomitant sinus, tooth, or tonsil infections. Fungal agents such as *Rhizopus* spp. and other mucormycosis agents, *Aspergillus* spp. and *Schizophyllum*, are rarely reported.

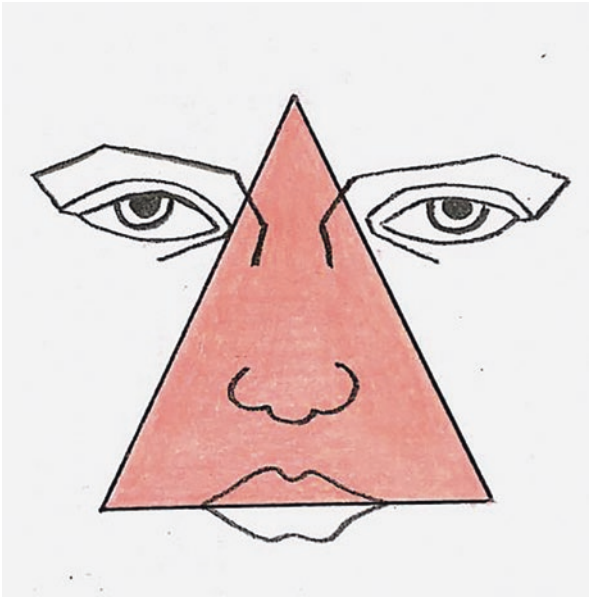

Fig. 23.5 The danger triangle of the face; infections involving the middle third of the face (e.g., the areas around the eyes and nose) may, although rarely, be complicated by septic cavernous thrombosis as the vessels in this area are without valves. (Courtesy Taylan Çelik, MD)

23.3.3 Epidemiology

In an 11-year study in children, it was reported that 8% (10/121) of 121 cases with pediatric CST had CavST. In this retrospective study, 10 pediatric patients were evaluated, and bilateral CavST was detected in 50% of the cases [9]. In another retrospective study conducted on children, 12 pediatric CavST cases (3–16 years, mean age 10 years, 58% male) between 2000 and 2013 were evaluated; 83% of the cases were bilateral, and sinusitis was found as a risk factor in 32% [10]. Although aseptic CavST is usually seen due to trauma or a prothrombotic etiology, infection associated with septic CavST draws attention [11]. Conditions that cause immunosuppression may also be risk factors for septic CavST [1].

23.3.4 Pathogenesis

The cavernous sinuses receive blood from the facial veins and pterygoid plexus via the facial and ophthalmic veins. Therefore, infections on the face, including the paranasal sinus, nose, orbit, tonsils, and soft palate, can easily spread to the cavernous sinus due to the absence of valves in these veins [1, 11]. Infections in the danger triangle around the nose on the face pose a greater risk in this respect (Fig. 23.5). Bilateral CavST development due to intercavernous spread is common in delayed CavST cases. In addition, orbital involvement, meningitis, subdural empyema, and sepsis may accompany due to proximity [11].

Primary infection sites most likely to cause septic CavST are sphenoid and/or ethmoid sinus, facial, and dental infections. Sphenoid and/or ethmoid sinus infections are increasingly reported together with cavernous sinus thrombosis [1, 2, 9]. Sphenoid sinusitis is the most common predisposing factor for cavernous sinus thrombosis. Because sphenoid sinus infection is challenging to diagnose, treatment is often delayed, allowing the infection to spread into the cavernous sinus. Infection from sphenoid sinusitis can spread directly through the emissary veins (thin-walled, valveless veins in the skull that pass through the bone tissue through small foramina and empty into the venous sinuses) or by destroying the porous sphenoid sinus lateral wall due to infection. Ethmoid sinus infection may extend laterally into the orbit and then spread to the cavernous sinus via the superior ophthalmic vein [1, 2]. Infections involving the danger triangle area of the face (Fig. 23.5), especially around the nose, drained by the ophthalmic vessels, may cause septic cavernous sinus thrombosis. Squeezing or emptying the nasal furuncles is one of the most common facial infections that cause complications. Dental abscesses/infections cause this complication less frequently; the infection spreads to the cavernous sinus via the pterygoid venous plexus and the emissary veins that cross the bone. Otitis media and its associated complication, mastoiditis, rarely cause CavST. Mastoid infection may spread to the lateral and sigmoid sinuses before reaching the cavernous sinuses via the inferior and superior petrosal sinuses, leading to septic LST more commonly. However, since the dural sinuses do not have valves, the infection may also spread retrogradely into the cavernous sinuses due to pressure gradients [1, 2].

Many previous case reports reported reversible narrowing of the ICA associated with CavST due to its adjacent relationship with the cavernous sinus (Figs. 23.4, 23.6, and 23.7). It is reported that 70% of the cases with ICA stenosis in the acute phase of the disease resolve within 6 months. The clinical significance of ICA stenosis is uncertain, but it may raise concerns about the potential for arterial ischemic stroke [10].

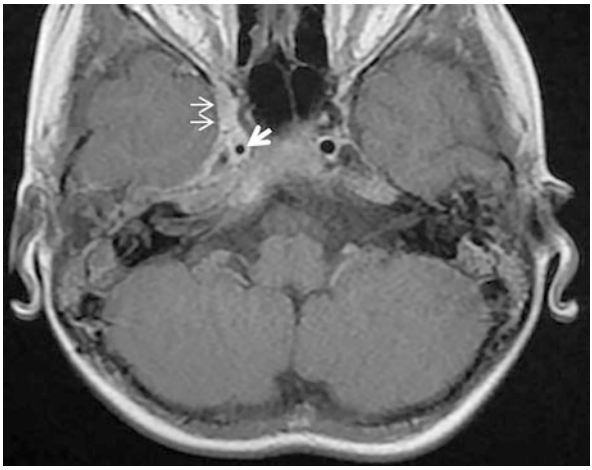

Fig. 23.6 Gradenigo syndrome. A 5-year-old patient complained of headache, diplopia, and restricted right eye movement. Axial T1-weighted contrast-enhanced MR image shows inflammation causing enlargement of the right cavernous sinus (double arrows) and diminished diameter of the right internal carotid artery (arrow). (Courtesy Zeynep Yazıcı, MD)

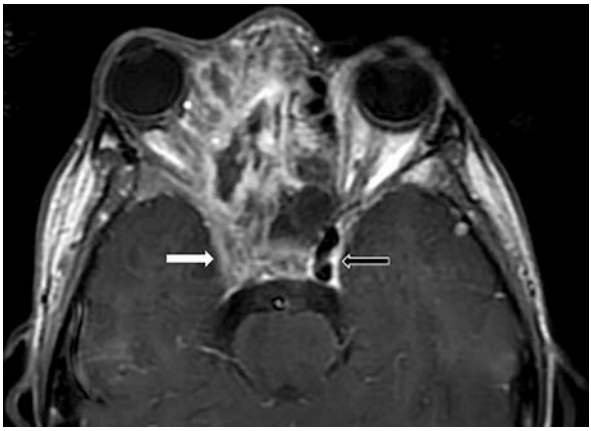

Fig. 23.7 Rhino-orbital mucormycosis causing cavernous sinus and internal carotid artery thrombosis. A 14-year-old patient with type 1 diabetes and ketoacidosis. Axial T1-weighted contrast-enhanced MR image shows enlargement and heterogeneous enhancement of the right cavernous sinus and absent flow void in the right internal carotid artery (white arrow) compared with the normal left cavernous sinus and left internal carotid artery (black arrow). Soft tissue inflammation and abscess formations involving the right orbit and ethmoid sinus are also seen. (Courtesy Zeynep Yazıcı, MD)

23.3.5 Clinical Manifestations

Headache is the most common early symptom in CavST and usually begins a few days before fever and periorbital edema. The character of the headache is typically sharp; the pain gets progressively worse, disrupts sleep, and is not relieved by painkillers. The pain is usually unilateral, occasionally reflected in the occipital region, but is more prominent in the retroorbital and frontal areas. In addition to headache, patients may have fever (94%), periorbital swelling (73%), and diplopia, which starts unilaterally but can spread to the other side via the intercavernous sinus connection within 24–48 h. Following eye-related symptoms, the infection may spread to the meninges; it may present with changes in mental status, such as sleepiness, confusion, or coma [1]. In a literature review for CavST in children covering the years 2003–2014, of 10 children with CavST between the ages of 11 and 17, half were boys. Headache (70%), fever (60%), and vomiting (60%) were reported as the most common symptoms [9]. Less common complaints may include photophobia and tearing [1]. Typically, symptoms progress within a few days. Cavernous sinus infection may rarely be a subacute or chronic process with an unexplained headache that begins a few months before the onset of ocular findings.

Cavernous sinus thrombosis classically presents as a clinical syndrome involving a combination of proptosis and chemosis of the involved eye and cranial nerve palsies and/or sensory loss [9]. In septic CavST, most patients present with fever and classical bilateral ptosis, proptosis, chemosis, and ocular muscle paralysis. However, physical findings may be subtle when patients are seen early. So, careful eye and

neurological system examination, especially paying attention to the cranial nerves, is necessary for early diagnosis.

Periorbital edema may be the earliest physical examination finding, and if it is accompanied by a headache, a more detailed physical examination should be performed on these patients. A fundoscopic examination is abnormal in two-thirds of patients. Papilledema or enlarged coiled retinal vessels occur in almost two-thirds of patients. Extraocular muscle weakness is an important finding in 50–88% of cases and is caused by dysfunction of the adjacent CN-III, CN-IV, and CN-VI (Fig. 23.4). Lateral gaze palsy (isolated CN-VI dysfunction) draws attention, especially in cases of chronic sphenoid sinusitis. Ptosis, mydriasis, and eye muscle weakness are caused by CN-III dysfunction. Complete paralysis of the nerve causes downward and lateral gaze. Proptosis and chemosis are thought to result from occlusion of the ophthalmic vessels and usually occur just before or at the same time as ophthalmoplegia. Mild hypo/hyperesthesia may occur in dermatomes innervated by the ophthalmic and maxillary branches of the CN-V.

23.3.6 Laboratory

In case of suspicion with clinical findings, it is important to confirm the diagnosis with laboratory methods, including imaging. Cavernous sinus thrombosis can lead to serious neurological sequelae if not detected on time. Cranial imaging is the most important laboratory approach in diagnosis.

23.3.6.1 Imaging

Although the diagnosis of CavST was made clinically in the past, imaging methods are required for diagnosis today [10]. The diagnosis of CavST should be considered in patients who present with signs of cranial nerve involvement localized to the cavernous sinus in addition to the symptom triad of progressive/continuous headache, mental status change, and vomiting and who have signs of infection and neuroimaging, specifically targeting this condition should be considered urgently [1, 2].

In this respect, various imaging methods can be used. Contrast-enhanced cranial magnetic resonance (MR) imaging and MR venography are the imaging modalities of choice. It has been reported that MR imaging is superior to computed tomography (CT) in septic CavST because it can detect all stages of thrombus and evaluate the extent of parenchymal damage. If MR imaging is unavailable, contrast-enhanced orbital CT and CT venography usually provide high sensitivity to identify thrombosis; however, they are less specific and less sensitive to characterize brain damage. If CT is used, it is preferred that the CT be a high-resolution CT ($\leq$3 mm slice thickness) [12]. Early venous phase, thickened cavernous sinus walls, and decreased/irregular intrasinus contrast can be demonstrated following contrast administration [1, 2, 9]. Contrast-enhanced MR or CT is considered the gold standard in diagnosing CavST [10]. Contrast-enhanced MR and CT venography are 100% sensitive in detecting CavST, while non-contrast MR and CT are not [11]. Computed

tomography and MR can also detect underlying ethmoid and sphenoid sinusitis and may guide the treatment. Other venous structures should also be evaluated in patients with CavST, as additional vein thrombosis is observed in 70% of the patients besides CavST [9]. If there is no other explainable cause, narrowing of the ICA accompanied by signs of surrounding cavernous sinus inflammation can be considered a finding that supports septic CavST. Computed tomography and MR imaging can also detect paranasal sinus infection with high sensitivity and contribute to determining the etiology and guiding the treatment. The presence of paranasal sinus infection may also be a guide for possible surgical intervention [1].

23.3.6.2 Other Laboratory Tests

Two sets of blood cultures should be sent before starting antibiotic therapy, which may be positive in approximately 70% of cases [13]. Peripheral white blood cell count is usually elevated (leukocytosis), which favors acute bacterial infection [1]. Studying acute phase reactants (such as CRP, procalcitonin, and ESR) may be beneficial in necessary cases. The tendency of high acute phase reactants to improve with treatment may be a guide in therapy. A prothrombotic examination is recommended in all patients to identify additional risk factors that may predispose them to thrombosis (prothrombotic genetic conditions such as antithrombin deficiency, protein C and protein S deficiency, factor V Leiden mutation, MTHFR gene mutation, and investigation of nephrotic syndrome and antiphospholipid antibodies) [9]. If the patient has no signs of supporting meningitis, a lumbar puncture is not required [1].

23.3.7 Differential Diagnosis

Many conditions are considered in the differential diagnosis of septic CavST, including headache, periorbital swelling, chemosis, and painful ophthalmoplegia. Orbital occlusion symptoms (proptosis, conjunctival injection, and chemosis) often accompany eye diseases. Most of these can be distinguished by neuroimaging assessment and/or clinical symptoms.

23.3.7.1 Periorbital and Orbital Cellulitis

Periorbital/orbital cellulitis and septic CavST have overlapping symptoms such as periorbital swelling, chemosis, and ophthalmoplegia. Also, septic cavernous sinus thrombosis is a complication of orbital cellulitis. For differential diagnosis of these patients, mydriatic pupil/pupillary, vision loss, papilledema, CN-V dysfunction, bilateral eye involvement, and detection of inflammatory cells in the CSF are clinical features that increase the possibility of cavernous sinus involvement. Cavernous sinus thrombosis should also be considered in cases where periorbital/orbital cellulitis is unresponsive to optimal treatment, and cranial nerve findings persist. Computed tomography or MR imaging can easily distinguish between the two diseases by demonstrating cavernous sinus involvement.

23.3.7.2 Intraorbital Abscess

The intraorbital abscess typically presents acutely with periorbital swelling, proptosis, chemosis, ophthalmoplegia, fever, decreased vision, and pain; however, there is usually no papilledema or pupillary involvement. Imaging studies can distinguish abscesses from cavernous sinus thrombosis.

23.3.7.3 Intracavernous Carotid Artery Aneurysm or Arteriovenous Fistula

These formations are usually accompanied by proptosis and pulsating pain. Patients do not have a fever or other signs of infection. Neuroimaging findings are distinctive.

23.3.7.4 Aseptic Cavernous Sinus Thrombosis

Aseptic CavST is distinguished from septic CavST, typically by the presence of aseptic disease, without fever on examination or history, as well as the absence of signs of sinus, mastoid, or facial infection on physical examination and/or laboratory, including imaging investigations.

23.3.8 Treatment

Antibiotics are the mainstay of septic CavST treatment. In selected cases, anticoagulants and surgery are additional treatments that can be applied. Early diagnosis and treatment are critical. Delays in treatment may be associated with morbidity and mortality [1, 2]. However, no clinical studies evaluated the risks and effects of CavST therapies in children.

23.3.8.1 Antibiotics

Empirical intravenous (IV) antibiotics should be started urgently to cover possible organisms expected to cause infection (Table 23.1). Treatment changes can be made according to blood culture results and treatment response. Empirical treatment should also include community-acquired MRSA. It would be appropriate to choose the antibiotics with high CSF penetration in septic CavST. First- and second-generation cephalosporins should be avoided in treating CNS infections due to poor CSF penetration. It is appropriate to plan the empirical parenteral initial regimen as vancomycin plus third-generation cephalosporins such as cefotaxime and ceftriaxone. If *Pseudomonas* coverage is desired (e.g., in patients with chronic sinusitis and known sinus colonization by *Pseudomonas*), cefepime should be used instead of ceftriaxone. An antibiotic with anaerobic coverage, such as metronidazole, should be added if a tooth or sinus infection is suspected. If a cephalosporin or metronidazole cannot be used, the combination of vancomycin plus meropenem is a reasonable empirical regimen for most patients. If meropenem is unavailable, imipenem can be used; however, since it may increase the risk of seizures, it is recommended to prefer meropenem. Antifungal therapy is rarely necessary and should only be used if a biopsy proves an invasive fungal infection.

Table 23.1 Antibiotics are used in the treatment of cerebral sinus thrombosis in children[a]

Antibiotics	Dose	Dose range (h)	Maximum dose
Cefotaxime	300 mg/kg/day	6	12,000 g/day
Ceftriaxone	100 mg/kg/day	12	4000 mg/day
Cefepime	150 mg/kg/day	8	6000 mg/day
Vancomycin	60 mg/kg/day	6–8	2000 mg/day
Metronidazole	40 mg/kg/day	6–8	4000 mg/day
Meropenem	120 mg/kg/day	8	6000 mg/day
Nafcillin	200 mg/kg/day	6	12,000 mg/day
Oxacillin	200 mg/kg/day	6	12,000 mg/day
Ceftaroline	2 month–2 year: 24 mg/kg/day	8	1200 mg/day
	≥2 year: ≤33 kg, 36 mg/kg/day >33 kg, 1200 mg/day	8–12	
Daptomycin	1–6 year: 12 mg/kg/day	24	
	7–11 year: 9 mg/kg/day		
	12–17 year: 7 mg/kg/day		
Linezolid	≤11 year: 30 mg/kg/day	8	1200 mg/day
	>11 year: 600 mg	12	
Trimetoprim–sülfametoksazol	10–20 mg/kg/day	6–12	320 mg/day

[a] Adapted and modified from Refs. [1, 14]

If *S. aureus* is sensitive to methicillin in the antibiotic susceptibility test, the treatment should be changed to nafcillin or oxacillin. If *S. aureus* is resistant to methicillin, vancomycin treatment should be continued. Ceftaroline, daptomycin, linezolid, or trimethoprim-sulfamethoxazole may be considered alternative agents if vancomycin cannot be used or if there are clinical signs such as fever, bacteremia, and mental status changes do not improve within 7 days despite treatment.

Duration of Antibiotic Therapy

Thrombus can reduce the penetration of antibiotics into the infection site, so long-term administration of IV antibiotics is recommended. A minimum of 3 weeks of treatment is usually required to achieve sterilization. The duration of treatment may be further extended based on clinical response and individual assessment of the patient's additional factors. In the presence of *S. aureus* and/or serious findings considering bacteremia, or if significant ophthalmoplegia or ocular edema persists at the end of the planned treatment, the duration may need to be extended. Since the recovery of cranial imaging findings is usually late, clinical parameters should be considered primarily for assessing the treatment duration.

23.3.8.2 Anticoagulation

The use of anticoagulants in septic CavST is controversial, and there are limited data on this subject. Findings support that adding anticoagulant therapy generally contributes to a more favorable prognosis in morbidity and mortality. In a retrospective study, a decrease in mortality was observed in patients with unilateral

involvement who applied early and received heparin (14%) compared to those who did not (36%) [15]. In another retrospective analysis, the addition of anticoagulant therapy in the early period, within the first 7 days of hospitalization, and antibiotic therapy, has been shown to reduce morbidity, including ophthalmoplegia, blindness, paralysis, hypopituitarism, and seizures, although it did not affect mortality. Although the exact duration of anticoagulant therapy is not precise, it is recommended to continue for 4–6 weeks, depending on the clinical response of the patient [12].

In a study involving children, covering the years 2003–2014, in which cases of ICA stenosis and arterial ischemic stroke were widely reported; therapeutic interventions, including anticoagulation, to prevent the progression of thrombosis or vasospasm, have been reported to be associated with favorable outcomes, contributing to the prevention of progressive infarction, although not completely preventing new infarctions [9]. Evidence-based data on the efficacy of anticoagulant therapy in children in septic CavST are limited or unavailable. Published treatment guidelines for children have been primarily estimated from data from adult studies [2]. In the authors' clinic, until new evidence-based data are available in children, it is recommended that anticoagulant therapy be given in addition to antibiotics in the treatment of septic CavST unless contraindicated.

The recommendations of the CavST treatment guidelines for adults can be summarized as follows [2]: Anticoagulant therapy is safe and may be beneficial in reducing mortality and long-term morbidity, even in intracranial hemorrhage. There is insufficient evidence to show whether heparin or low molecular weight heparin (LMWH) is superior. In critically ill patients who experience clinical worsening despite anticoagulant therapy, fibrinolytic or endovascular therapy may be lifesaving. The addition of aspirin or steroids is not recommended because of its association with higher mortality rates and poor outcomes. Duration of anticoagulant therapy should be at least 3–6 months in patients with CavST secondary to an infection, 6–12 months in patients with spontaneous CavST without persistent thrombophilia, on a lifelong basis in patients with severe thrombophilia such as severe protein C, protein S or antithrombin III deficiency, homozygous prothrombin or factor V Leiden mutation, and antiphospholipid antibody syndrome.

The British Committee for Standards in Haemotology recommends that children with CavST, and non-intracranial hemorrhage, receive anticoagulant therapy with LMWH or heparin as in all age groups [16].

In patients considered for anticoagulation, dose-adjusting anticoagulation is recommended initially at the routine treatment dose (heparin or LMWH) and keeping the thromboplastin time between 1.5 and 2.5. Warfarin should be avoided in the acute phase of the disease because of the difficulty in meticulously maintaining safe levels of anticoagulation.

The duration of anticoagulation has not been determined. The presence of infection is a significant risk factor for septic thrombosis. It is recommended to continue anticoagulation until signs of infection (e.g., periorbital edema, fever, and leukocytosis) are resolved and signs of cavernous sinus thrombosis are significantly resolved [1]. In a study in children, therapeutic anticoagulation was initiated in 10 of 12 patients with CavST who had ICA abnormalities. In this study, the median

anticoagulation duration was 3 months; 80% were treated with LMWH, and no bleeding complications were reported. These data are important to demonstrate that anticoagulation is safe to use, at least in this population [10].

Complications associated with anticoagulation are rare. In a cohort of 57 patients with CST associated with head or neck infections, the use of heparin was not associated with an increase in intracranial bleeding (26% vs. 25%) in patients receiving heparin compared with patients not receiving heparin [17]. These data support the safety of anticoagulation.

In the authors' clinic, in cases with septic CavST, low molecular weight heparin (enoxaparin 2 × 0.5–1 mg/kg/dose, subcutaneous) is started by monitoring coagulation parameters in addition to appropriate antibiotics. By tracking the imaging findings and clinical findings of the patient, LMWH is administered as long as the patient is using antibiotics and after all clinical findings have resolved; also, after the antibiotic therapy has been discontinued, LMWH is continued for a period, which can vary individually, with the recommendation of pediatric hematology experts. If there are no risk factors for thrombophilia or there has been no previous significant thrombotic attack in patients with clinical and radiological improvement, this extra period after stopping antibiotics is usually 2–4 weeks. If the patient has risk factors for thrombophilia, anticoagulant therapy is recommended for a more extended duration, with pediatric hematology consultation.

23.3.8.3 Surgery

There is no clear recommendation for surgery in CavST; the literature results are inconsistent. If a severe sphenoid sinus infection thought to cause CavST is detected on imaging, emergency surgical drainage might be considered in the early phase of treatment. Debridement of the infected sphenoid can accelerate healing [1]. In a study involving children, surgical debridement, functional endoscopic sinus surgery in 10 patients, and myringotomy in one patient were performed in 11 (92%) of 12 patients. However, the results were not different between children who had surgery and those who did not. Whether early surgical intervention may prevent complications is unclear and requires further investigation [10]. The authors consider that because the optimal response is usually assessed by the antibiotic and anticoagulant therapy, surgical treatment is not recommended unless there is an additional indication to require surgery.

23.3.8.4 Lack of Role for Glucocorticoids

There has been interest in using glucocorticoids to potentially reduce cranial nerve edema and orbital inflammation in patients with septic CavST; however, the limited data available indicate that they are not helpful [1].

23.3.9 Outcome

Morbidity and mortality may be high in CavST cases associated with sphenoid sinus infection [1]. Venous obstruction in severe cases can lead to infarction, malignant intracranial hypertension, herniation, and death. In surviving children,

intracranial hypertension and papilledema can cause vision loss [2]. Morbidity and mortality rates differ in different studies. Mortality associated with septic CavST has been reported as up to 30%. In addition, severe permanent sequelae such as oculomotor weakness, blindness, hemiparesis, or pituitary insufficiency may develop in 30% of cases [14]. More recent studies have reported mortality rates of 9–16% and morbidity rates of 15–38% [17, 18]. In another study and literature review involving children, the overall mortality rate in 52 cases was reported as 8% and the morbidity rate as 25% [10]. Significant mortality and sequelae rates highlight the importance of early diagnosis and comprehensive treatment in CavST.

23.3.10 Complication of Hearing Loss

In contrast to LST, CavST is not a kind of septic dural sinus thrombosis causing major HL. However, in the presence of accompanying recurrent/persistent acute or chronic otitis media, conductive or SNHL (due to involvement of the cochlear system and CN-VII) may develop. In addition, SNHL may develop in cases complicated by meningitis.

23.4 Septic Lateral Sinus Thrombosis

Lateral (transverse) sinus thrombosis is a rare but potentially fatal disease that usually affects the pediatric population, occurring in the sigmoid and lateral sinuses (Figs. 23.1, 23.2, 23.8a–c, and 23.9) as a complication of AOM and mastoiditis. The lateral sinuses are one of the major cerebral sinuses. They extend bilaterally from the lower part of the posterior cranium, laterally and transversely, and then open into the sigmoid sinuses, eventually draining into the internal jugular vein [19–21].

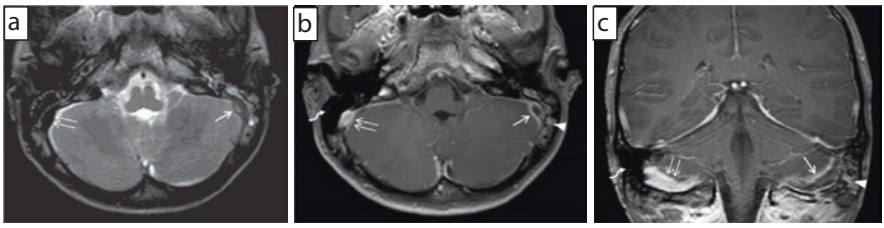

Fig. 23.8 (**a–c**) Purulent meningitis complicated with septic left sigmoid sinus thrombosis. A 15-year-old patient. (**a**) Axial T2-weighted MR image shows the absence of the flow void in the left sigmoid dural sinus owing to the thrombosis (arrow). The normal blood flow void is seen in the contralateral sigmoid sinus (double arrows). The left mastoid air cells are filled with fluid (asterisk). (**b**, **c**) T1-weighted contrast-enhanced axial (**b**) and coronal (**c**) MR images show no enhancement of the left sigmoid sinus but with surrounding dural enhancement (arrow). The normal right sigmoid sinus is enhanced vividly (double arrows). The left mastoid air cells (arrowhead) are opacified; the right mastoid air cells (curved arrow) appear normal. (Courtesy Zeynep Yazıcı, MD)

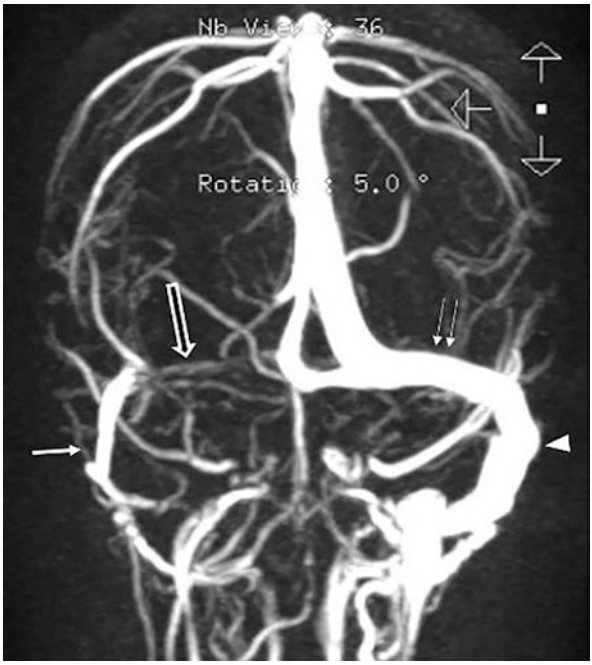

Fig. 23.9 Right transverse sinus thrombosis. A coronal 3D reconstruction image from contrast-enhanced MR venography shows a lack of flow in the proximal portion of the right transverse sinus (thick arrow). (Right sigmoid sinus [thin arrow], left transverse sinus [double arrow], left sigmoid sinus [arrowhead]). (Courtesy Zeynep Yazıcı, MD)

23.4.1 Microbiology

In most cases of septic LST, bacteria cannot be isolated in culture. One review reported that the culture isolated rate was 46% [22]. The most commonly isolated bacteria are *S. pyogenes*, *S. pneumoniae*, *S. aureus*, *H. influenza*, *P. aeruginosa*, *E. coli*, and upper respiratory tract anaerobes, including *Fusobacterium*) [23]. While there is primarily polymicrobial (aerobic and anaerobic bacteria) growth in adults, the rate of polymicrobial growth in children has been reported as 6%. When it occurs as a complication of chronic otitis media, the main pathogens are the microorganisms that cause chronic otitis media [1, 22].

23.4.2 Epidemiology

Septic LST is a rare condition in the pediatric age group. It has a high mortality rate (5–10%) and can be associated with severe clinical morbidities if not diagnosed and treated early [23]. Septic LST accounts for 2–20% of intracranial complications of AOM, but the probability of LST being associated with AOM is around 67% (autogenic LST) [22]. In one study, 13 (2.7%) of 475 patients with mastoiditis and AOM had MR-identifiable autogenic LST [20]. It occurs twice as often in boys as in girls and occurs at a mean age of 7.7 years [21, 22, 24]. It is most commonly seen on the right side. It has been reported that the prevalence of thrombophilia as a risk factor for LST in children varies between 10% and 78% [1, 16]. However, in one study, in

25 cases with pediatric autogenic LST, at least one of the thrombophilia-specific laboratory tests was positive in a significant proportion (96%). Among them, MTHFR (80%), protein S deficiency (44%), and heterozygote or homozygous FV Leiden mutation (24%) were found most frequently [1, 19].

23.4.3 Pathogenesis

Although different factors contribute to the development of autogenic LST, it most often occurs as a complication of acute or chronic otitis media. If AOM is not treated appropriately, the infection may spread to the mastoid and the lateral sinus [1, 23]. Due to the anatomical proximity of the lateral and sigmoid sinuses to the mastoid part of the temporal bone, the spread of infection in the mastoid and middle ear cavity to the lateral sinus through the veins draining into the sinuses is facilitated [20, 24]. Secondary to infection or inflammation of adjacent tissue, intravascular mural thrombus may develop due to cytokine release and activation of the coagulation pathway, activating the formation of thrombocytes and fibrin. This thrombus may spread or embolize into cerebral transverse, inferior, or superior petrosal venous sinuses and internal jugular veins [1, 19, 20, 23, 24]. In mastoiditis, the infection may reach the perisinus region from the mastoid air cell system and result in perisinus abscess and then spread to the dura and intimal layer of the sinuses, causing the formation of a mural thrombus, organized clot particle in the vein or venous sinus wall. If adequate treatment is not initiated promptly, the mural thrombus enlarges, necroses, and an intramural abscess occurs [21]. In addition, embolization of the disseminated infected thrombus into the systemic circulation causes septicemia. Thus, septic pulmonary embolism may occur as a rare complication of lateral sinus thrombosis [1, 21]. Disruption of regional venous drainage in LST, causing cochlear blood flow insufficiency and acute cochlear dysfunction, may result in hearing and balance problems. This condition is usually reversible, improves with the resolution of the disease, and the prognosis is generally good [6]. With untreated or inadequate treatment, progression of thrombosis, impaired venous circulation, and increased intracranial pressure may result in impaired absorption/drainage of CSF and, consequently, hydrocephalus [1, 20, 23]. Since thrombus formation is a protective mechanism that tries to localize the infection, a tendency to heal in thrombus is observed when the source of infection is removed [25]. Susceptibility to hypercoagulopathy in children appears to be an additional risk factor. Although the magnitude of this risk has not been systematically measured, a prothrombotic state was found in more than 70% of cases in an AOM-related series [1].

23.4.4 Clinical Manifestations

Septic LST often has a subacute onset. Symptoms usually begin a few weeks before the presentation and are associated with developing septic LST and the underlying infection [1]. The most common reason for admission is symptoms due to benign intracranial hypertension or pseudotumor cerebri [24].

In almost all patients, ear complaints such as ear pain suggestive of AOM, which started and persisted several weeks before the onset of headache, are usually the first symptom and may continue up the presentation [1, 20, 24]. In cases associated with chronic otitis media, ear discharge may be a presenting symptom [21]. The headache is usually severe, persistent, and localized on the side of the ear infection. The headache is thought to be due to intracranial hypertension related to LST, irritation of the CN-V, or a developing epidural abscess complication. Nausea and vomiting develop in about half of the cases. Other symptoms include vertigo, diplopia, photophobia, and neck pain or stiffness. Less frequently, patients may present with headache and neurologic symptoms without earache and may have radiological findings consistent with chronic otitis media that may be accompanied by cholesteatoma. In some patients, hemoptysis may develop due to septic pulmonary embolism [1].

Fever is present in approximately 80% of the cases, and the cases often appear ill. However, fever may not be evident in those associated with chronic otitis media. Most patients have an abnormal tympanic membrane examination; e.g., it is perforated in 40% and hyperemic in 20%. In more than half of the cases, posterior auricular swelling, edema, hyperemia, and sometimes tenderness are present, resulting from occlusion of the mastoid veins. This finding is called the Griesinger[1] sign and is considered clinically pathognomonic for septic LST. The most common findings in the neurological examination are papilledema, cranial nerve palsy (most commonly CN-VI), cerebellar findings (ataxia), and HL [1, 20, 24]. Bilateral papilledema due to high CSF pressure is present in half of the cases. In addition, a 15% loss of visual acuity develops. Unilateral CN-VI palsy has been reported in more than one-third of patients. Acute otitis media, CN-VI palsy, and CN-V irritation; temporoparietal and retroorbital pain in the trigeminal nerve region is known as Gradenigo[2] syndrome. It is rare, but LST should be considered when this symptom complex is detected. Nuchal rigidity is present in one-third to half of the patients and is likely the result of meningeal inflammation. Mental status is depressed in 14% of cases [1]. In a study in which 11 (73%) male and four (27%) female LST patients aged 9–60 years were evaluated over 5 years, it was reported that all patients had hearing difficulties, 11 (73%) conductive HL, and four (27%) mixed-type HL [20].

23.4.5 Laboratory

Computed tomography or MR can confirm otomastoid infection. Mastoid imaging findings are abnormal in all patients with septic LST and present with mastoid trabeculae loss, bone sclerosis, and lytic lesions of the temporal and parietal bones [1]. On contrast-enhanced CT or MR venography, filling defects due to thrombus and absence of flow in the dural sinus can be detected in patients with septic LST. In a

[1] Wilhelm Griesinger (1817–1868); German neurologist and psychiatrist.

[2] Guiseppe Gradenigo (1859–1926); Italian physician.

study evaluating 46 cases with surgically confirmed LST, contrast-enhanced CT had a sensitivity of 87%; MR was found to be 100% sensitive in 30 surgically confirmed cases [1, 22].

Round infiltrates caused by septic embolism that migrates from the sinus to the internal jugular vein and into the pulmonary venous circulation may rarely be seen on chest radiographs [1].

Two sets of blood cultures should be sent before starting antibiotic therapy. In CSF evaluation, CSF pressure increases due to impaired CSF absorption, and findings showing parameningeal inflammation may be detected for the cases considered as CNS infection. Gram stain and culture should also be sent from CSF [1]. There may be an increase in acute phase reactants such as leukocytosis, CRP, and ESR elevation for infection, supporting uncontrolled otitis and mastoid infection.

Children with LST may have underlying prothrombotic tendencies that cause thrombosis [20]. In a retrospective and 10-year study, acute unilateral HL due to ipsilateral LST developed in three cases out of 38 cases with CST. Oral contraceptive intake was found in two of them, and heterozygous factor V Leiden mutation was found in one [7]. Although some authors do not recommend routine evaluation for hypercoagulopathy, it should be kept in mind that in case series, 1/3–1/2 of children may have hypercoagulopathy, especially in the presence of AOM and chronic otitis media with evidence of thrombosis [1]. Therefore, it would be prudent to perform laboratory tests to evaluate hypercoagulopathy in these patients [20].

23.4.6 Differential Diagnosis

Septic LST should be suspected in a patient with acute/chronic otitis media who develops neurological findings such as headache, vertigo, CN-VI palsy, papilledema, and diplopia. Imaging methods such as contrast-enhanced MR and CT, MR, and CT venography should be performed to confirm the diagnosis and make a differential diagnosis [1, 22]. Lateral sinus thrombosis should be suspected in children with high intracranial pressure, previously diagnosed with acute/chronic otitis media, even if they do not have typical otomastoid complaints such as ear discharge or ear pain. The neuroradiological diagnosis of CST and LST can be difficult, given that anatomical variants of the dural venous sinus may be common in individuals. Some normal variants may mimic CST, such as prominent arachnoid granulations, hypoplasia, or aplasia of the intrasinus septum and dural sinuses [20].

23.4.7 Treatment

Antibiotics form the basis of the treatment approach in managing septic LST. If there is any indication, mastoidectomy and placement of the ventilation tube should be considered. Therefore, the necessity of mastoid surgery for eradication of the disease with antibiotics should be discussed in all these cases with LST. The presence of hypercoagulopathy may predispose to LST. Although the role of

anticoagulation in treatment is controversial, it is generally recommended. In patients with evidence of increased intracranial pressure, acetazolamide therapy is recommended [1, 20, 25].

23.4.7.1 Antibiotics

Intravenous antibiotics should be started immediately. The empirical antibiotic approach chosen is the same as in septic CavST. Methicillin-resistant *S. aureus* is rare in patients with septic LST compared to CavST. Therefore, the most appropriate initial empirical parenteral regimen is cefotaxime or ceftriaxone plus metronidazole. If *Pseudomonas* is suspected (e.g., patients with chronic otitis media and known *Pseudomonas* colonization), cefepime should be preferred instead of cefotaxime or ceftriaxone. Alternatively, meropenem may be preferred due to its effectiveness against *Pseudomonas*. There is no need to add metronidazole initially in patients who will be given meropenem. Empirical addition of vancomycin to routine therapy is recommended in patients with MRSA in previous cultures of the mastoid and critically ill patients until culture results are available. If microorganisms are identified in the samples taken, therapy should be modified to target organisms identified based on antibiotic susceptibility [1].

Since mastoiditis is the most common primary infection, antibiotics are usually recommended for at least 3–4 weeks or longer in the presence of mastoiditis, following clinical signs. A shorter period may be sufficient if the infection site has been surgically resected and the clinical signs have completely regressed [1].

23.4.7.2 Surgery

Although patients diagnosed with LST are considered an emergency in terms of surgery, it is a common opinion that surgical treatment is not a critical outcome determinant, and it would be prudent to consider it individually according to the patient [1, 19, 24]. A mastoidectomy may not be required in all cases of LST. In a pediatric series, three out of five patients had underlying otitis; he responded rapidly to antibiotic therapy and myringotomy and was shown to recover entirely without aggressive surgical intervention [1]. If surgery is planned, the lateral sinus should be evaluated beforehand. Although sometimes removing the thrombus from the lateral sinus can be considered, once the infection is under control, recanalization or collateral venous drainage may occur without additional surgical intervention [1, 23].

Therefore, it is generally recommended that mastoidectomy be planned, independent of LST, only in patients with erosive or coalescent mastoiditis, subperiosteal abscess, and erosion of the mastoid or internal cortical bone [19]. In a study evaluating 13 cases of mastoiditis with LST, surgery (nine mastoidectomies) was performed in 10, antibiotics were given only in three, and no mortality was detected in any of the cases. In addition, sigmoid sinus or internal jugular vein exploration was not performed in any patient in this study [20]. More aggressive options for thrombus removal, such as surgical lateral sinus drainage, are not routinely recommended. Internal jugular vein ligation is limited to cases of persistent septicemia or septic pulmonary embolism [22]. Surgeries such as external ventricular drainage, serial lumbar punctures, intracranial pressure monitoring, and endovascular

thrombectomy may be considered individually in patients with neurological deterioration despite maximal medical therapy [23].

23.4.7.3 Anticoagulation

Anticoagulation is not a major part of the routine management of septic LST in children [1]. Anticoagulation may be beneficial in preventing thrombus growth, maintaining intracranial drainage, and thus limiting increased intracranial pressure [23]. Although the indications for anticoagulation therapy are well-defined in adults, the role of anticoagulation in children is controversial [1, 24]. Indeed, thrombotic vessels often recanalize without anticoagulation when the infection that induces and/or accelerates thrombosis is resolved with appropriate antibiotic therapy [1]. Fifteen LST cases in children and adults (9–70 years old) were evaluated between 2010 and 2015 in India [20]. No coagulation defects were detected in any of them, none of them were given anticoagulant treatment, and no mortality was detected with antibiotic treatment alone. However, on the contrary, in another study, between 2006 and 2017, 25 pediatric cases (mean age 6, 68% male) were evaluated [19]. This study found positive genetic studies supporting thrombophilia in 96% (24/25) cases, and the authors recommended anticoagulant therapy in all cases. However, even if the risk is low, anticoagulant therapy may cause serious complications such as bleeding, drug interactions, thrombocytopenia, osteoporosis, and hemorrhagic skin necrosis [23]. In one study, anticoagulant treatment was initiated in 57.4% (39/68) of the cases. Postoperative imaging showed partial or complete recanalization of the sinuses in 84% of patients who received anticoagulant therapy and 75% of those who did not [21]. Studies suggest that anticoagulant therapy should primarily be used in "aseptic" patients with non-autogenic sigmoid sinus disease, but its role in septic LST is unclear [1, 19]. In addition to antibiotic treatment, anticoagulation treatment is recommended in the case of progressive thrombosis and lack of clinical improvement despite antibiotics and surgical drainage (persistent fever, etc.), detection of thrombus spreading to other regions (such as a proximal jugular vein, transverse sinus, and cavernous sinus) according to the first admission, neurological findings, and/or embolic events in the clinical picture, and patients with pre-existing hypercoagulopathy [1, 20]. In the authors' clinic, in septic LST, anticoagulant therapy is initiated as a supplement to antibiotics, and clinical and neurological findings are closely monitored until complete recovery is achieved and recanalization and blood flow are achieved in the thrombotic area on imaging. In cases with risk factors for thrombophilia, anticoagulant therapy can be extended with the recommendation of pediatric hematology.

Low molecular weight heparin is preferred in patients scheduled for anticoagulant therapy and should be started immediately after diagnosis [19]. If anticoagulant therapy is initiated, a standard duration has not been established [1]. Serial imaging with MR and MR venography is important to follow the spread of thrombus, especially in children who respond poorly to initial treatment [20]. In patients with clinical improvement, the first cranial imaging control should be performed at least 2 months later to decide the duration of LMWH treatment [19]. In one study, early recanalization was observed in approximately half of the cases (48%) after

appropriate treatment in the first 2 months, while the rate of recanalization at 6 months was reported to be 68–87% [19]. In another study on children, the mean recanalization time was 6 months (2–12 months) [20]. If hypercoagulopathy is documented, it is recommended to continue anticoagulant therapy for at least 6 months. In pediatric patients whose lateral sinus is not recanalized, prolonged anticoagulation should be continued. For other cases, anticoagulant therapy may be continued until symptoms and signs of infection, as well as LST, resolve or significantly improve (2–12 months) [1, 19, 20].

23.4.7.4 Treatment of Elevated Intracranial Pressure

In patients with elevated intracranial pressure, treatment with acetazolamide may be considered to reduce CSF pressure and relieve papilledema. In rare cases, patients whose intracranial pressure cannot be reduced may require serial lumbar punctures and/or ventricular drainage every 48 h. In the presence of hydrocephalus, permanent ventricular shunt placement may be necessary [1, 20].

23.4.8 Outcome

Mortality rates for LST today are lower than they used to be but still range from 5% to 10%, even in advanced centers [20]. Most patients recover completely, but chronic sequelae occur in 10–15%, including hydrocephalus, decreased visual acuity, hearing impairment, and rarely residual hemiparesis [1]. In one study, children with early recanalization of thrombosis were, on average, younger than children with persistent thrombosis [19]. In another study, persistent mild lateral gaze diplopia in one (7%) patient, severe unilateral SNHL in three (20%) patients, and prolonged papilledema (3 years) in one (7%) patient were reported [21]. In another study, 104 patients were evaluated. It was reported that 10% of the patients had morbidities such as papilledema, cranial nerve palsy, SNHL, paralysis, and hip septic arthritis at discharge; however, all complications were resolved in long-term follow-up [22]. In another study, the most common sequelae were visual field defects, headaches, HL, and seizures [24].

23.4.9 Hearing Loss

Lateral sinus thrombosis is the type of CST in which HL is most common at admission and after discharge. In a review evaluating 104 pediatric LSTs between 1993 and 2011, HL was seen in 10% of admission associated with otitis, improved with treatment, and did not draw attention to the prognosis [22]. In another review evaluating approximately 200 pediatric autogenic CSTs in the literature, HL was detected in six cases (3%) [23]. In another study in which 12 patients were evaluated, with a follow-up period of 3 months to 5 years (mean 19 months), 10 of 12 patients underwent formal audiological evaluation in the early follow-up period; HL was detected in 50% (five cases) cases (unilateral mild–moderate conduction type in three patients

and mixed-type HL in two patients). Hearing loss was reported to be temporary in four and permanent in one after long-term follow-up [20]. In another 10-year retrospective study, 3% (approximately 8) of 38 patients with CST developed acute unilateral HL due to ipsilateral LST with MR. Concurrent tinnitus and headache were also detected in two of them [7].

23.5 Septic Superior Sagittal Sinus Thrombosis

The superior sagittal sinus is the giant venous duct in the brain. Many cortical veins eventually empty into the superior sagittal sinus. Septic thrombotic occlusion is very rare because of the large size of the superior sagittal sinus. The most common infection associated with complete obstruction of the superior sagittal sinus is bacterial meningitis. Anterior segment thrombosis has sometimes been associated with frontal bacterial sinusitis. It may develop less frequently after facial plastic surgery and oral surgery [1].

Septic thrombosis of the superior sagittal sinus can lead to communicating hydrocephalus and hemorrhagic infarctions due to cortical vein thrombosis. When associated with meningitis, massive cerebral infarction, which can develop if complicated by meningitis-associated cerebral edema, rapidly leads to transtentorial brainstem herniation.

Diagnosis is made by demonstrating thrombus formation and decreased venous flow by cranial MR and MR venography.

If the superior sagittal sinus is completely occluded, the result is fatal. Anterior segment occlusion with frontal sinusitis presents with mild-to-moderate headache and resolves spontaneously following the development of collateral venous ducts. Although anticoagulants and thrombolytic therapy are generally applied in aseptic superior sagittal sinus thrombosis, their role in septic disease has not been defined [1].

23.6 Conclusion

In conclusion, although CST is rare in children, complications that impair quality of life, such as HL, are substantial. In particular, the LST is the most common type of CST with hearing loss. In cavernous sinus thrombosis, however, conductive type or SNHL may develop due to accompanying otitis media, although HL rarely causes it. The role of anticoagulant therapy in children is controversial; however, it is generally recommended because the infection that induces and/or accelerates thrombosis resolves with appropriate antibiotic therapy, and thrombotic vessels are often re-channeled. In general, anticoagulant therapy is recommended in patients with progression of thrombosis and clinical failure to resolve despite antibiotics and surgical drainage when indicated, detection of thrombus dissemination to other sites, clinical presentation accompanied by neurological findings, and/or embolic events, and pre-existing hypercoagulopathy. Pediatricians should consider the approaches for early detection and optimal treatment of complicated infections that may cause

septic CST, close follow-up of children with hypercoagulopathy for thrombosis, and early detection and/or treatment of adverse outcomes such as HL when CST develops.

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Viral Meningitis in Children and Hearing Loss

24

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24.1 Introduction

Hearing loss (HL) is a common cause of speech, language, and cognition delays. Hearing loss occurs in 1–3 newborns per 1000 births, with clinically significant or permanent HL in 1–2 per 1000 newborns and 2 per 1000 children [1, 2]. Early diagnosis of HL is critical, as improvement in speech and cognitive functions can be achieved with early intervention [3]. Pediatric HL can be categorized as congenital (genetic and non-genetic), acquired or sensorineural, conductive, and mixed [4]. Viral central nervous system (CNS) infections can lead to congenital and acquired HL, mainly sensorineural. This chapter will focus on acquired HL associated with viral meningitis and vaccines against viruses in children.

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Meningitis is inflammation of the meningeal membranes surrounding the brain and the spinal cord [5]. It is characterized by pleocytosis, defined as an increased leukocyte count in the cerebrospinal fluid (CSF). Meningitis can be broadly divided into two general classes, bacterial (septic) and aseptic meningitis. There are many infectious and non-infectious causes of aseptic meningitis. Because viruses are the most common cause of aseptic meningitis, the terms aseptic meningitis and viral meningitis (VM) are commonly used synonymously [6]. More than 100 virus strains have been directly or indirectly associated with human central or peripheral nervous system disorders [7]. Viral meningitis is the most common neurological disorder due to viruses [8].

24.2 Definition

Viral meningitis can be defined as a febrile illness accompanied by clinical signs and symptoms due to meningeal irritation without other neurological dysfunction, no evidence of bacterial pathogen in CSF examination in a patient who did not receive antibiotics before lumbar puncture (LP), and detection of viral deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) in the patient's CSF [9].

24.3 Epidemiology

The annual incidence of VM is estimated to be between 10 and 20 per 100,000 children [10]. This incidence peaks in children under the age of 1 and over the age of 5 years. A Denmark study showed that the incidence of aseptic meningitis decreases with age; 58.7 per 100,000 after birth, 38.7 per 100,000 in 6-month infants, and 15.6 per 100,000 in 5-year-old children [11]. In temperate climates, most cases occur in summer and autumn, reflecting the highest activity of enteroviral and arthropod infections [11]. In a study from Palestine, 58% of patients with enteroviral meningitis were detected in spring and summer [12]. The incidence of VM due to enteroviruses (EVs) and human parechovirus was twice of bacterial meningitis in the United Kingdom (UK) [13]. In many studies, viruses were found more frequently than bacteria among causative agents of meningitis. In Lebanon, 250 cases with confirmed meningitis were evaluated; 82.7% of cases were diagnosed with VM and only 17.3% with bacterial meningitis [14]. The widespread application of vaccines covering bacterial meningitis pathogens has led to an increase in the difference in favor of viruses in the etiology of meningitis.

24.4 Pathogenesis

Most viral pathogens affecting the CNS enter the host through respiratory secretions and the fecal–oral route and infect the mucosal surfaces of the respiratory and gastrointestinal tracts [15]. This is followed by viral replication in regional lymph

nodes. The primary viremia phase follows replication. In the primary viremia phase, the initial symptoms of the disease and spread to other organs occur. Central nervous system involvement develops in the secondary viremia phase following viral replication in other organs, particularly the liver and the spleen [16, 17]. The mechanisms related to viral transport from the circulatory system to the brain are unknown. When the virus reaches the vessels in the CNS, the transendothelial passage from the choroid plexus, meninges, or cerebral vessels occurs through different mechanisms, such as transport within migrating leukocytes, pinocytosis or colloidal transport, passage through the damaged endothelial barrier, and direct infection of endothelial cells [18, 19]. After entering the CNS, a strong inflammatory immune response is evoked and plays an important role in the clinical findings of the disease [20].

24.5 Etiology

Non-polio EVs are the most common causative agents of VM in children, accounting for 85% of cases [20]. Mumps, human parechoviruses, arboviruses such as West Nile virus (WNV), herpesviruses, including herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus (HHV) 6 and 7, lymphocytic choriomeningitis virus (LCMV), influenza, and rabies viruses are other important causes of VM.

24.6 Clinical Features

Clinical findings of VM include meningeal irritation signs and agent-specific systemic manifestations. Meningeal irritation signs are not specific to any virus and have no value for the differential diagnosis of other CNS infections such as bacterial meningitis, encephalitis, or brain abscesses [21]. There are no reliable clinical distinctions between viral and bacterial meningitis. Patients with bacterial meningitis tend to be more severely ill and may experience cognitive impairment, seizures, focal neurological deficits, and/or hypotension more than VM. Brudzinski's and Kernig's signs and nuchal rigidity are classical bedside tests to assess meningeal irritation, but their diagnostic accuracy is limited and difficult to evaluate in newborns and infants [22, 23]. Bulging fontanelle may be a valuable finding in newborns and infants, but sensitivity and specificity for VM are too low. Jolt accentuation of headache is a recently recognized physical examination technique to evaluate meningeal irritation. This test is interpreted as positive if the headache is exacerbated by rotating the head horizontally 2–3 times/s. The sensitivity and specificity of this test are found to be 65.3% and 70.4%, respectively, and considered low to use in emergency settings to exclude meningitis [24].

Neurologic manifestations of VM vary according to age. Newborns may have no neurologic symptoms or have irritability and lethargy [25]. Infants present with non-specific symptoms such as irritability, poor feeding, vomiting, diarrhea,

and short and fast breathing, accompanying acute-onset fever. Nuchal rigidity and bulging fontanelle can be detectable in newborns and infants. The appearance of seizures and focal neurological signs suggests the progression of encephalitis. Older children typically present with fever, chills, headache, nausea, vomiting, nuchal rigidity, difficulty concentrating, double vision, and photophobia [26–28].

Newborns with viral meningoencephalitis are at increased risk for severe systemic disease. Systemic manifestations may include pneumonia, necrotizing hepatitis, myocarditis, necrotizing enterocolitis, and a sepsis-like picture [16]. Severe systemic manifestations are rare in infants and older children unless there is an additional risk factor. They usually suffer from non-specific systemic symptoms such as loss of appetite, upper and lower respiratory problems, abdominal pain, myalgias, and manifestations of viral illness such as rash, conjunctivitis, herpangina, and pharyngitis [26–28]. Some clinical findings may be specific to the virus. For example, EV-A71 (EV-71) usually causes hand-foot-mouth disease and rhombencephalitis, EV-D68 (EV-68) causes acute flaccid myelitis, and parechovirus causes a clinical spectrum, including neonatal sepsis, meningitis, encephalitis, and paralysis in neonates [29–32].

24.7 Complications

Most patients with VM recover without complications. A small proportion may experience chronic headaches [6]. Serious complications, such as hepatic necrosis, necrotizing enterocolitis, and myocarditis, may develop in the neonatal period due to multi-organ involvement [5]. Enteroviral meningitis typically has a benign course, while enteroviral encephalitis can cause long-term neurological sequelae [33]. It progresses with significant morbidity and mortality in newborns and immunocompromised patients. In immunocompromised patients, especially with agammaglobulinemia or hypogammaglobulinemia, EV infection may become chronic and persists for months [34].

Some EV subtypes, such as EV-71 and EV-68, are associated with more severe neurological disease and a worse prognosis. Enteroviral infections' most common serious complications are meningoencephalitis, myocarditis, and pericarditis. Acute flaccid paralysis and rhombencephalitis are also among the neurological complications of enteroviral infection in children.

Neuropsychiatric disorders may also occur after VM but are typically not as severe as those that occur after bacterial meningitis [35]. Sleep disturbance may become evident as a complication of VM [36]. Statistically, significant retardation was found in the development of perceptual language in the 3-year follow-up of infants with a VM history in the first 3 months of life [37]. Another study showed an increased risk of attention deficit hyperactivity disorder in patients after EV-71 infection [38].

24.8 Diagnosis

In children with suspected meningitis, an LP should be done to collect CSF regardless of the presence or absence of meningeal irritation signs [22]. Intracranial hypertension should be excluded before LP to avoid herniation syndromes. Cerebrospinal fluid should be evaluated for color, opening pressure, Gram stain and bacterial culture, cell count and differential, glucose, protein, and viral polymerase chain reaction (PCR) studies. In addition, CSF lactate level (≥4.2 mmol/L) can be used for the differential diagnosis of viral and bacterial meningitis with 100% specificity [39]. The CSF analysis mainly aims to differentiate VM from bacterial meningitis. Cerebrospinal fluid pleocytosis is an essential criterion for the diagnosis of meningitis. White blood cell (WBC) count ranging from 10 to 500/mm^3 with mononuclear cell predominance supports VM; however, CSF pleocytosis is not observed in a group of infants (38%) and children (39%) in enteroviral meningitis, and 25% of patients may have neutrophilic predominance [40–42]. Eosinophilic pleocytosis can be seen in some EV types. The cloudy appearance of CSF is an excluding characteristic for VM. The CSF protein levels vary between normal and slightly elevated (<150 mg/dL), and glucose levels are normal or slightly reduced (≥40% of the serum value) in VM. The CSF protein levels can be inconsistently high in WNV meningitis. Hypoglycorrhachia is a frequently reported feature in mumps meningitis. Bacterial meningitis has a higher CSF protein level, a lower glucose level, and a higher CSF lactate level than VM [6]. Viral cultures are no longer used except in exceptional cases. Serological testing for EVs has no value in the diagnosis [40]. However, detecting virus-specific antibodies is very important for diagnosis in cases of meningitis due to arboviruses [43]. In cases of VM due to HSV, detecting immunoglobulin (Ig) M and IgG antibodies against HSV-1 and HSV-2 in serum and CSF may be helpful in the diagnosis.

The PCR is the gold standard test for diagnosing VM. The PCR test detects and quantifies viral RNA or DNA particles in CSF, and its sensitivity is 100% [44]. Targeted reverse transcriptase (RT)-PCR analysis can be used for EVs, but HSV or WNV may also be warranted in suspected cases. Multiplex PCR analysis detects many viral, bacterial, and fungal pathogens simultaneously, but its sensitivity may be low for HSV-1 and HSV-2. The PCR tests allow rapid diagnosis, shorten hospital stay, and reduce unnecessary antibiotic use [45]. In cases where CSF cannot be obtained, specimens such as throat and nasal swabs, blood, urine, and stool may be used, particularly in patients suspected of enteroviral meningitis.

The leukocyte count may be slightly increased in the complete blood count with lymphocyte predominance in VM. Acute phase reactants are not expected to reach very high levels unless complications develop [5]. Serum procalcitonin (PCT) levels above 1.20 ng/mL and serum C-reactive protein (CRP) levels above 40 mg/L show a high risk for bacterial meningitis [46]. Elevated myocardial enzymes in cases with pericarditis or myocarditis, hypertransaminasemia in cases of hepatitis, or radiological findings in patients with respiratory system infection may be seen as the accompanying systemic manifestations of viral infection.

Neuroimaging is not necessary for diagnosing VM. Severely depressed mental status (coma), papilledema, focal neurologic deficit (except sixth or seventh cranial nerve palsy), history of hydrocephalus and/or presence of a CSF shunt, and a recent history of CNS trauma or neurosurgery are indications for neuroimaging before LP. These findings are not expected in uncomplicated VM cases.

Detailed history and physical examination play an essential role in diagnosing VM. In addition to a thorough neurological examination, a careful systemic examination should also be performed. Acute bacterial meningitis must be excluded before the diagnosis of VM. Therefore, a CSF sample should be taken without delay. Clinical and CSF findings of VM and bacterial meningitis can sometimes overlap. Empirical antibiotic therapy should be started if CSF PCR analysis is negative and acute bacterial meningitis cannot be excluded. Bacterial meningitis is excluded mainly by the absence of microorganisms in CSF gram staining and lymphocytic pleocytosis in cell count [5–8]. The definitive diagnosis of VM is made by negative bacterial cultures and demonstrating the viral agent in CSF.

24.9 Treatment

Patients with confirmed VM usually do not need hospitalization. Children under 1 year of age, immunocompromised patients, and patients requiring empirical antibiotic therapy or intravenous fluid therapy should be hospitalized [47]. Care and treatment of patients should be carried out in a quiet, calm, and dim room, regardless of whether the patient is at home or in the hospital. Antipyretics, analgesics, and antiemetics can be used when needed [7]. The efficacy of corticosteroids against VM is not well-studied. Intravenous fluid therapy should be administered in cases where oral intake is poor, or fluid loss occurs due to vomiting, etc. [47]. Various algorithms have been developed to assess the likelihood of bacterial meningitis. However, the application of these algorithms may be misleading in children younger than 3 months, immunocompromised patients, patients in poor general condition, patients who received antibiotic treatment for another reason within 72 h before LP, and those who had a traumatic LP. Empirical antibiotic therapy should be given to these patients until the diagnosis of bacterial meningitis is definitively excluded [48].

Most children with uncomplicated VM do not require empirical antiviral therapy. However, in immunocompromised children, cases of acute encephalitis, or cases suspected of neonatal HSV infection, initiation of empirical antiviral therapy with acyclovir would be an appropriate approach. In clinically recovered patients, acyclovir treatment may be discontinued when CSF HSV PCR is negative or another diagnosis, such as EV PCR positivity, is established. Confirmed HSV meningitis is treated with acyclovir [49]. Acyclovir also can be used for VZV meningitis [50]. Psoromic acid is a new antiviral drug that inhibits the replication of HSV-1 and HSV-2 and can be an alternative to acyclovir in the future for treating HSV meningitis [51]. Enterovirus and parechovirus infections are mostly self-limited and require only symptomatic and supportive treatments. Experimental antiviral drugs can be used only for life-threatening conditions such as neonatal infections, severe myocarditis, or disseminated infections in immunocompromised patients. Using

intravenous immunoglobulin (IVIG) for complicated cases is controversial. Pleconaril inhibits enteroviral replication and has high CNS concentrations. It may alleviate clinical manifestations in selected patients with enteroviral meningitis [52].

24.10 Prognosis

Most patients with VM recover fully [5, 53]. The prognosis depends on the age of the child and the etiologic agent. In children, the duration of symptoms and clinical improvement is usually less than 1 week. The recovery phase is usually longer in adolescents and young adults, and some may complain of fatigue, irritability, decreased concentration, muscle weakness, and poor coordination for several weeks after the acute illness [20]. Enteroviral meningitis typically has a benign clinical course [53, 54]. The morbidity and mortality of enteroviral meningitis are not known precisely because it is common, and there is no obligation for notification. Mortality has been reported in up to 10% of immunocompromised individuals and newborn infants. Death is usually due to hepatic failure in echovirus infection and myocarditis in coxsackievirus infection [55, 56].

24.11 Prevention

Cesarean delivery decreases vertical transmission of HSV in women with active genital skin lesions when performed before the rupture of membranes. American College of Obstetricians and Gynecologists (ACOG) suggests oral acyclovir treatment before delivery [57]. Hand washing is a simple method to prevent the spread of EVs [33]. Personal protection measures to avoid mosquito and tick exposure are the mainstay of preventing the transmission of many viruses. In children hospitalized with the diagnosis of VM, contact precautions should be observed during the hospitalization.

Vaccines against some common VM pathogens are available, and others are under development. The mumps vaccine significantly reduced the incidence of mumps-related meningitis. Three inactivated EV-71 vaccines have recently been licensed in China [58]. Central nervous system infections due to influenza and some arboviruses, such as Japanese encephalitis and tick-borne encephalitis, can be prevented with vaccines. Vaccines for coronavirus disease 2019 (COVID-19) are expected to decrease severe neurologic and other systemic complications in adolescents.

24.12 Viral Meningitis in Children and Hearing Loss

Hearing loss is currently the second leading cause of years lived with a disability, and viral infections contribute to this high burden. Many viruses can cause congenital or acquired and unilateral or bilateral HL [59]. Direct or immune-mediated damage to inner ear structures and reactivation of latent viral infection in the inner ear are the

three main mechanisms of viral infection-triggered HL [59, 60]. Viral infection-related HL may occur in the late period of the disease, and it may be challenging to establish a cause-effect relationship. The severity of HL varies from mild or severe to profound [61, 62]. Hearing loss, especially in the first years of life, has a serious adverse effect on the patient's speech, language, and cognitive development [63].

Viruses mainly cause sensorineural HL (SNHL), but conductive HL (CHL) can be seen with opportunistic microorganisms in immunocompromised patients with ear infections. Problems in the outer or middle ear that impair the transmission of sound to the inner ear are called CHL. Conductive HL usually occurs acutely and is mostly temporary. Damage, disease, or disorders of inner ear structures such as the cochlea, inner ear hair cells, organ of Corti, or the eighth cranial nerve may cause SNHL.

There are hereditary and acquired causes of SNHL. In childhood, the etiology of acquired SNHL can be determined at around 10%. Bacterial meningitis is the most common cause of acquired SNHL, and virus infections are less common [61]. In a study conducted with a population of 220 infants with VM, delay or no response in auditory evoked potentials was found in 92.5% of the patients in the initial evaluation, but SNHL was detected in only two patients (0.9%) at follow-up [64]. A study conducted in China between 2015 and 2017 studying the etiology of HL showed that 60% of bilateral SNHL are due to preventable acquired causes. Among the acquired reasons, meningitis had a rate of 13.2% [65]. In a series of 200 patients with SNHL candidates for cochlear implantation in the UK, it was reported that meningitis was responsible for the etiology in 28% of the cases [62]. Neither study investigated the viral or bacterial etiology of meningitis.

24.13 Common Viruses Causing Intrauterine Infection-Related Congenital Hearing Loss

Cytomegalovirus, rubella virus, LCMV, and Zika virus cause intrauterine infection and congenital HL. However, HL related to congenital infections is out of the scope of this chapter.

24.14 Common Viruses Causing Meningitis and Acquired Hearing Loss in Children

24.14.1 Mumps and Hearing Loss

The mumps virus is a single-stranded RNA virus that belongs to the *Paramyxovirus* family. It is transmitted through infected respiratory secretions and primarily infects salivary glands. The central nervous system is the most common extra salivary organ involved in mumps cases. Aseptic meningitis and encephalitis are potential complications of mumps infection [59, 66, 67]. The risk of developing meningitis in mumps is 1–10%, and the risk of encephalitis is 0.1% [68]. Meningitis occurs after

about 5 days of parotitis but may occur before or after 2 weeks of parotid swelling [69, 70]. There is no salivary gland involvement in approximately half of the meningitis cases due to mumps infection [71]. Mumps meningitis is usually benign, and severe neurological sequelae and mortality are not expected. Encephalitis should be considered in patients who develop seizures, focal neurological signs, or cognitive abnormalities at follow-up.

Sensorineural HL is a well-known complication of mumps. Mumps virus can invade auditory structures directly as the sole neurologic manifestation of the disease, but the HL complication usually accompanies meningitis or meningoencephalitis. The incidence of HL range from 1 per 1000 to 1 per 20,000 in mumps cases [72]. Transient high frequency-range HL is frequent in mumps, and in an adult male (military) series, it was reported at 4% in frequency [73]. Although the risk of unilateral, prominent HL is reported as 1 per 20.000 in an old study, in a recent epidemiological study from Japan, of 68,812 patients with mumps, mumps-related deafness was reported in 102 patients (1 in 668 patients) [74, 75]. The incidence of mumps deafness was 7.2 times higher among 6- to 15-year-old children than among 0- to 5-year-old children with no sex difference [75].

Hearing loss usually has a sudden onset, but gradual onset is possible. Vertigo often accompanies HL [76]. Hearing loss mostly presents as unilateral and profound SNHL. Severe HL has a poor prognosis, but spontaneous recovery has been reported in mild cases. Some patients with mild HL can be overlooked; therefore, it is difficult to know the actual frequency of mumps deafness [77–80].

Acute Severe Hearing Loss Study Group, the Ministry of Health, Labor and Welfare of Japan, proposed the diagnostic criteria for mumps deafness in 1987 and revised it in 2013 (Table 24.1) [79, 80].

Serological tests for patients with sudden SNHL are recommended to be screened to detect mumps deafness, but it needs to be careful regarding false-positive results [81]. Elevated anti-mumps IgM antibody levels were reported in 5.7–7.2% of Japanese SNHL patients [82, 83]. The continuation of IgM positivity and IgM-positive cases in normal adults may have caused the rate to be high due to false positivity. After introducing the new enzyme immunoassay (EIA) test, anti-mumps IgM positivity was found to be 1% in sudden SNHL patients, lower than previously reported [84].

Table 24.1 Criteria for the diagnosis of mumps deafness[a]

Definite diagnosis
1. Patients with evident clinical signs of mumps, such as swelling of the parotid and submandibular glands and acute severe hearing loss during the period from 4 days before to 18 days after the appearance of such swelling.
2. Patients without evident clinical signs of mumps but immunoglobulin (Ig) M antibodies against the mumps virus are detected within 3 months after the onset of acute severe hearing loss.
Referent case: Patients in whom mumps deafness is suspected clinically.
1. Patients whose family members or friends have a mumps infection
2. Patients who have different periods to definite criterion 1

[a] Adapted from Ref. [80]

There is no effective treatment for mumps deafness. Most patients with mumps are refractory to therapies such as corticosteroids, vitamin B12, vasodilators, and hyperbaric oxygen therapy [79]. Therefore, vaccination against mumps has a priority. The incidence of mumps deafness has significantly decreased in countries where mumps vaccination is widely applied [85]. The first dose of the mumps vaccine for children is recommended at 12–18 months of age, and to eliminate mumps infection, the second dose is at 4–6 years of age.

Mumps occasionally causes bilateral HL. Cochlear implantation may be a good choice for these patients because the labyrinth might be a site of lesions following mumps in the majority of patients [86, 87]. Early cochlear implantation intervention showed good speech sound perception in these patients, but the same effect was not demonstrated in late implantation patients [88]. The low success rate of cochlear implantation is also reported for patients with retrolabyrinthine HL due to CNS damage caused by meningitis or meningoencephalitis [89].

24.14.2 Measles (Rubeola) and Hearing Loss

The measles virus (rubeola) is a single-stranded RNA virus belonging to the Paramyxovirus family, including the mumps virus. Measles was frequently causing epidemics in the pre-vaccine period with severe complications. Measles encephalitis occurs in approximately 1 in 1000 cases [90]. However, evidence of CNS involvement, such as CSF pleocytosis and transient electroencephalogram (EEG) abnormalities, can be observed in more than half of measles patients [90]. Sensorineural HL is one of the severe complications of measles [59]. Measles accounted for 4–9% of all cases of bilateral deafness due to profound SNHL before widespread vaccination [91]. Children are still at high risk for measles-associated HL in countries where live measles vaccination is rare.

Additionally, immigrations create an obstacle to global measles eradication. Hearing loss is typically bilateral, severe to profound, sensorineural, and may occur after measles encephalitis [90]. Degeneration of the organ of Corti and stria vascularis and cellular infiltration of the cochlea were shown in temporal bone studies on patients with measles and animal models [90, 92]. Otitis media is a frequent complication of measles caused by bacterial superinfection and may also play a role in the development of HL [93].

There is a theory that measles causes otosclerosis. Otosclerosis is an autoinflammatory disorder that causes stapes fixation and bone remodeling of the human otic capsule. It is a frequent cause of CHL, constituting 18–22% of all CHL. The relationship between the persistent measles virus infection and otosclerosis is controversial and needs further investigation [93].

Cochlear implantation is effective for patients with severe to profound SNHL in measles. Mild-to-moderate cases can be supported with hearing aids.

24.14.3 Varicella-Zoster Virus (VZV) and Hearing Loss

Varicella-zoster virus is a double-stranded enveloped DNA virus member of the Herpesviridae family. Varicella-zoster virus causes varicella (chickenpox) as a primary infection and herpes zoster (shingles) as reactivation of the latent virus staying in the sensory nerve ganglia. Hearing loss after herpes zoster infections is generally related to herpes zoster oticus or Ramsey Hunt syndrome, a well-known complication of the latent VZV infection within the geniculate ganglion. However, this complication is usually seen in advanced ages and immunocompromised patients. Pediatric herpes zoster infection rarely causes sudden HL without other neurologic involvements and recovers entirely within weeks to months [94]. Sudden HL may be the first symptom of chickenpox before the typical rash [95]. There are only a few case reports of VZV meningitis and HL in children. Schwab and Ryan [96] reported a previously healthy 5-year-old girl with VZV meningitis presented with fever, headache, and rash. She had a history of vaccination against VZV at 3 years of age. Cerebrospinal fluid was positive for VZV by PCR. Mild-to-moderate right SNHL was demonstrated at 6 weeks after discharge. The hearing ultimately returned to normal after 2 years. Hearing loss has a better prognosis than mumps and measles-related HL in VZV infections.

24.14.4 Influenza and Hearing Loss

Influenza viruses are single-stranded RNA virus members of the *Orthomyxoviridae* family. There are four types of influenza viruses, but only influenza A and B viruses cause seasonal epidemics in humans, especially in winter. Temporary HL is common during influenza. Middle ear effusion and Eustachian tube dysfunction due to congestion frequently cause mild HL and return to normal after congestion dissipates. Veltri et al. [97] studied the viral etiology in idiopathic sudden HL using viral serologic methods. Influenza virus group B was found in 14 patients (18%) and influenza group A3 in six (8%), respectively, but no information was reported about the type of HL. However, there are rare case reports in which HL was severe and permanent. Alsanosi et al. [98] reported a 2-year-old girl and a 3-month-old boy presented with sudden bilateral HL during a febrile illness. Influenza A (H1N1) was detected by PCR testing, and oseltamivir was used in both patients. Audiologic assessment showed severe and permanent SNHL. No comment was made on the pathogenesis of HL in these cases.

24.14.5 Epstein–Barr Virus (EBV) and Hearing Loss

The EBV is a DNA virus member of *Herpesviridae,* also known as human herpesvirus 4. The primary infection mostly occurs in infants and children; the virus becomes latent in the body. The CNS complications of primary EBV are rare (0.5–7.5%), and EBV meningitis usually occurs after the reactivation of the latent

virus [99, 100]. Epstein–Barr virus reactivation in latently infected B cells occurs by activation from abnormal lymphoid follicles in the CNS (chronic CNS inflammation) or transplantation into the CNS from latently infected memory B cells [101, 102]. Miyashita et al. [103] reported a 42-year-old man who presented with fever, headache, and liver dysfunction. Blood and CSF PCR tests were positive for EBV, and the patient was diagnosed with aseptic meningitis. Unilateral SNHL developed in the right ear after 20 days of disease onset. Hearing improved after corticosteroid therapy. The authors presumed that the HL was due to eighth cranial nerve neuritis related to the extension of inflammation from the meninges [103]. In the literature, there is no case report with the diagnosis of EBV meningitis who developed HL in children. Epstein–Barr virus-associated HL was presented in systemic EBV infections, mostly in adults [104, 105].

24.14.6 West Nile Virus (WNV) and Hearing Loss

West Nile virus is a neurotropic single-stranded RNA virus of the genus *Flavivirus* [59]. It circulates between insect vectors, mainly mosquitos and birds. West Nile virus was first isolated in Uganda in 1937 and then caused disease outbreaks throughout North America, Europe, the Middle East, and East Asia. West Nile Virus infection outbreaks are usually seen in the summer. Patients with WNV infection are generally asymptomatic, and only 20% of immunocompetent patients are symptomatic, mainly presenting with flu-like symptoms. Advanced age and immunosuppression are risk factors for severe neuroinvasive WNV diseases such as meningitis, meningoencephalitis, and rarely cochlear–vestibular impairment.

A 57-year-old woman with myasthenia gravis presented with meningoencephalitis, flaccid paralysis, and moderate SNHL; WNV infection was diagnosed [106]. Her hearing and motor function improved gradually after supportive treatment. The authors postulated that the neuroinvasive disease was enhanced by immunosuppressive drugs to treat myasthenia gravis. Acute-onset quadriplegia and bilateral SNHL were reported in a 41-year-old HIV-positive man with severe WNV meningoencephalitis [107], but this patient's hearing outcome details were not reported. Casetta et al. [108] described a 55-year-old previously healthy man with WNV neuroinvasive disease presenting with acute flaccid paralysis and bilateral SNHL. Three months later, audiological examinations showed no recovery in hearing.

Weatherhead et al. [109] followed up patients with WNV meningoencephalitis. After 1–3 years, they found hearing abnormalities in 16 of 35 patients (46%), and only five patients had a history of some HL before WNV infection. A 45-year-old man presented with bilateral moderate-to-severe SNHL and flaccid paralysis due to WNV meningoencephalitis [110]. This patient was aggressively treated with oral corticosteroids, and HL improved utterly. Parrino et al. [111] reported two cases with SNHL and balance abnormalities caused by WNV, one of them was diagnosed with meningoencephalitis. The hearing and balance abnormalities of these patients gradually improved after 6 months.

Acute flaccid paralysis seems to be a frequent clinical presentation of neuroinvasive WNV infection, and SNHL can accompany neurological pictures in WNV infection. Hearing loss due to neuroinvasive WNV infection usually recovers spontaneously, but permanent SNHL is not an unexpected finding.

24.14.7 Lassa Fever (LF) and Hearing Loss

Lassa fever (LF) is a viral hemorrhagic fever endemic to West Africa caused by the Lassa virus, a member of the *Arenavirus* family. Lassa fever primarily transmits to humans via contact with food or home stuff contaminated with infected *Mastomys* rats' urine or feces. Human-to-human transmission is rare. The case fatality rate of LF is approximately 15–20% [112]. It has been reported that chronic HL develops in one-third of LF survivors [113–115]. The prevalence of HL in LF is much more common than in other viruses causing HL [59]. Hearing loss may be unilateral or bilateral. Vertigo and balance abnormalities are also common among LF survivors. Hearing loss usually occurs during the convalescent phase of the disease, within 5–22 days after the end of the acute episode [112]. The proposed pathogenetic mechanisms of LF-associated HL are direct viral invasion, immune-mediated damage, vasculitis, and ribavirin, the only available antiviral agent for LF [112]. However, several studies have found no relationship between HL and ribavirin treatment in LF [116–118]. Cashman et al. [119] proposed a mechanism of autoimmune vasculitis as the cause of sudden-onset SNHL following LF. This theory was supported by studies showing histopathological changes in blood vessels of non-human primates infected with the Lassa virus resembling histopathological findings of polyarteritis nodosa [119, 120].

24.14.8 Enteroviruses and Hearing Loss

Enteroviruses are small RNA viruses belonging to the genus of *Picornaviruses*. There are many types of enteroviruses, such as echovirus, coxsackievirus, and poliovirus. Children are more susceptible to enteroviral infections. Enteroviral infections cause flu-like illnesses or no symptoms, mostly in summer and fall. Non-polio EVs are the leading cause of viral meningitis worldwide. Enteroviral meningitis is usually a benign and self-limited disease without sequela but rarely complicates with HL. Mentel et al. [121] reported high rates of PCR positivity for EVs in acute SNHL patients in contrast to a control group. However, only two case reports in the literature show a relationship between enteroviral meningitis and SNHL. Schattner et al. [122] reported a 27-year-old man with sudden-onset severe SNHL and aseptic meningitis caused by EV infection diagnosed with CSF PCR testing. The patient was treated with high-dose corticosteroids, and a dramatic improvement in hearing was observed at 10 days. The authors commented that EV infections might be associated not only with aseptic meningitis but also with viral cochleitis.

Enteroviruses can cause aseptic meningitis in immunocompromised patients. Recently, a 67-year-old woman with a history of mantle cell lymphoma on rituximab therapy presented with severe SNHL several months after a chronic febrile illness [123]. Cerebrospinal fluid examination showed mild mononuclear pleocytosis, low glucose, and normal protein levels, and the PCR test was positive for EV RNA. The auditory function of the patient showed limited improvement at follow-up, and she became a candidate for the cochlear implant.

24.14.9 Herpes Simplex Virus Type 1 (HSV-1) and Hearing Loss

Herpes simplex virus type 1 is a double-stranded DNA virus member of the Herpesviridae family [124]. The relationship of the *Herpesviridae* family to congenital or acquired sudden-onset HL has been known for a long time [59, 97, 125]. Herpes simplex virus type 1 infections may cause HL following primary infection or reactivation of the latent virus [126, 127]. There are also some case reports associated with HSV-1 meningitis or encephalitis [124, 125]. Herpes simplex virus type 1 infection-related HL is usually bilateral and severe [59]. Loss of outer hair cells and atrophy of the stria vascularis and the tectorial membrane have been shown in animals infected with HSV-1, and viral antigens were found within cochlear nerve fibers [59, 128]. Steroids are usually used in addition to antiviral agents to treat HSV-1-related HL, but a complete recovery is not common [129]. In cases without improvement, hearing aids or cochlear implantation can be used depending on the severity of HL.

24.14.10 Human Immunodeficiency Virus (HIV) and Hearing Loss

Human immunodeficiency virus is a retrovirus consisting of two identical single-stranded RNAs grouped within the *Lentiviruses*. It causes both congenital and acquired HL [59]. Bentivi et al. [130] systematically reviewed 26 articles that identified an association between HIV infection and HL and found a statistically significant relationship between these parameters with an odds ratio of 5364. Hearing loss in HIV-infected children ranges between 6% and 84%, but most studies reported a prevalence of 20–30% [131, 132]. In a study of 370 HIV-positive children in Uganda (mean age 38 months, range 6 months to 5 years), 33% developed HL [133]. Hearing loss can be unilateral or bilateral and conductive, sensorineural, or mixed in HIV infections [59]. Conductive HL is more frequent than sensorineural or mixed HL in HIV-infected children [132]. Htapcak et al. [131] reported the type of HL among 380 children with HIV infection, and HL was identified as conductive in 82%, sensorineural in 14%, and mixed in 4%.

Recurrent otitis media, otitis externa, acquired aural atresia, cholesteatoma, formation of aural polyps, and malignancy are the most common causes of CHL in patients with HIV infection [134]. Also, SNHL is more common in HIV-infected adults. Central and peripheral auditory system damages, opportunistic infections with VZV (herpes zoster oticus), CMV, HSV, toxoplasmosis, tuberculosis, cryptococcus, and syphilis, and ototoxic medications, mainly gentamicin, streptomycin, and antiretroviral drugs, may cause SNHL [59, 132]. Rarely, SNHL may be the only presenting symptom of HIV infection [135]. Sensorineural HL in HIV-infected patients is usually mild to moderate and predominantly includes high frequencies [136]. Human immunodeficiency virus-infected patients with mild-to-moderate SNHL may benefit from hearing aids. Cochlear implantation may treat patients with severe to profound SNHL [137].

24.14.11 Severe Acute Respiratory Syndrome Coronavirus 2 and Hearing Loss

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA virus member of the *Coronaviruses* family and the cause of the COVID-19 pandemic. Coronavirus disease 2019 is a respiratory and vascular disease, but CNS involvement is not rare. De Luca et al. [138] systematically reviewed the 19 articles that identified an association between SARS-CoV-2 and hearing impairment/sudden SNHL. All patients (age range 18–84 years) tested positive for COVID-19, and all had SNHL; additionally, four had tinnitus, two had vertigo, and two had nausea or vomiting. The authors concluded that hearing function might be affected by SARS-CoV-2 infection and proposed that the etiopathology might be related to a central and/or peripheral involvement of the auditory pathways. Tufatulin et al. [139] reported 87 children aged 5 months to 17 years who had confirmed COVID-19 disease had no HL or central auditory processing disorders. It seems that COVID-19-related hearing impairment is not common in the pediatric age group. However, Saki et al. [140] reported two cochlear-implanted children presented with sudden speech sound perception problems during COVID-19 disease. No evidence exists that maternal COVID-19 disease causes HL in infants [141]. As a result, auditory impairment can appear in patients with COVID-19. Children presented with sudden or gradual deterioration of speech during the pandemic, including cochlear-implanted children, should be investigated for COVID-19.

Clinical features of viral infections associated with acquired HL are summarized in Table 24.2.

Table 24.2 Clinical features of viral infections associated with acquired hearing loss

Disease or -causative viruses	Frequency of hearing loss	Type of hearing loss	Pathogenesis of hearing loss	Duration between symptom onset and hearing loss	Treatment of hearing loss
Enteroviruses (EVs)	High rates of PCR positivity for enteroviruses in acute SNHL patients Only two reported cases with enteroviral meningitis and SNHL	Bilateral SNHL	Meningitis Enteroviral cochleitis?	During the course of acute infection In immunocompromised cases, infectious symptoms may persist, and HL can occur in the chronic process	Responsive to corticosteroids Severe and permanent SNHL cases may be candidates for cochlear implantation
Epstein-Barr virus (EBV)	Extremely rare Not reported in children	Unilateral SNHL	EBV meningitis (primary or reactivation of the latent virus) Eighth cranial nerve neuritis	20 days after symptom-onset	Responsive to corticosteroids
Herpes simplex virus-1 (HSV-1)	Relatively common in primary HSV-1 infection or reactivation of the latent HSV-1 virus infection	Mostly bilateral SNHL	Loss of outer hair cells? Atrophy of stria vascularis and tectorial membrane? HSV-1 meningitis HSV-1 encephalitis	During the course of acute infection	Antiviral agents and corticosteroids; rare complete recovery Cochlear implantation may be helpful in severe SNHL
Human immunodeficiency virus (HIV)	20–30% (6–84%) in HIV-infected children	Unilateral or bilateral Conductive, sensorineural, or mixed HL	Recurrent otitis media, otitis externa, acquired aural atresia, cholesteatoma, formation of aural polyps, and malignancy for conductive HL Central and peripheral auditory system damages, opportunistic infections, ototoxic medications, and antiretroviral drugs for SNHL	During the course of the disease	Hearing aids for mild-to-moderate SNHL Cochlear implantation for severe to profound SNHL

Influenza viruses	Temporary HL common Severe and permanent HL rare	Bilateral Conductive in temporary HL and SNHL in permanent cases	Middle ear effusion or Eustachian tube dysfunction in temporary HL Not known in cases with permanent SNHL	During febrile illness	Ear nose and throat specialist consultation for conductive HL Hearing aids for mild-to-moderate cases of SNHL Cochlear implantation for severe to profound cases of SNHL
Lassa fever (LF)	More common than other viruses	Bilateral or unilateral SNHL	Direct viral invasion Immune-mediated damage Autoimmune vasculitis Ribavirin adverse effect?	5–22 days after the end of the acute disease	Ribavirin Persistent SNHL in one-third of survivors; hearing aids or cochlear implantation may be helpful according to the severity of hearing impairment
Measles	4–9% of all cases with bilateral deafness due to severe-profound SNHL before widespread vaccination	Bilateral SNHL Conductive HL in cases with otosclerosis	Degeneration of the organ Corti and stria vascularis Cellular infiltration of the cochlea Otosclerosis? Otitis media Meningoencephalitis	During the course of the disease	Hearing aids for mild-to-moderate SNHL Cochlear implantation for severe to profound SNHL
Mumps	Transient HL 4% Permanent HL 1/1000 to 1/20,000	Mostly unilateral SNHL	Invasion of auditory structures Meningitis or meningoencephalitis	4 days before to 18 days after the appearance of salivary gland swelling	No effective treatment Early cochlear implantation may be helpful in bilateral HL

Table 24.2 (continued)

Disease or -causative viruses	Frequency of hearing loss	Type of hearing loss	Pathogenesis of hearing loss	Duration between symptom onset and hearing loss	Treatment of hearing loss
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Rare in children	Unilateral or bilateral SNHL	Involvement of central auditory pathways or cochlea	During the active phase and recovery	Systemic or intratympanic corticosteroids may be helpful Cochlear implantation may be performed in severe and persistent cases
Varicella-zoster virus (VZV)	Rare	Mostly unilateral SNHL	Herpes zoster oticus Latent VZV infection within the geniculate ganglion VZV meningitis	Before the typical rash or during the active phase of chickenpox	Symptomatic Complete recovery within weeks and months
West Nile virus (WNV)	Rare	Bilateral SNHL	WNV meningitis WNV meningoencephalitis Cochlear–vestibular impairment	During the course of neuroinvasive WNV disease	Probable spontaneous recovery May respond to corticosteroids Cochlear implantation may be helpful in rare permanent SNHL

HL hearing loss, *PCR* polymerase chain reaction, *SNHL* sensorineural hearing loss

24.15 Viral Vaccines and Hearing Loss

24.15.1 Mumps Vaccine

The mumps vaccine rarely carries a risk for HL. A 7-year-old girl who developed unilateral HL 13 days after mumps vaccination was reported [142]. Another patient with a sudden unilateral total loss of cochleovestibular function following the mumps vaccine has been reported [143]. Bilateral HL was reported in a 5-year-old girl 18 days after mumps and measles-rubella vaccinations were administered separately. Corticosteroid treatment was inefficient in this patient, and after applying cochlear implantation to the right ear in third month of the disease, the hearing was improved [144].

Sporadic meningitis cases began to be reported after the administration of mumps vaccination in the UK in 1988. Urabe strain was used at that time, and the association of meningitis with vaccine strain was evidenced by nucleotide sequence. Mumps meningitis developed 18 days after measles–mumps–rubella (MMR) vaccination in two cases [145]. In Russia, among aseptic meningitis patients vaccinated against mumps by monovaccines or divaccines (mumps–measles) containing Leningrad-3 (L-3) strain in the previous 30 days before disease onset, only seven cases with HL were detected during 2009–2019 [146]. However, the incidence of vaccine-induced HL and meningitis is lower than that of natural infection.

24.15.2 Measles Vaccine

The widespread use of live measles virus vaccination has dramatically reduced the mortality and morbidity of measles. However, transient and mild local and systemic adverse effects may be seen following vaccination. Hearing loss is an infrequent complication of measles vaccination. There are rare case reports of who developed SNHL after measles or MMR vaccines; however, an association between the measles vaccine and HL is not clear and which component of the MMR vaccine is responsible for HL needs to be proven [142, 147–150].

24.15.3 Influenza Vaccine

A 17-year-old girl developed sudden bilateral HL, dizziness, nausea, and bilateral tinnitus 14 h after the H1N1 influenza vaccination. The patient's hearing improved after oral prednisolone and vitamin B complex therapy, and pure tone audiometry showed a hearing threshold of 30 dB in both ears after 1 month of treatment [151]. Recently, Kolarav et al. [152] reported a 79-year-old diabetic woman presented with acute bilateral HL, vertigo, impaired balance, and left-sided temporal headache 2 days after seasonal influenza vaccination (H1N1 and H3N2). Otolaryngological examination and neuroimaging of the patient were found normal, and audiometry

showed SNHL on both sides. The hearing adverse effects could be speculated due to thimerosal or gentamycin within the vaccine, but both were in trace amounts in the influenza vaccine to cause ototoxicity.

24.15.4 Hepatitis B Vaccine

An 11-year-old boy complained of sudden left HL, tinnitus, vertigo, and nausea after 48 h of the second hepatitis B vaccine (HBV) dose [153]. A marked left SNHL was present after 2 years. In adults, Biacebe and Bonfils [154] reported a 42-year-old man with right fluctuant SNHL and tinnitus after the second dose of HBV, and Davanipour et al. [155] reported a 37-year-old woman with unilateral SNHL and tinnitus. Tinnitus regressed, and hearing thresholds were normalized within 6 months in both patients [154, 155]. The exact mechanism of HL could not be explained in these cases. It was emphasized that it could be related to autoimmunity, but extensive immunological examinations were not performed.

24.15.5 Rabies Vaccine

Rabies is a fatal disease and can be prevented with prompt administration of the rabies vaccine and rabies immunoglobulin. Several formulations and dosing schedules exist for rabies vaccines. Rabies vaccines produced in animal nervous tissue were used in the past with a high incidence of neurological complications, predominantly acute peripheral neuropathy [156]. Nowadays, the human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCECV), and purified Vero cell rabies vaccine (PVRV) are available worldwide and replaced the old-type vaccines [157, 158]. These vaccines are inactivated, and adverse effects are primarily local reactions at the injection site and mild systemic signs such as headache, fever, myalgia, arthralgia, nausea, weakness, and rare systemic hypersensitivity reactions [159–163]. Case reports of neurological complications such as Guillain–Barre syndrome, acute disseminated encephalomyelitis, and facial paralysis with new-type rabies vaccines have rarely been reported; however, no evidence of causality exists [157, 164]. Cases of HL after rabies vaccine administration have also been rarely reported. An 11-year-old boy developed unilateral HL after the first dose of PCECV progressed with repeating doses but responded to systemic corticosteroids [165]. A 33-year-old man developed profound sudden-onset unilateral SNHL with tinnitus and vertigo within 24 h of administering the second dose of PVRV [166]. Sensorineural HL was also reported after HDCV in an 11-year-old boy [167]. These cases had no history of upper respiratory infection, systemic illness, ototoxic medication, trauma, and normal otoscopic examination.

Characteristics of viral vaccines associated with HL are summarized in Table 24.3.

Table 24.3 Characteristics of viral vaccines associated with hearing loss

Vaccine type	Frequency of hearing loss	Type of hearing loss	Duration between vaccination and hearing loss	Cause of hearing adverse effects	Treatment of hearing loss
Hepatitis B	Extremely rare	Unilateral SNHL	Within 48 h	Not known Autoimmunity? Mercury salts?	HL and tinnitus may be reversible in 6 months or persist Cochlear implantation may be helpful if HL persists
Influenza	Extremely rare	Bilateral SNHL	14–24 h	Not known Thimerosal? Gentamycin?	Responsive to corticosteroids
Measles	Extremely rare	Unilateral or bilateral SNHL	22 days–14 months	Not known	No response to corticosteroids Cochlear implantation may be helpful
Mumps	Rare	Mostly unilateral, rarely bilateral SNHL	13–18 days	Not known	No response to corticosteroids Cochlear implantation may be helpful
Rabies	Rare	Unilateral SNHL	Within 24 h	Not known	Responsive to systemic or intratympanic corticosteroids

HL hearing loss, *SNHL* sensorineural hearing loss

24.16 Conclusion

Viral infections may cause HL directly affect the auditory structures, or HL may occur during meningitis or meningoencephalitis. Viral infection-related HL is mainly sensorineural, ranges from mild to severe, and is unilateral or bilateral. The patients or parents usually notice severe HL, but mild or unilateral HL may be overlooked. Hearing loss may cause cognitive disabilities and lower longitudinal educational attainment, even in mild or unilateral cases when not treated. Therefore, hearing functions should be monitored during VM or meningoencephalitis and viral infections that cause HL frequently. Early intervention for hearing impairment will positively affect cognitive performance. Some of the viral infections that cause acquired HL are also preventable diseases with vaccination. Widespread vaccination against viruses that can cause HL will significantly contribute to public health in terms of hearing.

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Meningoencephalitis in Children and Hearing Loss

25

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25.1 Introduction

Encephalitis is the inflammation of the brain parenchyma. The most common signs and symptoms include fever, headache, vomiting, altered mental status, seizures, and focal neurologic deficits. Altered mental status is the main feature differentiating encephalitis from uncomplicated meningitis, which usually presents fever, headache, and nuchal rigidity. Since encephalitis is often accompanied by meningitis, the term meningoencephalitis is generally used interchangeably with encephalitis [1, 2].

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This chapter includes the pathogens that can cause meningoencephalitis and hearing loss (HL). For some pathogens, such as human immunodeficiency virus (HIV), HL may result from the direct effects of HIV, ototoxic drugs, and/or opportunistic infections in the middle ear and brain [3]. Since such distinction is challenging in most cases, the most common pathogens responsible for both meningoencephalitis and HL will be reviewed. Congenital infections are a significant cause of HL in the pediatric population [3]. Inflammation in the brain parenchyma is seen in most congenital infections; therefore, this subject will also be discussed under the topic of HL in meningoencephalitis.

25.2 Definition

The diagnosis of encephalitis is based on the presence of brain parenchymal inflammation associated with a neurologic deficit. Although a neuropathological examination is the gold standard for diagnosis, it is rarely applied [1, 2]. Diagnosis is usually based on clinical, laboratory, electroencephalography (EEG), and neuroradiological features in clinical practice. In 2013, the International Encephalitis Consortium (IEC) presented a consensus on the case definition of encephalitis and diagnostic guidelines to investigate infectious or autoimmune etiologies in patients with suspected encephalitis [4].

According to IEC, the diagnostic criteria for encephalitis include altered mental status (defined as an altered level of consciousness or personality change) for more than 24 h without any definable etiology as a major criterion and the presence of the following additional minor criteria (two for possible and three or more for probable or confirmed diagnoses): fever higher than 38 °C within 72 h, seizures not related to a preexisting epileptic disorder, new-onset focal neurologic findings, cerebrospinal fluid (CSF) leukocyte count greater than 5/mm^3, brain parenchymal changes in neuroimaging, and EEG abnormalities consistent with encephalitis. Confirmed cases require pathological, microbiological, or serological evidence of a pathogen known to cause encephalitis [4].

The upper limit of the CSF leukocyte count is accepted as 15/mm^3 in newborns aged ≤28 days and 9/mm^3 in infants aged 29–60 days [4, 5]. It is important to differentiate encephalopathy from encephalitis. Encephalopathy is diffuse cerebral dysfunction associated with alteration in mental status or behavior. Encephalopathy is a broader term encompassing various etiologies, including toxic–metabolic and endocrine disorders (e.g., hypoglycemia, hyperammonemia, hepatic failure, hypoxia, and diabetic ketoacidosis) and systemic or central nervous system (CNS) infections [6, 7]. Encephalopathy lasting >24 h is a major criterion of encephalitis, but additional findings are required, as described above [4].

25.3 Pathogenesis

In infectious encephalitis, the pathogen can enter the CNS via different routes, mainly the bloodstream, as in cases of enteroviruses, human parechoviruses, arboviruses, and most bacteria. The pathogen crosses the blood–brain barrier through the choroid plexus or vascular endothelium. The intra-neuronal route by retrograde axonal transport is used by viruses, such as the herpes simplex virus (HSV)-1 and rabies [1, 2].

Viruses can cause neurologic manifestations either directly by invading the brain parenchyma or post-infectiously by triggering an autoimmune response, leading to acute disseminated encephalomyelitis (ADEM), or the combination of both mechanisms as observed in patients with post-herpetic autoimmune encephalitis [8, 9]. Neurotropic viruses, such as enteroviruses, human parechoviruses, HSV-1, arboviruses, and rabies, directly invade neurons. Herpes simplex virus 1 can cause encephalitis during the primary infection (usually in children) or the reactivation of the latent virus (usually in adults) [1]. In HSV-1 encephalitis, host susceptibility is seen in patients with Toll-like receptor 3 (TLR3) deficiency [10].

For some pathogens, including influenza and *Bartonella henselae,* the pathogen cannot be identified through a brain biopsy or CSF analysis, but there is evidence of a recent infection. The mechanisms by which these pathogens cause neurologic symptoms are not well understood. In influenza-associated encephalopathy/encephalitis, edema and apoptosis of neurons are seen. However, the direct invasion of the brain by influenza is almost never revealed. Therefore, it has been suggested to use the term "encephalopathy" instead of "encephalitis." The cytokine storm is proposed to be responsible for neurological complications in influenza-associated encephalopathy/encephalitis [1, 2, 7].

25.4 Etiology

Meningoencephalitis may be due to an infectious or non-infectious etiology, such as autoimmune encephalitis and ADEM. The underlying etiology can be defined in only less than half of the cases diagnosed with encephalitis, even with extensive testing [4, 11]. Among infectious causes, viruses are the most common pathogens, while bacteria, fungi, and parasites can also be the causative agents for encephalitis. The most common viral causes in children are enteroviruses, herpesviruses, human parechovirus, and arboviruses [12–16]. A prospective multicenter study from Australia evaluated 526 children (0–14 years old) suspected of encephalitis over a period of 3.5 years. Among 287 children who met the criteria for confirmed encephalitis, 57% had infectious causes (enterovirus in 10%, parechovirus in 10%, bacterial meningoencephalitis in 8%, influenza in 6%, HSV in 6%, and *Mycoplasma pneumonia* in 6%) and 25% had immune-mediated encephalitis [14]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, was also identified as a cause of meningoencephalitis in rare cases [17, 18].

The immune-mediated causes of encephalitis include ADEM and autoimmune encephalitis, e.g., anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Among the unexplained causes of encephalitis, autoimmune encephalitis presents the most common etiology, according to studies conducted in recent years [19, 20].

25.5 Clinical Features

Clinical findings depend on the pathogenicity of the offending agent, host factors, anatomic localization of the affected part of the CNS, and the severity of involvement [2]. Initial manifestations include nonspecific symptoms, such as fever, sore throat, headache, abdominal complaints, nausea, and vomiting, followed by altered mental status, irritability, behavioral changes, and seizures. Hemiparesis, cranial nerve palsies, and bladder/bowel dysfunction can also be seen. Neurologic findings may be stable, fluctuating, or progressive. Cerebellar findings can be observed in varicella encephalitis. Patients with anti-NMDAR encephalitis can also present with psychiatric symptoms, orofacial dyskinesia, and autonomic instability [1, 2, 14].

25.6 Diagnosis

A detailed patient history, including immunization, travel history, contact with animals, geographic risk factors, and immune status, should be obtained. The physical examination should include the assessment of the mental status, with particular attention to focal neurologic findings, e.g., cranial nerve palsies, paresis in the extremities, cerebellar signs, and increased intracranial pressure signs. Alteration in mental status may be difficult to define in infants and young children who usually present with irritability. A lumbar puncture (LP) should be performed if there are no contraindications (coagulopathy, suspected mass lesion, increased intracranial pressure, etc.). Neuroimaging is usually performed before LP to exclude intracranial mass lesions or intracranial hypertension with mass effect. Magnetic resonance imaging (MRI) is the preferred neuroimaging modality, but computed tomography (CT) can be performed before LP if this modality is unavailable. However, MRI is more sensitive and specific than CT in the setting of encephalitis [2]. Patients suspected of encephalitis should also undergo EEG, which can show nonspecific generalized slowing or distinctive patterns, such as periodic lateralizing epileptiform anomalies in temporal regions suggestive of HSV encephalitis. EEG is also diagnostic in non-convulsive status epilepticus, which presents with encephalopathy and is included in the differential diagnosis of encephalitis [1, 2, 21]. The International Encephalitis Consortium has proposed a diagnostic algorithm for children with suspected encephalitis: CSF analysis, including opening pressure, protein, glucose, cell count, gram stain, culture, HSV-1/2 polymerase chain reaction (PCR) test, enterovirus PCR test; routine blood cultures, serology including Epstein–Barr virus (EBV)

and *M. pneumonia*, holding acute serum, and convalescent serum at 10–14 days for possible paired antibody testing, neuroimaging (MRI if available), EEG, *M. pneumonia* PCR on a throat swab sample, or throat and stool cultures; and further tests if additional CNS involvement is present. Additional tests are recommended according to host factors, geographic factors, exposure, and specific signs and symptoms [3]. Rapid multiplex PCR assay to detect several microbial targets (bacteria, viruses, and fungi) simultaneously, and in the COVID era, SARS-CoV-2 PCR testing are routinely used in most clinics in patients with suspected meningoencephalitis.

25.7 Treatment

Encephalitis is a neurologic emergency with significant morbidity and mortality. Treatment is supportive for each system involved. Patients usually require intensive care due to cardiorespiratory compromise, altered mental status, bulbar dysfunction, intracranial hypertension, and/or refractory seizures.

Empirical antibacterial and acyclovir treatment should be started promptly for patients with suspected meningoencephalitis. Antibacterial treatment can be stopped after the CSF culture is confirmed to be sterile. Acyclovir treatment should be continued until HSV encephalitis is ruled out.

Acyclovir is recommended for HSV and varicella-zoster virus (VZV), ganciclovir for cytomegalovirus (CMV), and antiretroviral treatment for human immunodeficiency virus (HIV). Oseltamivir is prescribed for influenza-associated encephalitis/encephalopathy, although it has not been proven to be efficacious. Intravenous immunoglobulin (IVIG) and steroids can be added to the treatment if the cytokine storm is suspected in the pathogenesis of influenza-associated encephalitis/encephalopathy. *Mycoplasma pneumonia* infections can be treated with macrolides, although there is no evidence that they affect outcomes. All bacterial, fungal, and protozoal pathogens have specific treatments [1, 2, 13, 22].

The first-line treatment of ADEM and autoimmune encephalitis includes immune therapy with steroids and immunoglobulins. Immunotherapy can be started with antibiotic and antiviral treatments while waiting for the results of microbiological analyses [23].

25.8 Prevention

Vaccination for mumps, measles, varicella, influenza, and pertussis significantly decreases the risk of encephalitis caused by these agents. Postexposure prophylaxis with the rabies vaccine and immunoglobulin is recommended for rabies-related encephalitis. Protection against tick bites and mosquitoes decreases the risk of arboviral and tick-borne encephalitis [1, 12, 24].

25.9 Prognosis

The prognosis depends on the pathogen, clinical features, and host factors. Younger age at presentation, seizures, focal neurologic signs, coma, duration of hospital stay, and abnormal neuroimaging findings are associated with poorer outcomes [2]. Intensive care unit admission is required in 40–49% of children with encephalitis [13, 14]. Mortality ranges from 0.8% to 5.7% [16, 24–26].

Neurologic sequelae, including cognitive and motor deficits, behavioral problems, epilepsy, visual defects, and hearing impairment, are reported in approximately half of the children with encephalitis [2, 27–29]. In a study investigating minor neurologic dysfunction and cognitive performance in 42 children with encephalitis, 71% of the patients had minor neurologic dysfunction, and 13% had an intelligence quotient (IQ) <85 [30].

Herpes simplex virus encephalitis is associated with poorer outcomes, while enteroviral encephalitis has better outcomes except in neonates with disseminated disease [31]. West Nile virus (WNV) encephalitis has a better prognosis in children than in adults. Rabies and *Naegleria fowleri* encephalitis have a mortality rate reaching almost 100% [1].

25.10 Hearing Loss in Meningoencephalitis

Hearing loss can be seen after meningoencephalitis, although it is not as frequent as in bacterial meningitis [31]. Viral causes account for most cases of meningoencephalitis. In a study of 34 patients with sensorineural HL (SNHL), the objective signs of viral infection were found in 12 patients (VZV in nine, mumps in two, and herpes virus hominis in one). High-frequency HL was observed in seven cases, and the low-frequency type in five cases. Most patients had pleocytosis and an increased protein level in the CSF analysis. Hearing improved in all cases and returned to normal in 10 patients. The authors concluded that reversible SNHL could occur due to viral-induced meningoencephalitis [32]. Etiologic agents responsible for HL and encephalitis are summarized in Table 25.1.

Table 25.1 Summary of pathogens causing meningoencephalitis and hearing loss

Etiology	Clinical presentation	Diagnosis	Association with hearing loss	Treatment and prevention
Congenital infections				
Cytomegalovirus (CMV)	Asymptomatic or intracranial calcifications, hepatosplenomegaly, microcephaly, cataract, chorioretinitis, anemia, thrombocytopenia, developmental delay, bone abnormalities	From birth to 3 weeks: viral culture or PCR test from the urine or saliva samples; detection of CMV by PCR test in the newborn screening dried blood spot	Hearing loss is the most common complication; 1/3 of symptomatic, 1/10 of asymptomatic children with congenital CMV will develop hearing loss	Ganciclovir or valganciclovir; no effective vaccine is present; neonatal screening program is recommended in some countries
Rubella virus	Cataracts, microphthalmia, chorioretinitis, microcephaly, congenital heart disease, hepatosplenomegaly, developmental delay	IgM, persisting high titers of rubella-IgG, PCR test, or virus isolation	Most common complication; 90% of congenital rubella cases have SNHL	Supportive treatment; immunization early in childhood and rubella antibody screening before pregnancy
Toxoplasma gondii	Chorioretinitis, intracranial calcification, hepatosplenomegaly, developmental delay	CSF PCR and serologic testing (positive IgM and/or IgA or increase in IgG during the first year) in patients with typical clinical findings or the presence of maternal toxoplasma infection	In congenital toxoplasmosis, the prevalence of SNHL is 28% in the untreated group, 12% in the treated group	Treatment is recommended in congenital toxoplasmosis (antiparasitic treatment and folinic acid) and pregnant women with acute toxoplasmosis; prevention by avoiding exposure

(continued)

Table 25.1 (continued)

Etiology	Clinical presentation	Diagnosis	Association with hearing loss	Treatment and prevention
Zika virus (ZV)	Severe microcephaly, hydrocephaly, intracranial calcification, spasticity, subcortical calcification, gyral anomaly, optic atrophy	RNA in serum, urine, or CSF from birth to 2 days; negative RNA does not exclude diagnosis; positive IgM test and negative RNA test indicate probable infection	SNHL is reported in 5.8% of patients with microcephaly	No treatment, prevention by avoiding exposure (mosquito-borne)
Lymphocytic choriomeningitis virus (LCMV)	Microcephaly, hydrocephaly, pachygyria, intracranial calcification, chorioretinitis	Serologic testing is reliable since population seroprevalence is low	SNHL is rare (visual impairment is more common)	No proven treatment, prevention by avoiding exposure (rodent-borne)
Congenital and acquired infections				
Treponema pallidum	Congenital infection: Fever, hepatomegaly, lymphadenopathy, bone marrow suppression, rash, rhinitis, bone lesions, meningitis	CSF Venereal Disease Research Laboratory (VDRL) test (sensitive but not specific), serum rapid plasma reagin (RPR) with fluorescent treponemal antibody absorption test	SNHL occurs as a late finding in congenital syphilis (between 8 and 10 years of age)	Penicillin treatment; screening of pregnant women for syphilis
Human immunodeficiency virus (HIV)	Neurologic involvement in HIV infection may be associated with primary infection with HIV, opportunistic infections, and adverse events related to treatment	Serology, HIV DNA or RNA; HIV nucleic acid testing to detect HIV DNA or RNA in infants born to HIV-infected mothers	Otitis is the most common opportunistic infection; conductive hearing loss is more common; hearing loss is reported at 6–84%	Antiretroviral treatment and treatment of opportunistic infections

Table 25.1 (continued)

Etiology	Clinical presentation	Diagnosis	Association with hearing loss	Treatment and prevention
Herpes simplex virus (HSV) type 1–2	May be acquired prenatally, perinatally (most common), or postnatally; characteristic presentations: localized disease with skin, eye, and mucous membrane involvement; CNS involvement; disseminated disease (sepsis, multiorgan involvement, high mortality)	Blood-CSF PCR testing; false-negative results may occur; if clinical suspicion is strong, repeat lumbar puncture and CSF PCR test	In HSV encephalitis, hearing loss is rare, but when present, it is bilateral and severe; hearing loss may be independent of encephalitis; seropositivity is high in idiopathic sudden SNHL	Acyclovir treatment; in the presence of maternal genital herpes infection, acyclovir treatment may be given to reduce the risk of transmission
Acquired infections				
Measles virus	Fever, cough, nasal congestion, conjunctivitis, rash, and runny nose, maculopapular rash; complications include pneumonia, subacute sclerosing panencephalitis	IgM, viral culture, or PCR test	Before vaccination, 5–10% of patients with measles have profound hearing loss	Supportive treatment, ribavirin in selected patients, vitamin A; vaccine-preventable disease
Mumps	Fever, headache, myalgia, followed by parotitis; complications include orchitis, pancreatitis, aseptic meningitis, encephalitis	IgM, PCR test	3.5% of patients with mumps had hearing loss; hearing loss is usually unilateral and may be seen in asymptomatic patients	Supportive treatment, vaccine-preventable disease

(continued)

Table 25.1 (continued)

Etiology	Clinical presentation	Diagnosis	Association with hearing loss	Treatment and prevention
Varicella-zoster virus (VZV)	Primary infection results in chickenpox, characterized by vesicular lesions; Herpes zoster results from the reactivation of the latent virus; Ramsay Hunt or herpes zoster oticus results in ear pain, ipsilateral peripheral facial nerve palsy, and a vesicular rash on the ear or oral mucosa	Serum IgM, PCR of skin lesions, CSF PCR	Residual hearing loss is reported at 5%	Acyclovir, valacyclovir, or famciclovir, and steroids are recommended; vaccine-preventable disease
West Nile virus (WNV)	A common cause of arthropod-borne encephalitis; usually asymptomatic; 20% present with West Nile fever, <1% develop neurologic complications	Serum IgM/IgG, CSF IgM	Rare; hearing loss may be transient or permanent	Supportive treatment; protection against mosquito bites is recommended for the prevention
Dengue virus	Arthropod-born virus; transmitted through mosquitoes; asymptomatic or may cause fever, rash, headache, myalgias, hemorrhagic fever	Serum or CSF IgM, PCR	Rare; mild but irreversible	Supportive treatment; prevention by mosquito control and vaccination
Lassa virus	Transmitted through contact with rodent excretions; usually asymptomatic; symptomatic cases present with fever, cough, chest pain, rarely pulmonary edema, bleeding from mucosal sites; meningitis or meningoencephalitis is seen in 15% of cases	IgM/IgG antibodies, Lassa virus antigen in serum, and PCR analysis	SNHL is the most common neurologic complication, and hearing recovery is achieved in less than half of the cases	Supportive treatment, ribavirin

Table 25.1 (continued)

Etiology	Clinical presentation	Diagnosis	Association with hearing loss	Treatment and prevention
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	In pediatric cases, usually asymptomatic or mild respiratory symptoms; neurologic involvement is reported but rare	PCR	Rare	Supportive care; antiviral treatment in selected cases; vaccination available
Cryptococcus neoformans, *Cryptococcus gattii*	Neurologic and pulmonary manifestations may be seen; cryptococcal meningoencephalitis is a common opportunistic infection	Serum or CSF cryptococcal antigen test; direct visualization by India ink, fungal culture	Mostly SNHL; hearing loss is reported at 8–73%	Antifungal treatment

CSF cerebrospinal fluid, *DNA* deoxyribonucleic acid, *Ig* immunoglobulin, *PCR* polymerase chain reaction, *RNA* ribonucleic acid, *SNHL* sensorineural hearing loss

25.11 Congenital Infections Causing Hearing Loss

Hearing loss is frequently reported after congenital infections. The acronym TORCH complex, which stands for "toxoplasmosis, others, rubella, cytomegalovirus, and herpes simplex virus (HSV) infections," is a group of congenital infections transmitted vertically from the maternal host to the fetus during pregnancy or delivery or after birth. Other infections include *Treponema pallidum,* hepatitis viruses, parvovirus B19, HIV, Zika virus, and lymphocytic choriomeningitis virus (LCMV) infections [33–35]. TORCH infections cause multiorgan anomalies in the fetus. Hearing loss is common in TORCH infections and is usually associated with CNS involvement, including developmental delay, hydrocephaly, microcephaly, migrational neuronal abnormalities, and intracranial calcifications [33, 36].

25.11.1 Cytomegalovirus (CMV) Infection

Cytomegalovirus belongs to the Herpesviridae family. Like other herpesviruses, CMV enters a latent phase after primary infection and can be subsequently reactivated, especially in the immunocompromised states. Primary CMV infection occurs in 1–4% of pregnancies and is usually asymptomatic or presents with flu-like symptoms, fatigue, and rash. In mothers with primary infection, the rate of CMV transmission to the fetus is as high as 50%, while it is less than 2% in mothers with CMV

reactivation [37]. The prevalence of congenital CMV infection is reported as 0.58–0.67%. Higher maternal seroprevalence, low socioeconomic status, and younger maternal age are associated with higher rates of congenital CMV infection [38, 39]. In utero transmission at an earlier gestational age has the most significant risk for neurologic sequelae with respect to intrapartum and postpartum transmission [40]. Approximately 10% of fetuses who acquire CMV will have clinical signs, and an additional 10–15% will develop late-onset sequelae. Infants with congenital CMV infection may be asymptomatic or have varying signs, including microcephaly, developmental delay, leukodystrophy, polymicrogyria, intracranial calcification, cataract, chorioretinitis, petechiae, hepatosplenomegaly, and hemolytic anemia.

Hearing loss is the most common long-term sequela of congenital CMV infection, and CMV is the leading acquired cause of SNHL in children [3, 41]. In a systemic review, 12.6% of newborns with congenital CMV infection had SNHL, observed in one-third of symptomatic children and one out of 10 asymptomatic children [39]. Approximately 3–5% of patients with congenital CMV infection will develop bilateral moderate to profound SNHL. It is estimated that among pediatric cases of bilateral moderate to profound SNHL, 15–20% are attributable to congenital CMV [42]. SNHL can manifest months or years after birth.

Fowler et al. [43] evaluated 307 children with asymptomatic congenital CMV infection and reported that 7.2% developed SNHL during follow-up. Among children with SNHL, further hearing deterioration was observed in 50% and delayed-onset SNHL in 18%. Newborn hearing screening will miss these patients, and continuous monitoring is recommended in patients with congenital CMV infection. A recent study consisting of 92 congenital asymptomatic CMV cases detected during hospital-based screening reported that the prevalence of SNHL at the age of 18 years was 25% [44]. After 5 years of age, the rate of SNHL development did not significantly differ between infected and uninfected children. Bilateral HL, more severe involvement, and progression are more common in symptomatic patients [3, 39]. Hearing loss in CMV may be directly due to viral components or associated with the host's immune response. Human and guinea pig studies have shown the inflammation of the cochlea and the presence of viral particles in the inner ear [45].

Treatment with ganciclovir or valganciclovir followed by prolonged prophylactic courses of antiviral medication is recommended in symptomatic neonates since this treatment has been shown to improve audiologic and neurodevelopmental outcomes. At present, antiviral therapy for asymptomatic infants with congenital CMV infection has not been shown to improve hearing outcomes [41, 46]. Currently, there is no treatment for CMV in pregnant women. CMV-specific hyperimmune globulin therapy for pregnant women with primary CMV infection has been studied in large trials but has not been proven to be efficacious and should be restricted to research studies only [47, 48]. No effective vaccine is available against this virus. Strategies for primary infection prevention include encouraging frequent handwashing and avoiding saliva or urine of children aged <6 years [3]. A universal screening approach at birth is recommended in some countries because early recognition of congenital CMV will allow closer follow-up and early intervention for HL [49].

25.11.2 Rubella Virus Infection

The rubella virus, belonging to the Togaviridae family, is the causative agent of rubella disease, also known as "German measles" [50]. It is usually a self-limited disease characterized by fever and rash. However, if the infection occurs just before conception or in the first trimester of pregnancy, it may result in congenital rubella syndrome (CRS) in up to 90% of cases. Congenital rubella syndrome is characterized by stillbirth or birth defects, including SNHL, cataracts, microphthalmia, chorioretinitis, glaucoma, microcephaly, congenital heart disease, and hepatosplenomegaly [51]. Hearing loss is the most common sequela, with up to 90% of CRS cases having SNHL [52–54]. Hearing loss is usually detected in affected babies at six to 12 months, although it may be present at birth.

Congenital rubella syndrome is a leading cause of a vaccine-preventable disease. In the pre-vaccine era, CRS was seen in 0.8–4 per 1000 live births [55]. After vaccination policies, rubella and CRS have been eliminated in the majority of the European region, Western Pacific countries, and American Health Organization Region [56]. However, CRS cases still occur, especially in regions where vaccination coverage is low [57, 58]. Therefore, it is recommended that women should undergo antibody screening before pregnancy, and rubella vaccination is applied if necessary [57].

25.11.3 Toxoplasmosis

Toxoplasma gondii is a protozoan that infects both humans and animals. The seropositivity of *T. gondii* varies between countries, and 10–90% of the population is infected. Human infection can result from ingestion or handling raw or undercooked meat containing tissue cysts, contact with cats, or consuming food contaminated by oocysts passing from infected cat feces [58, 59]. In immunocompetent healthy adults, it is usually a self-limiting disease. In immunosuppressed patients, such as those with HIV or congenital infection, *T. gondii* can cause severe disease. Congenital toxoplasmosis occurs following maternal transmission, after acute primary infection within 3 months of conception or pregnancy. It can result in abortion, neonatal death, chorioretinitis, hydrocephaly, intracranial calcification, developmental delay, epilepsy, rash, hepatosplenomegaly, and sepsis-like illness [59, 60]. Epidemiologic studies have documented that children with SNHL have increased seroprevalence of *T. gondii* [61, 62]. In a systematic review, the prevalence of SNHL was reported as 0–26% in patients with congenital toxoplasmosis. The prevalence of toxoplasmosis-associated SNHL was 28% in the untreated group and 12% in those treated with antiprotozoal therapy before 2.5 months of age [63].

Toxoplasma gondii has been detected in infected children's inner ear and brain [61]. The temporal bone histopathological samples obtained from the autopsy of three cases with congenital toxoplasmosis revealed parasites in the stria vascularis, spiral ligament, saccular macula, or internal auditory canal. However, one of the cases had intact neurosensory elements presenting with the loss of spiral ganglion

cells, possibly due to meningoencephalitis. The authors concluded that HL in congenital toxoplasmosis could be sensorial, neural, or sensorineural [64].

Antiparasitic treatment with a combination of folinic acid is recommended for symptomatic and asymptomatic infants diagnosed with congenital toxoplasmosis [60]. For pregnant women with acute toxoplasmosis, spiramycin is recommended in the first trimester, after which the treatment depends on the presence of fetal infection. A combination of pyrimethamine, sulfadiazine, and folinic acid should be offered for women in cases where a fetal infection has been confirmed [65]. The treatment of toxoplasmosis in immunocompetent people is generally not recommended except for ocular involvement [66]. Prevention strategies include avoiding exposure to undercooked meat, untreated water, cat feces, and soil [60].

25.11.4 Zika Virus Infection

Zika virus is an arbovirus that belongs to the Flaviviridae family. It is a mosquito-borne virus first isolated from a monkey in the Zika forest in Uganda. It was identified in humans in 1952. Zika virus is also transmitted from mother to fetus or through sexual contact, transfusion of blood products, organ transplantation, or laboratory exposure [67]. Most people with Zika virus infection are asymptomatic. Symptomatic cases usually have mild complaints, including fever, rash, conjunctivitis, myalgia, and headache. However, in 2015, after an outbreak of rash illness in Brazil, the Zika virus was associated with Guillain–Barré syndrome and congenital microcephaly [68]. Intrauterine encephalitis was confirmed in a case report, demonstrating Zika virus particles in the brain of an electively aborted microcephalic fetus [69]. Microcephaly in congenital Zika virus infection is generally severe. Other common findings are a partially collapsed skull, hydrocephaly, subcortical calcifications, abnormal gyral patterns, and cerebellar hypoplasia. The additional findings of congenital Zika virus infection include microphthalmia, optic atrophy, visual impairment, SNHL, epilepsy, hypertonia, and extrapyramidal involvement [70].

Sensorineural HL is reported in 5.8% of patients with microcephaly. Children with congenital Zika virus infection should be followed up for hearing function, even with normal initial screening tests [71]. There is no treatment or vaccination for Zika virus infection. Prevention is based on avoiding travel to areas where the virus is seen and protective measures against sexual transmission and mosquito bites [72].

25.11.5 Lymphocytic Choriomeningitis Virus (LCMV) Infection

Lymphocytic choriomeningitis virus is a rodent-borne pathogen that belongs to the Arenaviridae family. Humans can be infected through exposure to the secretions of house mice, rats, and hamsters. The symptoms range from mild to severe.

Most cases are mild and may be overlooked. Severe infections include meningitis and encephalitis, or a congenital syndrome may occur [73]. Lymphocytic choriomeningitis virus infection can result in abortion during pregnancy or severe neurologic sequelae, including microcephaly, hydrocephaly, pachygyria, intracranial calcification, chorioretinitis, and HL. The mortality is approximately 35% in congenitally infected children, and 70% of these cases present with neurological sequelae [74].

In contrast to other TORCH infections, such as CMV and rubella, visual impairment and microcephaly are more common than HL in LCMV infection. There is currently no efficient antiviral therapy [74]. Hearing loss in LCMV infection can be profound to severe. The severity of HL can vary between ears [3].

25.12 Congenital and Acquired Infections Causing Hearing Loss

25.12.1 Syphilis

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum.* The disease course follows primary, secondary, latent, and tertiary stages over 10 years in infected individuals. During pregnancy, maternal transmission to the fetus results in congenital syphilis. Early congenital syphilis is defined as the onset of clinical symptoms before 2 years of age, while late congenital syphilis is defined if the symptoms occur after 2 years. Untreated maternal syphilis leads to abortion, prematurity, intrauterine growth retardation, and long-term sequelae, including fever, hepatomegaly, lymphadenopathy, bone marrow suppression, maculopapular rash, rhinitis, condyloma lata, and bone lesions. Neurological sequelae include acute syphilitic leptomeningitis and chronic meningovascular syphilis resulting in cranial nerve palsies. Late findings of congenital syphilis result from persistent inflammation and scarring of tissues [75, 76]. Sensorineural HL in congenital syphilis occurs as a late finding, generally presenting with sudden onset, bilateral, profound HL between 8 and 10 years of age. Accompanying vestibular symptoms are usually absent [77].

Neurosyphilis refers to the infection of the CNS by *T. pallidum*. It can occur at any time after the initial infection. Hearing loss during syphilis is called otosyphilis, associated with neurosyphilis or isolated abnormality. In a study of 329 patients with syphilis and CSF abnormalities, 50.5% had normal hearing, 4.6% had isolated low-frequency loss, 28.3% had isolated high-frequency loss, and 16.7% had both low- and high-frequency loss. The authors found that older age and CSF pleocytosis increased the likelihood of HL and impaired hearing recovery after treatment [78]. In adults, SNHL is usually asymmetric, fluctuating, and accompanied by tinnitus and vertigo [78]. Penicillin therapy is effective for all stages of syphilis. Screening of pregnant women for syphilis is recommended [76].

25.12.2 Human Immunodeficiency Virus (HIV) Infection

The human immunodeficiency virus is a retrovirus that causes acquired immune deficiency syndrome (AIDS), a sexually transmitted disease, but vertical transmission from mother to fetus can also occur. The human immunodeficiency virus preferentially infects CD4+ T cells, consequently leading to immunosuppression and resulting in opportunistic infections. In HIV infection, involvement of the neurological system includes meningoencephalitis, ADEM, cranial neuropathies, polyneuropathy, movement disorders, and seizures [79]. Neurological abnormalities can be attributed to primary infection with HIV, opportunistic infections, and adverse events associated with treatments. In a study of 78 HIV-infected children, 46 had neurological abnormalities in the form of pyramidal tract signs in 33, hemiparesis in five, peripheral neuropathies in four, visual impairment in 18, and hearing impairment in five [80].

Hearing loss in HIV-infected patients may be associated with the direct action of the virus in the auditory system and the auditory complications of opportunistic infections, such as syphilis, toxoplasmosis, and HSV or ototoxic drugs. Hearing loss may be conductive, sensorineural, mixed, unilateral or bilateral, sudden or progressive [3, 81, 82]. In a study of 23 HIV-infected children, otitis was the most common opportunistic infection (61%) [81]. Audiometric tests revealed type B curves in 67% and type A curves in 11%. In another study including 23 HIV-infected children, conductive HL was found in six children and SNHL in two. Most patients with conductive HL had a history of otitis media. Audiologic abnormalities were more common in children with prolonged HIV-1, higher viral loads, or lower CD4+ cell counts [83]. Therefore, regular hearing screening is recommended for patients with HIV infection.

25.12.3 Herpes Simplex Virus (HSV) Infection

Herpes simplex virus 1 and HSV-2 are encapsulated, double-stranded deoxyribonucleic acid (DNA) viruses of the Herpesviridae family and are highly prevalent among humans. Herpes Simplex Virus-1 is typically associated with labial herpes, and HSV-2 with genital herpes. However, either virus can be present in areas other than their typical territories [84]. After the initial infection, the virus remains within the nerve cells in a latent state. Usually, viral reactivation is asymptomatic or limited to epithelia. Rarely, it can result in severe infections, such as encephalitis [85].

Herpes simplex virus 2 is the leading cause in newborns, while HSV-1 can also occur after the neonatal period [1, 2]. Herpes simplex encephalitis is one of the most common causes of neonatal encephalitis. It can be acquired prenatally, perinatally (most common), and postnatally. Neonatal HSV infection may present in three forms: localized infection to the skin, eye, and mouth (SEM); encephalitis; and disseminated disease. Encephalitis may be seen in both SEM disease and disseminated HSV. Hence, any neonate with suspected HSV disease, even those with isolated SEM disease, should have blood and CSF PCR tests for HSV.

Herpes simplex encephalitis is the most common cause of sporadic encephalitis. Typical neuroradiological involvement includes the mesio-temporal and orbitofrontal lobes and insular cortex. Extratemporal involvement can also occur. The CSF HSV-PCR test is highly sensitive for the diagnosis, but false-negative results can also be obtained, albeit rarely. Therefore, if clinical and radiologic findings suggest HSV encephalitis, acyclovir treatment should be continued. Delayed acyclovir treatment is associated with a poorer prognosis. Before acyclovir treatment, the case fatality rate of HSV encephalitis was 70%; however, even with efficient antiviral treatment, >35% of patients still suffer from severe sequelae or death [1, 86, 87]. Autoimmune encephalitis may occur after HSV encephalitis. In a prospective study including 51 patients with HSV encephalitis, 27% had developed autoimmune encephalitis. Of the patients with autoimmune encephalitis, 64% had N-methyl-D-aspartate receptor (NMDAR) antibodies, and 36% had other neuronal antibodies [88].

In HSV encephalitis, HL is rare, and when present, it is bilateral, severe, and associated with severe neurological complications [3]. In a review, SNHL after neonatal HSV infection was described in five case reports following disseminated HSV-2 infections. The patients had apparent clinical sequelae, and comorbid conditions were present. There were no reports of delayed-onset SNHL following perinatal infection [89].

Herpes simplex encephalitis typically involves the temporal lobes. Bilateral temporal involvement may lead to cortical deafness. Kaga et al. [90] described four children with HSV encephalitis, with only mild–moderate SNHL but severe auditory agnosia due to bilateral auditory cortex lesions. Currently, acyclovir is used in the treatment of HSV encephalitis. Early treatment is associated with a better prognosis [86].

Herpes simplex viruses may also cause HL in the setting of infections other than encephalitis. In a cohort of 232 patients with idiopathic sudden SNHL, two subgroups with HSV immunoglobulin (Ig) M seropositivity and seronegativity were compared [91]. No significant difference was found between the patients with and without HSV reactivation in prognosis. In another survey, including 1054 children referred to the clinic suspected of hearing impairment, a high prevalence of HL was found in those with HSV infection. It was noted that 82 (8%) children had a positive IgM test for HSV-1, and 8 (0.8%) had a positive IgM test for HSV-2. Hearing impairment was bilateral in 46 cases, profound in 7, moderate to severe in 23, and mild in 16 [92].

25.13 Acquired Infections Causing Hearing Loss

25.13.1 Measles

Measles is caused by the measles virus, which belongs to the Paramyxoviridae family. It is a highly contagious vaccine-preventable disease characterized by fever, cough, nasal congestion, conjunctivitis, rash, and runny nose. It has been eliminated

in high-income countries; however, it has started to reappear due to vaccine hesitancy. Mortality is usually related to respiratory or neurological complications. Neurological complications include primary measles encephalitis, acute post-infectious encephalomyelitis, subacute sclerosing panencephalitis (SSPE), and measles inclusion body encephalitis. Encephalitis occurs in up to one in every 1000 patients. Treatment is usually supportive. Prevention with the vaccine is vital since there is no specific treatment. Vitamin A supplement is associated with decreased morbidity and mortality [93, 94].

The measles virus can cause HL. Before vaccination, 5–10% of patients with profound HL were associated with measles [95]. Measles is still a common cause of HL in areas with low vaccination rates. Hearing loss in measles may be associated with otitis media, a common complication of measles, or it can follow encephalitis. Hearing loss associated with the measles virus is usually bilateral and moderate to profound in severity [3, 96].

25.13.2 Mumps

Mumps disease is caused by the mumps virus belonging to the Paramyxoviridae family. Patients clinically present with a prodromal phase, including fever, headache, and myalgia, followed by parotitis. Complications include orchitis, pancreatitis, aseptic meningitis, encephalitis, and deafness. Cerebrospinal fluid pleocytosis occurs in nearly half of patients that usually have mild meningeal signs and no other signs of meningitis. Manifest meningitis occurs in 1–10%, and encephalitis occurs in 0.1% of patients with mumps infection [95, 97]. Before vaccination, mumps was one of the leading causes of meningoencephalitis [2]. In Japan, where the mumps vaccination coverage is low, Ohfuji et al. [98] reported the incidence of complications (per 1000 mumps cases) as 6.6 for orchitis, 5.8 for meningitis, 1.3 for deafness, 0.5 for pancreatitis, and 0.3 for encephalitis in the period from 2005 to 2017.

Hearing loss associated with mumps is usually unilateral, mild to severe, and sensorineural. Rarely profound bilateral HL occurs. Hearing loss may also be seen in asymptomatic patients. In Israel, HL was detected in 3.5% of 79 patients with mumps meningoencephalitis [99]. Kanra et al. [100], who investigated whether patients with meningoencephalitis were more prone to HL, found that HL was more severe in these patients than in mumps cases without meningoencephalitis. Children with unilateral HL may remain undiagnosed; therefore, patients with mumps infection should be screened with audiological tests [101].

25.13.3 Varicella-Zoster Virus (VZV) Infection

Varicella-zoster virus belongs to the Herpesviridae family. It is a neurotropic virus that causes lifelong infection in the trigeminal and dorsal root ganglia. Vaccination plays an important role in the prevention of VZV infection. Primary infection results

in varicella infection, also known as chickenpox. Varicella is highly contagious and characterized by vesicular lesions throughout the body. Herpes zoster results from the reactivation of the latent virus [102]. Both varicella and herpes zoster can cause neurological complications, including encephalitis, cerebellitis, ADEM, myelitis, and vasculopathy [103]. Neurological manifestations may be present in the absence of rash, and the risk is higher in immunocompromised patients. Encephalitis incidence is 0.3 per 1000 patients with chickenpox, and the case fatality rate is 17%. In patients with herpes zoster, the rate of encephalitis is 0.5–5% [2]. Diagnosis is confirmed based on the intrathecal synthesis of VZV antibodies and/or the CSF VZV-PCR test. If skin lesions are present, VZV-PCR from the lesion would also be diagnostic. Patients usually respond to acyclovir; steroid treatment may be considered additionally [102, 103].

Among neurological complications, cranial neuropathies can occur, and the facial nerve is the most commonly affected cranial nerve [102]. Ramsay Hunt syndrome or herpes zoster oticus is caused by the reactivation of VZV in the geniculate ganglion and results in ear pain, ipsilateral peripheral facial nerve palsy, and a vesicular rash on the ear or oral mucosa. Vestibulocochlear nerve involvement can also occur due to the proximity of the geniculate ganglion to the eighth cranial nerve, leading to SNHL, tinnitus, nausea, vomiting, and vertigo [104]. In a study evaluating 120 patients with Ramsay Hunt syndrome, 24% had abnormal hearing, and 23% had vertigo [105]. There was no correlation between facial palsy and HL. The overall incidence of residual HL was 5%. Factors associated with a poor prognosis for hearing recovery were older age, retrocochlear HL, presence of vertigo, more severe initial HL, HL within speech frequency ranges, and male gender [105]. A combination of antiviral agents, including acyclovir, valacyclovir, or famciclovir, and steroids, is recommended. If possible, treatment should be started within the first 3 days [103].

25.13.4 West Nile Virus (WNV) Infection

West Nile virus, a member of the Flaviviridae family, is the most common cause of arthropod-borne encephalitis in the United States of America (USA) [1]. West Nile virus is distributed throughout Africa, Europe, North America, the Middle East, and West Asia. It is transmitted to humans by mosquitoes, usually Culex species. Birds are the hosts of the WNV. Most cases of WNV infection are asymptomatic. Approximately 20% of infected people develop West Nile fever. Clinical findings include fever, malaise, headache, myalgia, lymphadenopathy, and rash. Less than 1% of patients with WNV infection develop neurological complications, e.g., meningitis, encephalitis, and myelitis [106]. Older age and immunocompromised status are associated with higher morbidity and mortality [107, 108].

Hearing loss associated with WNF infection is reported rarely. It may be transient or permanent [108–110]. In a study designed to analyze long-term complications in patients with WNV infection, among the 35 patients with WNV encephalitis, hearing abnormalities were found in 16 (46%), of whom five had developed these

abnormalities prior to WNV infection [111]. The authors commented that it was impossible to differentiate whether HL was related to WNV infection, secondary to previous HL, or age-related abnormality in these patients. The treatment of WNV infection is mainly supportive. Protection against mosquito bites is recommended for prevention [106].

25.13.5 Dengue Virus Infection

Dengue virus is an arbovirus belonging to the Flaviviridae family. Dengue disease is endemic to tropical and subtropical regions and transmitted to humans by *Aedes* mosquitoes. Infection with the Dengue virus may be asymptomatic or cause fever, rash, headache, myalgias, and hemorrhagic fever [112]. Neurological involvements associated with the Dengue virus include encephalopathy, encephalitis, and Guillain–Barre syndrome [113]. Treatment is supportive. Prevention measures include mosquito control and vaccination. A tetravalent dengue vaccine comprising four recombinant, live, attenuated viruses (CYD-TDV) is currently licensed in several countries [114].

Hearing loss in dengue disease is rarely reported. In a prospective study, among 10 patients with dengue disease, three had HL, and one was asymptomatic. Although they had mild SNHL, there was no improvement [115].

25.13.6 Lassa Virus Infection

Lassa fever is caused by the Lassa virus that belongs to the Arenaviridae family. The disease is endemic in West Africa. It is transmitted through direct contact with rodent feces or urine or by inhaling aerosolized rodent excretions. Human-to-human transmission occurs due to exposure to the virus through blood, urine, feces, or bodily secretions. Approximately 80% of patients are asymptomatic. Symptomatic patients present with fever, cough, sore throat, and chest pain. Severe cases can develop facial swelling, pulmonary edema, HL, and bleeding from mucosal sites. The disease may progress to multiorgan failure. The mortality rate is reported as 1–15% [116].

Encephalitis, meningitis, or encephalopathy is seen in 15% of cases [117]. Diagnosis is established by PCR-based or antibody-based tests against the Lassa virus [118]. Ribavirin is the recommended treatment, and early initiation is associated with a better prognosis [117].

The most common neurological complication of Lassa fever is SNHL, reported in up to one-third of patients [119]. Hearing loss usually occurs in the recovery phase, suggesting that it is caused by an immunological response rather than direct viral damage. Hearing loss can be unilateral or bilateral, and recovery is achieved in less than half of the cases. There is no correlation between the occurrence of HL and the severity of the disease [117, 119].

25.13.7 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

In 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in Wuhan after a cluster of pneumonia cases. The disease was responsible for the coronavirus disease of 2019 (COVID-19), which spread rapidly, causing a global pandemic. As of today, it has caused more than 6,500,000 deaths globally [120]. Especially in the pediatric population, most cases are asymptomatic or have mild respiratory symptoms. Encephalitis and HL are rarely reported in patients with COVID-19 [121]. Data regarding HL associated with COVID-19 are sparse. There are case reports of HL in patients with COVID-19 [122, 123]. Mustafa et al. [124] investigated the audiological profile of 20 asymptomatic COVID-19 cases and reported that the high-frequency pure-tone thresholds and transient evoked otoacoustic emissions were worse in the COVID-19-positive group. Kilic et al. [125] performed SARS-CoV-2 PCR testing on five patients with sudden SNHL and found positivity in one patient. More data are needed to determine if SARS-CoV-2 affects HL.

25.13.8 Cryptococcosis

Cryptococcosis is an invasive fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii.* It is transmitted by inhaling yeasts through soil contaminated with bird feces [1]. *Cryptococcus neoformans* is more common and has a worldwide distribution; however, *C. gattii* has also been increasingly reported in Pacific Northwest and causes illness in immunocompetent hosts at a greater rate than *C. neoformans* [1, 126].

Cryptococcal meningoencephalitis is a common opportunistic infection and typically causes subacute or chronic presentation in contrast to viral and bacterial encephalitides [1]. Patients with HIV are at the highest risk of developing the disease. Other immunosuppressive states with an increased risk of cryptococcal meningoencephalitis include chronic steroid use, history of solid organ transplant, and organ failure [127]. Diagnosis is confirmed by demonstrating cryptococci based on CSF Indian ink evaluation, cryptococcal antigen testing, PCR testing, and fungal culture analysis. The treatment includes a combination of amphotericin B and flucytosine. Increased intracranial hypertension is seen in most patients before or after therapy and should be treated aggressively [126, 127].

Hearing loss is a complication of cryptococcal meningoencephalitis. It is usually bilateral, progressive, stable, or fluctuating. It may involve the cochlear or neural component. In a study consisting of 11 immunocompetent children with cryptococcal meningitis, only one (9%) patient had HL [128]. In another study, of the 26 HIV-negative cryptococcal meningitis cases, eight (30.8%) had SNHL [129]. Among the seven survivors, hearing improved in three, stabilized in two, and progressed in two. In a recent study analyzing the audiologic complications of

29 HIV-negative patients with cryptococcal meningitis, 73% had HL, and 90% were sensorineural [130]. Among patients with SNHL, the severity of HL was mild or moderate in the majority of patients. Hearing improved at 43% and stabilized at 38%. Internal auditory canal enhancement on MRI was associated with significantly more HL. Routine hearing surveillance in patients with cryptococcal meningitis was recommended [130].

25.14 Autoimmune Encephalitis

Hearing loss in the course of autoimmune encephalitis is rarely reported and may result from the involvement of the organ of Corti and/or the cochlear nuclei in the brainstem [131]. Hearing loss is usually associated with the radiological involvement of the temporal lobe and/or brainstem in reported cases. It can be the presenting symptom in some patients [132–134].

In a cohort of paraneoplastic autoimmune Kelch-like protein-11 IgG seropositive cases, HL was present in 15/39 (39%) patients [134]. Radiologically, the temporal lobes, brainstem, and cerebellum were involved. The disease typically presented with rhombencephalitis, with clinical findings, including ataxia, diplopia, dysarthria, vertigo, HL, and tinnitus. Hearing loss was refractory to treatment. In an adult patient, bilateral HL was the initial symptom of anti-NMDAR encephalitis and significantly improved after immunotherapy [133].

25.15 Conclusion

Hearing loss can be seen after meningoencephalitis, although it is not as common as in meningitis. Hearing loss may be independent of or associated with encephalitis; however, it is usually more severe if the latter is the case. Hearing loss can occur in the acute phase of the disease, during recovery, or years later. In children, TORCH infections are a significant cause of HL, and the result of neonatal hearing screening may be normal in most of these patients. Early diagnosis and specific treatment of the offending pathogen may change the prognosis. Common childhood vaccines can prevent infections, including mumps, measles, rubella, and varicella, important causes of HL. Periodic and long-term follow-up is recommended in patients with infections that cause HL.

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Part IV

Bacterial Infections

Bacterial Infections in Children and Hearing Loss: An Overview

26

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26.1 Introduction

A person who cannot hear and someone with normal hearing, with hearing thresholds of 20 decibels (dB) or better in both ears, is diagnosed as having hearing loss (HL). Hearing loss may be mild, moderate, severe, or profound. It can affect one or both ears leading to difficulty hearing conversational speech or loud sounds [1]. "Hard of hearing" refers to people with HL ranging from mild to severe. People with hearing difficulties usually communicate through spoken language and benefit from hearing aids, cochlear implants, and other assistive devices and captioning. "Deaf" people mostly have profound HL, implying little or no hearing. They often use sign language for communication.

The World Health Organization (WHO) reported that over 5% of the world's population, 432 million adults and 34 million children, have HL [1]. By 2050, over 700 million people, one in every 10 people, will have disabling HL. "Disabling" HL

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refers to HL greater than 35 dB in the better-hearing ear. Nearly 80% of people with disabling HL live in low- and middle-income countries. The prevalence of HL increases with age; among those older than 60 years, over 25% are affected by disabling HL [1]. Early identification of HL in early childhood is critical since HL in the first year of life can lead to delays in speech, language, and cognitive development [2]. Those developmental delays secondary to hearing problems are usually retainable.

Nearly 2–3 out of every 1000 children in the United States of America (USA) are born with a detectable level of HL in one or both ears [3], and among deaf children, more than 90% of them are born to normal hearing parents [4]. Before introducing the pneumococcal conjugate vaccine, nearly five out of six children experienced middle ear infections by the age of 3 years; almost all children developed transient HL related to middle ear infections from birth to 11 years of age [5, 6].

26.2 Mechanisms and Causes of Hearing Loss

Hearing loss in children may occur during intrauterine life and after birth. Hearing loss can be categorized into three groups according to the mechanisms of hearing impairment.

26.2.1 Conductive Hearing Loss

Conductive HL is caused by a problem in the outer or middle ear that interferes with sound conduction to the inner ear. It can occur from the outer parts of the ear (pinna, external auditory canal) to the stapes footplate and oval window. In children, conductive HL is most often transient (e.g., otitis media with effusion), but it can be permanent (e.g., aural atresia or chronic adhesive otitis media).

Two infections are among the most common causes of conductive HL in children. The first is otitis externa, which develops after local trauma to the ear canal or when impacted cerumen becomes contaminated by bacteria after swimming or showering. Hearing loss may occur if there is a considerable accumulation of debris, edema, or inflammation in the ear canal.

Acute otitis media (AOM) is the other most common childhood disorder associated with conductive HL. By 3 years, most children will experience at least one episode of AOM, and many will have experienced at least three episodes. Acute otitis media leads to fluid accumulation in the middle ear space that prevents tympanic membrane vibration, thereby diminishing the movement of the ossicular chain. Hearing loss persists until the resorption of fluid from the middle ear space. Middle ear effusion can last 6 weeks despite adequate therapy in many patients. The fluid accumulation, also one of the causes of conductive HL, sometimes leads to tympanic membrane perforation,

26.2.2 Sensorineural Hearing Loss

Sensorineural HL (SNHL) results from damage, disease, or other disorders affecting the inner ear (e.g., the cochlea) and/or the auditory (eighth cranial) nerve. Sensorineural HL can be categorized as congenital, including hereditary and nonhereditary causes, and acquired. Congenital SNHL may occur secondary to congenital malformations, intrauterine infections, medications, or toxins that have a teratogenic effect on the developing ear of the fetus. Congenital SNHL is mainly caused by cytomegalovirus (CMV), rubella virus, and Zika virus infections or secondary to congenital toxoplasmosis or syphilis. Hearing loss in these conditions frequently is progressive.

26.2.3 Mixed Hearing Loss

Mixed HL refers to a combination of conductive HL and SNHL.

26.3 Congenital Bacterial Infections and Hearing Loss

Not so many well-defined bacterial congenital infections exist. The best-defined and well-known congenital bacterial infection is tuberculosis.

26.3.1 Congenital Tuberculosis and Hearing Loss

According to the WHO, one-third of the world population has tuberculosis infection, and 20 million people suffer from the tuberculosis disease [7]. On the other hand, congenital tuberculosis (cTB) is rarely seen, and the actual incidence is unknown. Also, it is challenging to differentiate cTB from postnatally acquired tuberculosis disease. The onset of cTB is heterogeneous in the age of presentation; clinical signs and symptoms may differ with age. It may be asymptomatic at birth, and many symptoms can occur within days to weeks.

Congenital tuberculosis occurs after *Mycobacterium tuberculosis* complex bacillaemia during pregnancy, leading to infection of the placenta or the maternal genital tract. After that, the mycobacteria may pass to the fetus hematogenous from the placenta to the umbilical vein or by the aspiration or ingestion of amniotic fluid [8]. The hematogenous spread may lead to one or more primary complexes in the liver or lungs. Also, aspiration or ingestion of infected amniotic fluid results in primary complex formation in the lungs or gastrointestinal tract. The liver and lungs are the two most involved sites in cTB [9]. The first diagnostic criteria for cTB were defined by Beitzke in 1935 [10]. Cantwell et al. [11] revised the criteria for the diagnosis of cTB in 1994, and up to 1982, less than 300 cases of cTB were reported [11].

According to the Cantwell criteria, the infant must have proved tuberculous lesions, plus at least one of the followings should be met for the diagnosis of cTB: (1) detection of tuberculosis-specific lesions in the first week of life, (2) presence of a primary hepatic complex or caseating granulomas, (3) documented tuberculosis infection of the endometrium or placenta, or (4) exclusion of the possibility of postnatal transmission by a thorough investigation of contacts, including the infant's hospital attendants, and by adherence to existing recommendations for treating infants exposed to tuberculosis [11].

Congenital tuberculosis symptoms may present at birth but are more common in the first 2–4 weeks of life. Clinical manifestations of cTB may be varied, nonspecific, and difficult to differentiate from neonatal bacterial or viral sepsis. The mortality rate of cTB is 21–100% [12]. Also, central nervous system (CNS) involvement in cTB is higher [9]. Many CNS-related complications, such as encephalomalacia, hydrocephalus, cerebral infarction, and cerebral atrophy, can be seen if the patients survive [13]. The CNS-related complications might lead to HL, but the incidence of HL related to cTB is unknown. Since not many reported cases exist, data about cTB and HL could be obtained from published case reports and series. However, a hearing evaluation was not done or mentioned in most of these reports.

Peng et al. [12] analyzed 170 cases of cTB in the literature between 1946 and 2009. Excluding one case of giving up treatment, 68 (40%) patients died of 169, and HL was detected in 1.5% of the survivors. Li et al. [9] reviewed Chinese journals reporting 92 cTB cases between 1976 and 2018 in China. Forty (44%) patients died, among the survivors, eight were cured, and 39 patients improved. However, the authors did not mention long-term sequelae, including HL [9]. Du et al. [14] reported 10 cases of cTB treated in Beijing Children's Hospital, between 2009 and 2018 that were followed up for at least 6 months. Among 10 cTB cases, hearing scanning was not done in seven patients, but three cases passed hearing tests. Chotpitayasunondh et al. [15] reported nine cTB cases diagnosed from 1979 to 1998; the fatality rate was 33.3%, and no sequelae were found in the survivors.

Hearing impairment in cTB could be secondary to ear involvement. Aldan-Aguirre et al. [16] reported a premature infant of 25 weeks' gestational age presented at 8 weeks with otorrhea from the left ear, later developing facial paralysis and cervical lymphadenitis. Cultures from ear discharge and the biopsy material taken during a surgical procedure revealed the presence of the *M. tuberculosis* complex. The patient developed necrotizing otitis media, left temporal bone osteomyelitis, and cervical lymphadenitis. The infant's mother was found to have an endometrial biopsy positive for M. *tuberculosis*, suggesting a cTB diagnosis. After initiating anti-TB treatment, the brainstem auditory-evoked response (BAER) test showed a mild left-sided conductive HL with a normal sensory reserve for both ears [16]. Ng et al. [17] reported a premature infant of 28 weeks gestational age with congenital tuberculous otitis that led to ipsilateral HL detected by the BAER test.

Although TB in the newborn period may present as otomastoiditis, isolated otitis media without systemic involvement is rare, and so far, only a few cases have been reported. Naranbhai et al. [18] reported two premature infants with isolated ear discharge diagnosed with congenital tuberculous otitis treated successfully without sequelae.

26.4 Acute Bacterial Meningitis and Hearing Loss

26.4.1 Acute Bacterial Meningitis in Neonatal Period

Acute bacterial meningitis (ABM) is more commonly seen in the first 28 days of life than in another period [19]. The incidence of ABM in the neonatal period ranges from 0.25 to 0.32 per 1000 live births [20, 21]. However, the prevalence of HL may be 10–20 times higher in high-risk infants who require treatment in neonatal intensive care units (NICUs) [22].

26.4.1.1 Etiology

In high-income countries, *Streptococcus agalactiae* (group B streptococcus [GBS]), *Escherichia coli*, and other gram-negative bacilli are the most common causes of neonatal meningitis [23]. Moreover, *Enterococcus* spp., coagulase-negative staphylococci (CONS), *Staphylococcus aureus*, *Listeria monocytogenes*, *Streptococcus pyogenes* (group A streptococcus [GAS]), and alpha-hemolytic streptococci can cause ABM, especially among preterm and very low birth weight (VLBW, <1500 g) infants [24]. *Neisseria meningitidis*, *Streptococcus pneumoniae*, and non-typeable *Haemophilus influenzae* also rarely cause meningitis in newborn infants. On the other hand, in low- and middle-income countries, the etiology of ABM in infants differs geographically, but GBS remains a prominent cause [25].

26.4.1.2 Hearing Loss Related to Neonatal Acute Bacterial Meningitis

Neonatal ABM can lead to severe long-term sequelae in 12–29% and mild neurological impairment in 15–38% of survivors [26, 27]. Stevens et al. [28] investigated the long-term outcome of neonatal meningitis between 1985 and 1987 in England and Wales. A total of 111 children who had neonatal meningitis were compared with 113 matched controls from their birth hospital and 49 controls from general practices. They were evaluated at nearly a mean age of 9 years. The authors reported 3.6% SNHL in the neonatal meningitis group but no occurrence of HL in either control group. Among the neonatal meningitis group, one case (0.9%) had a severe bilateral SNHL and had been infected with *E. coli.* One had a severe unilateral SNHL and had been infected with a non-*E. coli* gram-negative bacillus, and one had a moderate unilateral SNHL and had been infected with *L. monocytogenes*; the fourth child required a hearing aid but could not be tested because of learning difficulties [28].

Libster et al. [29] investigated long-term outcomes of GBS meningitis in children between 1988 and 2006 in two hospitals in the USA. They determined that 90 children with GBS meningitis and five patients died during the acute illness. Among 85 survivors, 43 children could be evaluated at the age of 3–12 years; 24 (56%) were reported functioning normally, 11 (25%) had mild–moderate, and 8 (19%) had severe long-term neurodevelopmental impairment. Four children (9.5%) were detected as having SNHL.

Doctor et al. [30] investigated the consequences of meningitis in 64 VLBW infants who had culture-proven episodes of meningitis over 18 years from 1977 to 1995. The authors investigated neurodevelopmental outcomes of 39 of 45 (87%) meningitis survivors compared to non-meningitis survivors followed up to 20 months of corrected age [30]. Causes of meningitis were CONS in 43%, other gram-positive bacteria in 19%, gram-negative bacteria in 17%, and *Candida* species in 20% of episodes. They reported HL in 2 (5%) of 39 meningitis survivors and 2% in the control group [30].

Maqbool et al. [31] investigated the incidence of neonatal HL in high-risk neonates in a tertiary teaching hospital in India. During the one-year prospective study period, high-risk neonates were screened for hearing impairment using the BAER test. Two hundred neonates aged between 7 and 28 days among patients with high risk for HL, such as a family history of hereditary childhood SNHL, intrauterine infections, craniofacial anomalies, including those with morphologic abnormalities of the pinna and ear canal, birth weight <1500 g (VLBW), hyperbilirubinemia at a serum level requiring exchange transfusion, ototoxic medications, including but not limited to the aminoglycosides, used for more than 5 days or multiple courses or in combination with loop diuretics, bacterial meningitis, Apgar scores of <4 at the first or <6 at the fifth minute, needing mechanical ventilation for more than 5 days, stigmata, or other findings associated with a syndrome known to include SNHL and/or conductive HL were randomly selected [31]. Among 200 infants, 32 had HL with initial BAER testing. A total of 20 neonates had HL with BAER testing on follow-up. The significant risk factors for HL were ototoxic medications, hyperbilirubinemia requiring exchange transfusion, and perinatal asphyxia in 45%, 30%, and 26% of neonates with high risk, respectively. Bacterial meningitis was present in 10% of neonates. The presence of meningitis, stigmata, and/or syndrome associated with HL and craniofacial anomalies was found to be independent risk factors for HL in high-risk infant groups.

Thangavelu et al. [32] investigated HL in 4512 neonates hospitalized in the NICU in Germany between 2009 and 2014. They found the prevalence of HL at 1.6% and permanent HL at 0.9%. They revealed that craniofacial anomalies, hyperbilirubinemia requiring exchange transfusion, oxygen supplementation to a newborn with gestation age 36 weeks or older, and hydrops fetalis were associated with permanent HL. On the other hand, commonly known risk factors such as perinatal infections, meningitis, sepsis, and ototoxic drugs did not show significance related to HL in the study cohort. Coenraad et al. [33] investigated risk factors in infants with SNHL diagnosed after failure on neonatal hearing screening (NHS) admitted to the NICU between 2004 and 2009 in Rotterdam. Each patient was matched with two same-gender and postconceptional age controls. A total of 3316 infants were screened with BAER testing, and SNHL was diagnosed in 58 infants. They revealed that the presence of dysmorphic features, low APGAR score at 1 min, sepsis, meningitis, cerebral bleeding, and cerebral infarction were significantly related to SNHL [33].

26.4.2 Acute Bacterial Meningitis Beyond Neonatal Period

Bacterial meningitis causes 250,000 deaths worldwide yearly and severe disabilities in survivors [34]. Permanent HL rates range from 2.5% to 18% in children with bacterial meningitis [35–38]. Invasion of bacteria to the cochlea and labyrinth, damage to the eighth cranial nerve by bacterial toxins, disruption of microcirculation, and toxic effects of antibiotics used in the treatment are among the mechanisms proposed to explain HL. In a study of 124 children aged 4 weeks to 16 years recently diagnosed with bacterial meningitis from 21 hospitals in England and South Wales, 92 (74%) had meningococcal, 18 (15%) pneumococcal meningitis, and one case each of meningitis due to *H. influenzae* type b, *L. monocytogenes*, and GBS [35]. In the remaining 11 cases (8%), all had cerebrospinal fluid (CSF) neutrophil pleocytosis, and the pathogen was unknown. All patients showed obvious HL at the initial evaluation. Three children had permanent, 13 (10.5%) had reversible SNHL, and nine recovered within 48 h of diagnosis.

The impact on the development of the child after meningitis can be devastating. A cochlear implant offers a serious treatment possibility for severe SNHL developing after ABM. In cases of post-meningitis HL, it is particularly important to place a cochlear implant as early as possible due to possible intracochlear ossification, thus avoiding the insertion of electrodes into the cochlear lumen.

26.4.2.1 Etiology

While ABM is becoming less common in high-income countries because of the widespread use of vaccines against *H. influenzae* type b (Hib), *S. pneumoniae,* and *N. meningitidis*, and the introduction of intrapartum antibiotic prophylaxis for GBS, ABM still occurs worldwide, with a peak incidence in young children [39–41]. After the global introduction of the *Hib* and pneumococcal conjugate vaccines to the infant immunization schedule, the epidemiology of ABM has been changing, leading to a decrement in ABM incidence [42].

The etiology of ABM in children can vary by age, geographic region, acquisition route, and host factors. For example, GBS and *E. coli* are the most common pathogens in neonates and young infants; however, enteric gram-negative bacilli, *S. pneumoniae*, and *N. meningitidis* are less common in this age group. In older infants and children, *S. pneumoniae* and *N. meningitidis* are the most common, accounting for approximately 60–70% of cases [43]. Furthermore, *N. meningitidis* is the most commonly observed pathogen in adolescents, accounting for nearly half of all cases [43]. Even with a 50–60% decline in the overall incidence of pneumococcal meningitis in the USA with the widespread pneumococcal vaccination, *S. pneumoniae* remains the most common cause of ABM in children [44]. The most common frequent agents vary from region to region. For example, in the meningitis belt in sub-Saharan Africa, *N. meningitidis accounts nearly 50–60% of cases* [45]. In the European region, *N. meningitidis* accounts for approximately 30–50% of cases, followed by *S.* pneumoniae (20–40%), GBS (10–15%), and *H. influenzae* (5–15%) [46]. In North America, *S. pneumoniae* is the most frequent pathogen, accounting for 35–60% of cases, followed by *N. meningitidis* (15–25%), *H. influenzae* (15–20%,

predominantly non-type b in the post-Hib vaccine era), GBS (10–15%), *E. coli* (7%), and *L. monocytogenes* (2–3%) [42, 43].

Hearing loss is the most common significant sequela in survivors of childhood ABM [47]. Also, the most important cause of acquired HL is ABM in childhood, as 10–34% of survivors develop HL with different severity [48].

26.4.2.2 Hearing Loss Related to *Streptococcus pneumoniae* Meningitis

Sensorineural HL after *S. pneumoniae* meningitis is more frequent as two- to three-fold of HL resulting from meningitis with other bacterial agents in childhood [49, 50]. The rate of HL due to pneumococcal meningitis may range from 20% to 52% [51]. Adachi et al. [51] reported 155 children with meningitis; 27 (24%) children developed HL, and 13 of them (12%) developed profound HL in 112 children with bacterial growth in CSF culture. Moreover, of 22 patients in whom CSF culture yielded S *pneumoniae* growth, 11 (50%) developed HL, and seven (32%) showed profound HL.

Karpinen et al. [52] reported HL in Angola in 30% of children with *S. pneumoniae* meningitis. Wooley et al. [53] reported that 59 (13.7%) developed HL in 432 children with meningitis, and the HL was bilateral in 44 (74.6%) and unilateral in 15 (25.4%) patients. They also revealed that 15 (23.8%) of the 63 (14.6%) children with *S. pneumoniae* meningitis in the 432 cases had resultant HL. Wellman et al. [54] evaluated HL in 79 children with ABM, 68 (86%) underwent hearing testing, 11 (13.9%) of them had an SNHL, and nine (80%) of these cases with SNHL were associated with *S. pneumoniae* meningitis.

Richardson et al. [35] investigated HL and long-term outcomes of pediatric meningitis between 1993 and 1995 in England. Etiological agents were *N. meningitidis* in 92 (74%) and *S. pneumoniae* in 18 (15%) of a total of 124 children with meningitis. In this study, 83 children underwent audiological tests, and three children (2.4%) had permanent SNHL.

Most previous studies reported HL before implementing Hib and conjugated pneumococcal vaccines. According to the largest cohort after the Hib vaccine, HL after non-Hib meningitis developed in 7% of children [49]. The leading risk factors of HL after bacterial non-Hib meningitis were symptoms for ≥2 days before admission, absence of petechiae, CSF glucose ≤10.8 mg/dL, meningitis due to *S. pneumoniae*, and presence of ataxia [49, 50].

Although the benefit of dexamethasone for the prevention of HL after non-Hib meningitis is controversial, in a recent meta-analysis, it was stated give evidence that the adjunctive administration of dexamethasone has a significant effect on decreasing the possibility of HL and severe neurological sequelae in children with bacterial meningitis but has no significant effect on the follow-up mortality [55, 56].

26.4.2.3 Hearing Loss Related to *Haemophilus influenzae* Type b Meningitis

After developing and using the Hib conjugate vaccine, invasive Hib infections and Hib meningitis have become rare in countries implementing Hib vaccines in routine childhood vaccination schedules [57]. The invasive Hib disease can still be seen in

infants below 1 year of age whose Hib vaccine series has not been completed or administered, such as in several low-income countries [52]. Karppinen et al. [52] compared HL in ABM caused by Hib, *S. pneumoniae,* or *N. meningitidis* among children aged 2 months to 13 years in Angola. The HL caused by Hib meningitis was significantly greater at >40 dB. When children with any HL were divided into two groups, infants (*n* 117) and children ≥1 year of age (*n* 103), a significant difference was found for *S. pneumoniae* and Hib versus other agents. In infants, HL at a threshold >60 dB was caused more by pneumococcal meningitis, whereas Hib was the more common causative agent among older children [52].

A meta-analysis that included patients (*n* 2693) from low- and middle-income countries showed that the median risk for HL after meningitis was 11% for *S. pneumoniae* and 5% for Hib and *N. meningitidis* [48].

26.5 Use of Corticosteroids in Bacterial Meningitis for Preventing Hearing Loss

According to the analysis by Brouwer et al. [58], steroids prevented any HL in 146 (14.6%) of 1001 corticosteroid-treated patients versus 196 (20.4%) of 960 in the control group and severe HL in 57 (7.3%) of 772 corticosteroid-treated patients versus 86 (11.2%) of 752 in the control group [58].

The mechanism of dexamethasone shows that it decreases proinflammatory cytokine production such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), increases the production of anti-inflammatory cytokines, inhibits reactive oxygen species (ROS) production by leukocytes, and decreases leukocyte adherence. Furthermore, dexamethasone decreases intracranial pressure (ICP), brain edema, and CSF pleocytosis with pneumococcal cell wall-induced meningeal inflammation [59–64].

The use of dexamethasone in Hib meningitis has positive evidence for the prevention of post-meningitis HL and other neurological complications. Subgroup analysis yielded no difference in mortality for corticosteroid treatment between low- and high-income countries. For children in high-income countries, corticosteroid treatment seems protective against severe HL and other short-term neurological sequelae [56].

26.6 Conclusion

Several bacterial infections in children can cause HL. Early recognition and treatment of these infections will stop the process leading to HL. In some selected cases, the appropriate class, dose, and duration of prompt antibiotic therapy for the agents causing meningitis and dexamethasone therapy will mostly prevent HL.

The surviving children from ABM should be evaluated for SNHL. If a hearing screening or follow-up reveals abnormal results, they may be consulted for early cochlear implantation before chronic cochlear ossification develops.

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Group B Streptococcal Infections in Children and Hearing Loss

27

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27.1 Introduction

Streptococcus agalactiae, also known as group B streptococcus (GBS), is an important cause of bacterial infection—in neonates and early infancy. In this early period, GBS may cause sepsis, meningitis, pneumonia, and other focal infections [1]. It commonly colonizes the gastrointestinal and genital tracts of pregnant women. Vaginal and cervical colonization is usually asymptomatic; however, maternal colonization is the primary risk factor for GBS infection in neonates and young infants [2]. The clinical disease can present as bacteremia, meningitis, pneumonia, septic arthritis, osteomyelitis, cellulitis, and adenitis. Moderate or severe neurodevelopmental impairment is common among survivors with GBS meningitis; 18% of survivors with an average follow-up of 18 months are affected [3]. Hearing loss may also occur in patients with GBS meningitis. The frequency and complications of meningitis may vary according to the time of infection [1].

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27.2 Etiology

Group B streptococci, gram-positive diplococci, usually create a limited beta hemolysis zone on 5% sheep blood agar. There are ten different types according to the structures of capsular polysaccharides. In the United States of America (USA), the most seen types, which account for approximately 99%, are Ia, Ib, II, III, IV, and V in newborns [1]. Type III causes about 30% of early-onset GBS disease (EOD) and 60% of late-onset GBS disease (LOD).

27.3 Epidemiology

27.3.1 Maternal Colonization

Vaginal, rectal, urethral, and pharyngeal asymptomatic colonization develops within approximately one-third of healthy young females [4]. Vaginal and cervical colonization is usually asymptomatic; however, identifying risk factors is critical to predicting neonatal disease. The main risk factors for vaginal colonization are African American ethnicity, obesity, frequent sexual intercourse, multiple sex partners, male-to-female oral sex, tampon use, and uncommon hand washing [4]. Colonization prevalence is high in women under 20 years [4]. Studies in pregnant women show that colonization in vagina or rectum ratios differs between 18% and 35% [4]. This variable rate depends on the region where the sample was taken, the microbiological method used, and the trimester of pregnancy in which the cultures were obtained. Culture samples taken 5 weeks before term pregnancy are ideal for predicting colonization at birth. Another significant colonization is in the urinary system, which may manifest as asymptomatic bacteriuria, and it causes an increase in the risk of developing EOD in newborns [4–7].

27.3.2 Infant Colonization

The most critical factor for colonization and infection in newborns is the presence of high inoculum of GBS within maternal genitourinary or gastrointestinal tracts of the mother at birth [6]. Although only 1–12% of newborns of non-colonized mothers are colonized, vertical transmission from colonized mothers to their infants averages 50%, reported between 41% and 72% [4, 8, 9]. Ingestion of the GBS by the infant occurs during ascending via the ruptured membranes before birth or while passage through the birth canal. Dense maternal inoculum, 10^5 colony-forming units/mL, in the genital tract significantly increases vertical transmission and colonization to newborns [8, 10]. The most crucial risk factors in developing EOD are premature birth, a history of premature membrane rupture ≥18 h, a history of

intrapartum fever (≥38 °C), intra-amniotic infection, bacteriuria of GBS throughout the last pregnancy, or a history of invasive GBS disease in a previous infant [1]. In some studies, multiple pregnancies have been revealed to increase the GBS disease risk [11]. Maternal intrapartum antibiotic administration generally reduces the vertical transmission of GBS [4, 7].

Rarely, community-acquired or healthcare-associated horizontal transmissions may be seen. Transmission from infants or healthcare personnel with colonization to newborns may develop, but such outbreaks are sporadic [12]. After discharge, neonates and young infants can acquire GBS horizontally from mother or colonized household contacts and develop late-onset bacteremia, meningitis, or other focal infections. Breast milk may be a mode of transmission for LOD, and postpartum mastitis of the mother has been found in most reported cases. However, the role of breast milk in LOD has not yet been established [13].

27.3.3 Incidence of Disease

Worldwide, the incidence of GBS diseases in infants is nearly 0.5 per 1000 live births [14, 15]. Still, the incidence varies from region to region, with the highest incidence in Africa and the lowest incidence in Asian countries [14]. The disease burden is very high all over the world. In the USA in 2015, 205,000 (uncertainty range [UR]: 101,000–327,000) EOD and 114,000 (UR: 440,00–326,000) LOD were diagnosed in newborns. Of whom, approximately 7000 (UR: 0–19,000) had neonatal encephalopathy, and 57,000 (UR: 12,000–104,000) had fatal infection and/or miscarriage [16]. A study conducted in the USA between 1998 and 2007 showed that GBS was the cause of meningitis in 86% of infants under 2 months, and the infection was fatal in 11% of cases [17]. Africa accounted for 54% of estimated cases and 65% of fetal/infant deaths [17].

Intrapartum antibiotic prophylaxis (IAP) for EOD was implemented in 1996 with joint consensus by the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), the American College of Nurse-Midwives (ACNM), the American College of Obstetricians and Gynecologists (ACOG), and other stakeholder organizations [18]. With universal maternal antenatal screening and IAP, the national EOD incidence, GBS in the USA, fell from 1.8 cases per 1000 live births in 1990 to 0.23 in 2015 [19]. Nonetheless, the effect of IAP on the incidence of LOD is unknown. In 2018, the incidence of LOD exceeded that of EOD at 0.28 cases per 1000 live births [1]. Almost 30% of neonates with EOD and up to 55% of newborns with LOD and late-late-onset GBS disease (late-LOD) are premature infants [20–22]. The schema of classification and the transmission of GBS disease vertically in infants after using IAP is shown in Fig. 27.1. Late-late-onset GBS disease constitutes 7–13% of pediatric GBS infections [23, 24].

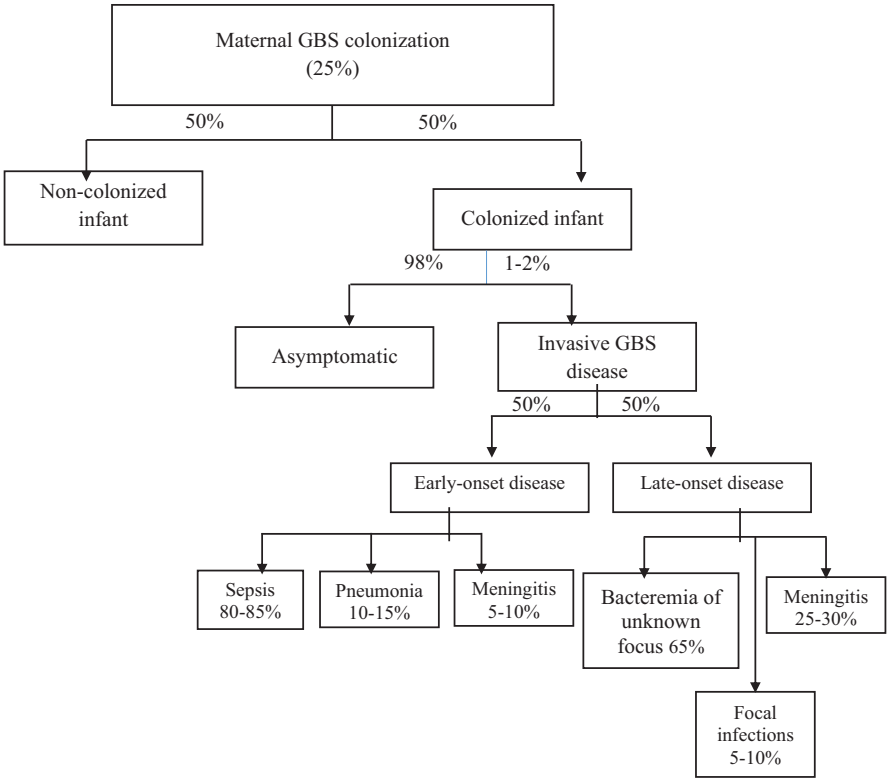

Fig. 27.1 Flow chart of vertical transmission and disease classification of group B streptococcal (GBS) disease in infants after using intrapartum chemoprophylaxis. (Adapted and modified from Refs. [4, 7])

27.4 Terminology

Early-Onset GBS Disease (EOD): Infection is usually seen in the first 24 h following birth but includes infections that develop up to 6 days after delivery [1, 2].

Late-Onset GBS Disease (LOD): The term covers infections between the 7th–89th days. Infection is usually seen until the 4th–5th weeks following birth [1, 2].

Late-Late-Onset (or Very Late-Onset) GBS Disease: Infection occurs in infants over 3 months [1, 2]. It is usually seen in infants born before the 28th gestational week and those with a history of immunodeficiency [23, 25]. Group B streptococcal disease is rare in infants and children over 3 months and lacks sufficient information [26].

27.5 Clinical Manifestations

27.5.1 Clinical Manifestations in Early-Onset Disease

Early-onset GBS infection most commonly manifests as generalized sepsis, pneumonia, or meningitis. In more than 90% of cases, clinical signs appear in the first 24 h after birth. Newborns of mothers who receive IAP are less likely to develop sepsis, need ventilator support, or have proven GBS bacteremia [27]. Early-onset GBS disease presents with sepsis in 80–85% of patients. The clinical signs of sepsis are nonspecific; it can present with irritability, lethargy, respiratory symptoms, hyper- or hypothermia, circulatory disorder, and hypotension. Pneumonia occurs in approximately 10% of patients with EOD, usually manifesting with difficult breathing, hypoxia, and increased respiratory effort [28]. In addition, GBS pneumonia can cause persistent pulmonary hypertension in infants. Meningitis occurs in 7% of patients with EOD [28]. Classic central nervous system findings of meningitis are not generally seen in newborns with EOD, and patients often present with respiratory system findings [29]. Payne et al. [30] determined that birth weight <2500 g, apnea, hypotension, absolute neutrophil count <1500 cells/mm^3, initial pH <7.25, and presence of pleural effusion in chest X-ray on admission are associated with fatal outcomes in EOD.

27.5.2 Clinical Manifestations in Late-Onset Disease

Sixty-five percent of infants with GBS infection present with bacteremia without a focus [28]. Meningitis (25–30%) and focal infections can also be seen [31]. Compared with those with EOD, infants with LOD with meningitis are less likely to be in shock and more likely to have clinically significant seizures [32]. The clinical manifestations of meningitis are often indistinguishable from those in neonatal sepsis. The most common clinical findings are hyper- or hypothermia, irritability or lethargy, and vomiting. Typical clinical findings of meningitis, such as bulging fontanel, nuchal rigidity, and focal neurological findings, are more common in LOD than in EOD. Upper respiratory tract infection findings can be seen in 20–30% of patients with LOD [33]. Focal infections, including arthritis, osteomyelitis, and cellulitis-adenitis syndrome, may occur in infants with LOD [7]. Less common clinical syndromes are urinary tract infections, sometimes concomitant with structural abnormalities, otitis media, necrotizing fasciitis, endocarditis, and other conditions [1, 2, 4, 7].

27.5.3 Clinical Manifestations in Late-Late-Onset Disease

The late-late-onset GBS disease most commonly develops in premature neonates, especially <28 weeks of gestation. Infants generally present as bacteremia without a focus, but rarely focal sites of infection may be seen. A comparison of characteristics of early-, late-, and late-late-onset GBS infections is depicted in Table 27.1.

Table 27.1 Comparison of early, late, and late-late-onset group B streptococcus (GBS) infection characteristics[a]

Disease characteristics	Early-onset GBS disease (EOD)	Late-onset GBS disease (LOD)	Late-late-onset GBS disease
Age at onset	<7 days; mean, 8 h; median, 1 h	7–89 days; mean, 36 days; median, 27 days	≥90 days
Maternal obstetric complications	Common	Preterm delivery	Varies
Frequency of prematurity	Frequent (≈25%)	Frequent (≈50%)	Typical
Clinical findings	Acute respiratory distress, apnea, and hypotension common	Fever, irritability, nonspecific signs, occasionally fulminant	Fever, irritability, nonspecific signs
Clinical diagnosis	– Septicemia (80–85%) – Pneumonia (10–15%) – Meningitis (5–10%)	– Bacteremia without focus (65%) – Meningitis (25–35%) – Soft tissue, bone, joint infection, or pneumonia (5–10%)	– Bacteremia without focus (common) – Bacteremia with a focus (occasional)
Common capsular type	Ia, II, III, V	III (>50%), Ia, V	III, Ia, V
Case fatality rate	5–15%	2–6%	<5%

[a] Adapted and modified from Refs. [4, 7]

Group B streptococcal infections can also affect older infants, children, and pregnant and non-pregnant women. Invasive disease due to GBS in non-pregnant adults presents with skin, soft tissue, and bone infections in 36%, unidentified bacteremia in 30%, urosepsis in 14%, pneumonia in 9%, peritonitis in 7%, septic arthritis in 4%, meningitis in 4%, catheter infection in 3%, and endocarditis in 2% [34].

Data on the frequency of GBS disease in children beyond infancy are limited. In a population-based evaluation of invasive GBS disease in Atlanta, 219 (52%) of 424 patients were children, and 205 (48%) patients were adults [22]. The study reported that 46% of all patients were newborns, 4% were infants aged 1–12 months, and 2% were children aged 1–17 years. In another study, 143 pediatric patients with a positive GBS culture from the normally sterile body fluid were identified, and medical records of 18 (13%) patients >3 months old with their first GBS infection were reviewed [23]. The age range was 15 weeks to 18 years, with the median age being 13 months. Five infants had premature birth, and two were infected with the human immunodeficiency virus (HIV). The most common (50%) clinical manifestation was bacteremia without a focus, seen in nine patients. Other clinical manifestations were sepsis and bullous desquamation in one infant with HIV infection, meningitis in two adolescents with ventriculoperitoneal shunts (VPS), septic arthritis, endocarditis, central venous catheter, and ventriculostomy infections. Apart from the diseases described above, GBS can present other infections in infants and children in very different localizations, as depicted in Table 27.2 [4, 7, 35–37].

Table 27.2 Unusual clinical features of infants and children with group B streptococcal infection[a]

Localization and type of infection		
Central nervous system	**Respiratory tract**	**Genitourinary tract**
Abscess	Epiglottitis	Renal abscess
Cerebritis	Supraglottitis	Urinary tract infection
Chronic meningitis	Tracheitis	Epididymo-orchitis[b]
Eosinophilic meningitis	Pleural empyema	**Skin and soft tissue infection**
Subdural empyema	**Cardiovascular**	Breast abscess
Ventriculitis	Endocarditis	Bursitis
Diabetes insipidus	Myocarditis	Cellulitis/adenitis
White matter injury[c]	Pericarditis	Dactylitis
Transverse myelitis[d]	**Abdomen**	Fasciitis
Eye	Adrenal abscess	Impetigo neonatorum
Conjunctivitis	Delayed-onset diaphragmatic hernia	Purpura fulminans
Endophthalmitis	Gallbladder distention	Omphalitis
Ear and sinus	Peritonitis	Rhabdomyolysis
Ethmoiditis		Scalp abscess
Otitis media/mastoiditis		

[a] Adapted and modified from Refs. [4, 7]
[b] Ref. [37]
[c] Ref. [35]
[d] Ref. [36]

27.6 Laboratory Investigation and Diagnosis

The definitive GBS infection diagnosis requires a GBS culture obtained from a normally sterile region, including blood, CSF, pleural fluid, bone aspirate, joint fluid, or soft tissue. Detection of GBS in the skin, umbilicus, or mucous membranes does not always support the actual infection, so these results should be evaluated with caution. Blood culture is recommended in infants with suspected GBS disease. A complete blood count (CBC) is beneficial in suspected EOD or LOD, mainly when used with other sepsis biomarkers. Leukopenia, neutropenia, or a high proportion of immature-to-total neutrophils may be seen; however, their sensitivities are insufficient. In EOD, the test's sensitivity is increased when the CBC is analyzed 6–12 h after birth [38].

Lumbar puncture (LP) should be performed before antibiotic administration if there is strong clinical suspicion of infection. It is challenging to distinguish meningitis accompanying early neonatal sepsis from bacteremia without a focus clinically; also, meningitis is detected in only 10–38% of patients without bacteremia [39]. Therefore, an LP should be performed regardless of whether there is evidence of meningeal infection if there is clinical suspicion of disease. Even in infants with focal infection signs, concomitant meningitis can be detected; GBS was isolated in the CSF in 24% of patients followed up for cellulitis and/or adenitis [40]. Cell count,

protein and glucose levels, Gram staining, and culture tests in the CSF should be performed.

In the study of Levent et al. [41], three of 53 patients with GBS meningitis died, and 11 were followed up with severe neurologic disorders such as resistant seizures and hypertonicity. These 14 patients who died or had neurological complications at discharge were more likely to present with seizures during the admission hours, require pressor support, have a coma or semicoma, and have an initial CSF glucose <20 mg/dL, or protein ≥300 mg/dL than were the 39 infants with normal neurologic examinations.

Lumbar puncture is usually unnecessary in evaluating EOD in newborns appearing well [2]. There is no growth in CSF culture for various reasons in some patients, but the yield of diagnosis can be increased if polymerase chain reaction (PCR) is used. The diagnosis rate may increase with new molecular methods, but more studies are needed. A chest radiograph is recommended for newborns with respiratory symptoms and urine culture with a urinary catheter or suprapubic aspiration for infants aged over 6 days [2]. Imaging methods can be used because surgical drainage may be required in infants with bone and joint infections. Radiographic examination of the kidneys and urinary system may be needed in those with urinary tract infections.

27.7 Treatment

27.7.1 Empirical and Specific Treatment

Empirical treatment for possible bacterial agents should be started in newborns and infants with suspicion of infection. The combination of ampicillin plus gentamicin used in neonatal infections is effective in GBS infection. However, when GBS is demonstrated by culture growth, treatment with penicillin G or ampicillin alone is sufficient [4, 7]. Penicillin G is effective in GBS disease and has less effect in altering the microbiome than ampicillin, which can be used as an alternative for bloodstream infection.

Regardless of gestational age, high-dose ampicillin (300 mg/kg/day) with gentamicin should be given to newborns with suspected meningitis and clinical conditions when LP is unsuitable [4]. Although ampicillin plus cefotaxime or ceftriaxone combination is generally preferred in LOD, if vancomycin is preferred in empirical therapy and GBS meningitis cannot be excluded, penicillin or ampicillin should be added to treatment because vancomycin is inhibitory rather than bactericidal in vitro and CSF concentrations may not exceed the minimal inhibitory concentration (MIC) if a high inoculum of GBS is present [32].

Initial empirical therapy, definitive therapy, and duration of treatment for GBS infections are shown in Table 27.3. Ten days of treatment is sufficient in GBS bacteremia, and the course of antibiotic therapy is 14 days in uncomplicated meningitis. If meningitis due to GBS has been diagnosed, it is recommended to perform a

Table 27.3 Initial empirical and definitive therapy and duration of treatment for group B streptococcus (GBS) infection[a]

Empirical treatment[b]	Antibiotics	Duration
Septicemia		
Early onset	Ampicillin (150 mg/kg/day) plus gentamicin	10 days
Late onset (term infant readmitted)	Ampicillin (300 mg/kg/day) plus gentamicin or cefotaxime until meningitis is excluded; then ampicillin	10 days
Late onset (inpatient)	Vancomycin plus gentamicin or amikacin	10–14 days
Meningitis		
Early onset	Ampicillin (300 mg/kg/day) plus gentamicin plus cefotaxime	Until cerebrospinal fluid sterility and penicillin susceptibility documented
Late onset	Ampicillin (300 mg/kg/day) plus gentamicin or amikacin plus cefotaxime	Until cerebrospinal fluid sterility and penicillin susceptibility documented
Specific treatment		
Bloodstream infection[c]	Ampicillin (150 mg/kg/day) or penicillin G (200,000 U/kg/day)	10 days
Meningitis	Penicillin G (400,000–500,000 U/kg/day)	14–21 days
Arthritis	Penicillin G (200,000–300,000 U/kg/day)	2–3 weeks
Osteomyelitis	Penicillin G (200,000–300,000 U/kg/day)	3–4 weeks
Endocarditis	Penicillin G (200,000–300,000 U/kg/day)	4 weeks

[a] Adapted and modified from Ref. [7]
[b] Empiric therapy is always followed by definitive treatment
[c] Assumes that lumbar puncture to exclude meningitis has been performed and that cerebrospinal fluid has no detectable abnormalities

follow-up LP to show that the CSF has become sterile after 24–48 h. Babies with a positive culture should be evaluated for very high bacterial inoculum, severe infection such as ventriculitis accompanied by an obstruction, cerebritis, subdural empyema, septic thrombophlebitis, and an insufficient dose of antibiotics. When polymorphonuclear leukocytes in CSF are over 30% of the total cells, and the protein level is >200 mg/dL, a new evaluation may be required; the duration of the antibiotics should be extended [32]. If complications develop, the course of treatment can be extended [1].

Contrast-enhanced neuroimaging should be performed before treatment discontinuation in patients with delayed CSF sterilization, prolonged signs of infection, fever duration >5 days, cerebritis, abscess, subdural empyema, or venous thrombosis [4].

Generally, analyzing the MIC and minimal bactericidal concentration (MBC) of penicillin for GBS isolates is unnecessary. Insufficient clinical or bacteriologic improvement despite penicillin or ampicillin usage, unexplained relapse or recurrent infection, and the disease developed in a congenital or acquired immunodeficiency infant, necessitates studying MIC and MBC [7].

27.7.2 Supportive Treatment

Although clinical practices usually focus on the specific treatment, prompt and effective supportive treatment is also very important. Because pneumonia can be present, especially in EOD, early respiratory failure findings should be reviewed, and necessary respiratory support should be started. In the presence of constant metabolic acidosis or delayed capillary refill time, the initiation of shock therapy should be considered. Patients with respiratory and circulatory failure signs or meningitis should be admitted to the neonatal intensive care unit. Severe anemia, acidosis, and hypoxemia should be corrected, and anticonvulsant therapy should be initiated promptly for concurrent seizures. Lastly, in persistent pulmonary hypertension or failure of conventional respiratory therapy, extracorporeal membrane oxygenation (ECMO) might be regarded [4].

27.7.3 Adjunctive Treatment

Adjunctive therapy should be considered in infants with life-threatening infections. These treatment approaches were not proven and not in the guidelines but can be used as a supplement on a case-by-case basis. Several adjunctive therapies reported in the literature are intravenous immunoglobulin (IVIG), monoclonal antibodies to GBS polysaccharide antigen, growth factors including granulocyte colony-stimulating factor (G-CSF), and granulocyte-monocyte colony-stimulating factor (GM-CSF) for neutropenia and leukocyte transfusion [4, 7].

27.8 Recurrent Infection

Recurrent GBS infection might develop in 0.5–4.5% of infected newborns [42]. The pathogenesis of the recurrent infections remains unclear. In a population-based study, 14 (24%) of 84 infants with recurrent invasive GBS disease were twins or triplets, in 64 (76%) bacteremia, in 16 (19%) meningitis and bacteremia, in three (4%) meningitis, in six (7%) cellulitis (five had a positive blood culture) were determined [43]. Among the infants with available information, 42 of 74 (57%) were preterm, 30 of 50 (60%) were boys, and 28 of 42 (67%) were delivered vaginally. Recurrence of GBS disease occurred at a median age of 40 (8–141) days. The third episode of GBS disease was seen in 11 (13%) infants. In this study, multiple births were an important risk factor for recurrent infection [43].

Recurrent GBS disease is attributable to subclinical persistent mucosal colonization associated with several factors, such as deficient host immunity, inadequate therapy dose or period, microbial hypervirulence, or resistance [44]. Neonatal GBS infection associated with high relapses can also be attributed to repeated exposition to exogenous causes, such as contaminated breast milk [44, 45]. Recommendations, when faced with recurrent infection, are as follows: validate the isolate's penicillin sensitivity via MIC testing, evaluate serum immunoglobulins and HIV status, administer empiric treatment 1 week more than the usual regimen, and regard oral

rifampin treatment subsequently to completing the parenteral therapy to eliminate mucosal colonization [7]; however, the last is not recommended for routine use [46]. Nevertheless, the recommendation to continue treatment 1 week more than the ordinary course for recurrent GBS disease has little data support [4].

27.9 Outcome

The outcome in newborns, infants, and children varies according to the infant's gestational age, the onset time (EOD, LOD, late-LOD), the localization, and the severity of the infection. Mortality is 2–3% in EOD and 1–3% in LOD. Mortality is higher in preterm infants: 20–30% in EOD and 5–8% in LOD [4, 28, 32]. A study examining 15,429 infants younger than 90 days in England reported that GBS-attributable mortality per 1000 live births decreased from 0.044 in 2001 to 0.014 in 2017 [47]. Factors affecting mortality in EOD consist of preterm birth, low birth weight (<2500 g), hypotension, shock, apnea, seizures, neutropenia, and thrombocytopenia [41, 48, 49].

In 20–30% of patients followed up for early- or late-onset meningitis investigated for long-term sequelae, permanent severe neurologic impairment such as cerebral palsy, motor deficits, bilateral sensorineural hearing loss (SNHL), cortical blindness, or significantly delayed development and learning disorders were diagnosed [1, 2, 4, 7]. Approximately one-quarter of patients develop hydrocephalus requiring VPS, seizure controllable with medication, or mild delayed learning and development. Although the incidence of GBS infection is low in Europe, the incidences of mortality and cerebral palsy were high in a cohort study from Norway [50]. The study concluded that preterm birth and low Apgar scores moderately increased the development of cerebral palsy. In another study comparing 2258 patients with invasive GBS disease and 22,462 controls without a history of GBS infection in Denmark and the Netherlands, there was an association between GBS meningitis and increased mortality at 5 years of age detected [51]. In addition, any invasive GBS disease was correlated to an increase in the risk of neurodevelopmental impairment at the age of 10 years.

GBS infections also create a serious disease and patient burden. The invasive GBS disease was correlated to more common outpatient clinic visits and admissions to the hospital in children aged 5 years or younger [51]. The hearing loss (HL) incidence throughout the GBS infection is unknown, but all GBS meningitis patients should have diagnostic auditory brainstem response (ABR) testing.

27.10 Group B Streptococcal Infections in Children and Hearing Loss

Hearing loss within the first years of life, generally preventable, may result in delays in speech, language, and cognitive development [52–54]. Therefore, early identification of whether a temporary or permanent HL is vital in the child's communication and development [55–58].

In GBS invasive infection, an inflammatory response may occur in the host during bacteria's ongoing replication and digestion, damaging some tissues [59]. Immune complexes circulate long in newborns with GBS disease and cause end-organ damage [60]. In addition, immune complexes containing GBS components cause the release of cytokines such as leukotriene B4 and IL-6. The IL-6 release from monocytes is induced by group B and type III capsular polysaccharides, and group B antigen stimulates TNF-α release [61]. Like other gram-positive agents, GBS cell walls have peptidoglycan and lipoteichoic acid. Various proinflammatory cytokines, including TNF-α, IL-1, IL-6, and G-CSF, are elicited by gram-positive agents' peptidoglycan [62, 63]. Moreover, lipoteichoic acid stimulates IL-1β, IL-6, and TNF-α releases [64, 65].

The cytokine responses, especially proinflammatory cytokines, are important in morbidities such as HL caused by bacterial meningitis, otitis media, and labyrinthitis ossification [66]. Tumor necrosing factor-alpha is essential in HL's pathogenesis. Aminpour et al. [67] revealed that TNF-α blockade via anti-TNF-α antibody caused a remarkable improvement of postmeningitic HL and cochlear damage induced by *Streptococcus pneumoniae* meningitis. In contrast, the exposition of non-infected animals to the intrathecal flow of TNF-α caused HL, like in bacterial meningitis. The mechanisms of HL in pneumococci have been demonstrated, and it can be thought that similar mechanisms play a role in GBS infections.

The frequency of HL and the mechanism behind GBS meningitis are still unknown; more studies are needed to determine efficient treatments of GBS meningitis-related HL processes, including regulating cytokines and antioxidants and promoting cochlear implants in patients with permanent, profound HL.

27.11 Prevention

As with many infectious diseases, it is critical to prevent GBS infections, given the serious mortality and morbidity in early infancy. There are several different preventive approaches to reduce GBS infection, mainly maternal prophylaxis to reduce transmission, infant prophylaxis to minimalize colonization, and immunoprophylaxis to enhance protection against the disease. However, infant prophylaxis is not recommended because it is not yet effective, according to studies [1, 68].

27.11.1 Intrapartum Antibiotic Prophylaxis (IAP)

Following the reports of Boyer and Gotoff [69], stating that the incidence of GBS-induced neonatal sepsis decreased significantly with intrapartum intravenous (IV) ampicillin administration to females with preterm labor or preterm premature rupture of membranes, obstetric and pediatric professional organizations have initiated studies to find the most effective approach in terms of both clinical and cost-effectiveness. Intrapartum antibiotic prophylaxis for EOD was implemented in 1996 with a consensus recommended by the AAFP, the AAP, the ACNM, the ACOG,

and other stakeholder organizations [18]. This consensus includes risk- or culture-based approaches. The risk-based approach recommends giving IAP in one of the following risk factors; premature labor <37 weeks, GBS bacteriuria, body temperature ≥100.4 °F (38 °C) at birth, prolonged premature rupture of membranes over 18 h, or a history of GBS infection in a previous infant. In the culture-based approach, IAP is recommended for all females having GBS isolated in vaginal and rectal cultures at 35–37th gestational weeks, disregarding risk factors. With these approaches, there has been a reduction of approximately 70% in EOD incidence [24, 68].

In a population-based study conducted in 2002 comparing these two approaches, the culture-based approach was 50% more efficient in preventing EOD [70]. It has also been shown that the mothers of 62% of infants who develop EOD have no identified risk factors. Therefore, in 2002, the Centers for Disease Control and Prevention (CDC) recommended universal vaginal and rectal culture screening for all women between 35 and 37 weeks of pregnancy and recommended giving intrapartum prophylaxis to GBS carriers [21]. Table 27.4 shows the indications and the non-indication conditions of IAP use in EOD. A beta-lactam antibiotic (penicillin is preferred) is effective in prophylaxis against GBS-induced EOD when given four doses or longer before birth [71]. The risk-based approach should be chosen only in patients whose culture results are unknown at birth [7].

Table 27.4 Indications and non-indication conditions for maternal intrapartum prophylaxis to prevent early-onset group B streptococcal (GBS) infection[a]

Intrapartum GBS prophylaxis indicated	Intrapartum GBS prophylaxis not indicated
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy
GBS bacteriuria during any trimester of current pregnancy[b]	GBS bacteriuria during previous pregnancy
Positive GBS vaginal–rectal screening culture within the preceding 5 weeks[b]	Negative vaginal–rectal screening culture, regardless of intrapartum risk factors
Unknown GBS status at the onset of labor and any of the following: • Delivery at <37 weeks' gestation • Prolonged rupture of membranes for ≥18 h • Intrapartum temperature ≥100.4 °F (38 °C)[c] • Intrapartum nucleic acid amplification test (NAAT) positive for GBS[d]	Cesarean delivery is performed before the onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age

[a] Adapted and modified from Ref. [68]

[b] Intrapartum chemoprophylaxis is not indicated in this circumstance if a cesarean delivery is performed before the onset of labor on a woman with intact membranes

[c] If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis

[d] GBS nucleic acid amplification tests (NAATs) are optional and may not be available in all settings. If intrapartum NAAT is negative for GBS, but any other above intrapartum risk factor is present, then intrapartum GBS prophylaxis is indicated

The CDC renewed its guidelines to include approaches and algorithms in 2010 [68]. These new recommendations included descriptive laboratory methods for demonstrating GBS colonization in pregnancy, screening and IAP administration algorithms for females with preterm labor and premature rupture of membranes, prophylaxis approaches in penicillin allergy, and a revised algorithm for neonatal care. Empirical management of a newborn for secondary prevention of EOD is shown in Fig. 27.2.

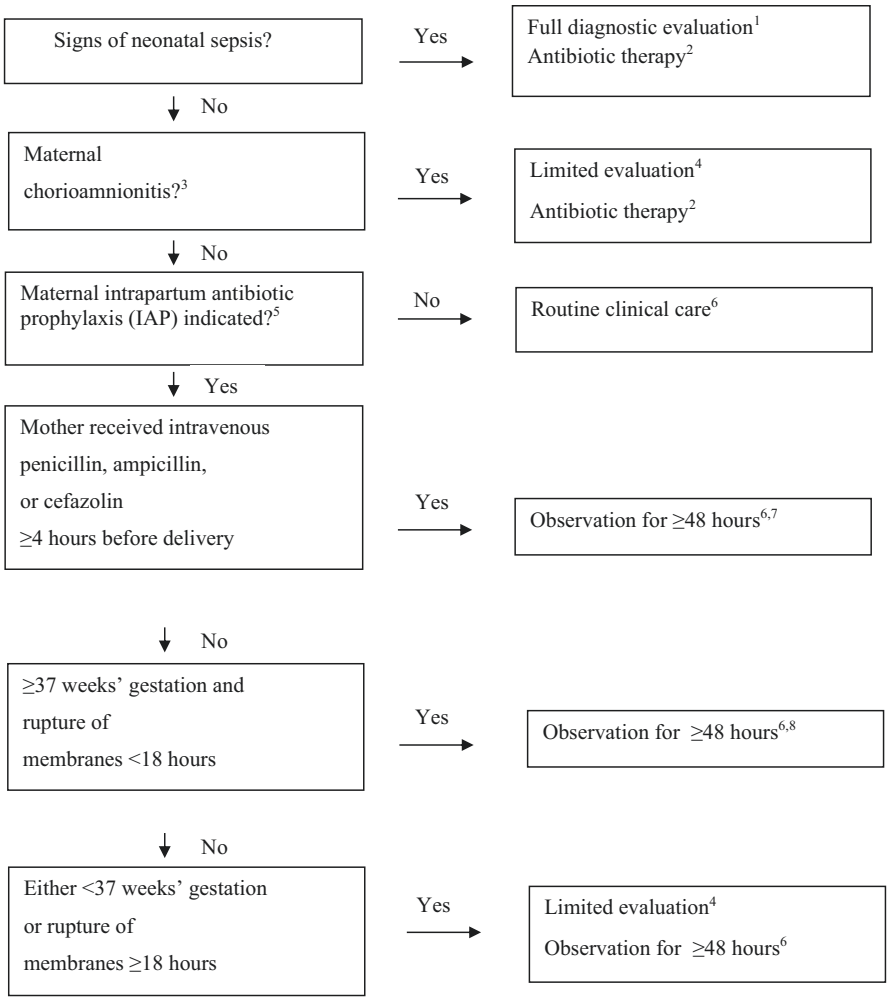

Fig. 27.2 Empirical management of a newborn for secondary prevention of early-onset group B streptococcal infection. (Adapted and modified from Ref. [68])

In maternal chemoprophylaxis, IV penicillin G (initial dose, 5 million units; following doses, 2.5–3 million units every 4 h until delivery) is preferred [68, 70]. As an alternative to penicillin, ampicillin (initial dose, 2 g; following doses, 1 g every 4 h) can be administered for prophylaxis. Clindamycin and erythromycin resistance rates should be considered when choosing prophylaxis in women with penicillin allergy [72, 73]. If the anaphylaxis risk is low, cefazolin (initial dose, 2 g; following doses, 1 g every 8 h) may also be used for prophylaxis. Clindamycin (900 mg every 8 h) may be used if the organism is susceptible based on susceptibility testing. Erythromycin is not an acceptable alternative [68]. When there is no susceptibility test, the results are unknown, or if there is clindamycin resistance, vancomycin (1 g every 12 h) may be administered as an alternative therapy. However, the vancomycin efficiency is not known.

27.11.2 Immunoprophylaxis

Although IAP is an effective approach, about 30% of women use antibiotics; there is still a possibility of antimicrobial resistance development, the inability to prevent late-onset GBS infections, and the inability to avoid miscarriage and fetal death caused by GBS disease. Vaccine studies to prevent GBS infection and disease are ongoing. Maternal immunization can improve the drawbacks of IAP and decrease the invasive GBS infection global burden in pregnant women and newborns. Monovalent, divalent, and trivalent GBS vaccines against serotypes Ia, Ib, II, III, and V were previously studied in non-pregnant and pregnant women. These vaccines have been proven safe and cause increased GBS antibodies after vaccination in newborns [74, 75]. A recent phase 1/2 study about the safety and immunogenicity of a novel hexavalent group B streptococcus conjugate vaccine (GBS6), including serotypes Ia, Ib, II, III, IV, and VI, determined that GBS6 was well tolerated and caused robust immune responses in women during 6 months [76]. Hopefully, with new studies and a valid and effective vaccine, GBS infections will decrease, and infants can be protected from GBS disease soon.

27.12 Conclusion

The most critical risk in neonatal GBS disease is morbidity, including cerebral palsy, intellectual disorder, seizures, visual disturbances, and HL, which are long term. Neurologic sequelae are more common, especially in infants with GBS meningitis. There are insufficient data on the frequency of HL in GBS meningitis. However, HL is one of the most critical sequelae after bacterial meningitis. Prompt diagnosis and treatment are crucial, and infants with GBS disease or meningitis should have a rapid and complete hearing assessment. These infants need regular follow-ups for HL and, once identified, referred for early cochlear implantation.

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Pneumococcal Meningitis in Children and Hearing Loss

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28.1 Introduction

Streptococcus pneumoniae, first isolated in 1881 by two scientists separately, remains a significant pathogen in public health today. Louis Pasteur identified the bacterium in France and named it "*microbe septicemique de la salive.*" George

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Miller Stenberg also identified the agent in the blood of a rabbit injected with human saliva subcutaneously termed "*Micrococcus pasteri*" in the United States of America (USA) [1–3]. By the end of the 1880s, it was established that this bacterium was one of the leading causes of pneumonia, meningitis, arthritis, otitis, and endocarditis [4]. By the 1940s, 80 distinct serotypes of pneumococci were detected, and by 2020, the serotypes would be 100 [5].

28.2 Etiology

28.2.1 Microbiology

Streptococcus pneumoniae is a facultative anaerobic bacteria with lancet-shaped gram-positive staining. It requires a medium containing 5% carbon dioxide and a source of catalase enzyme, such as blood, for growing. Pneumococci lack catalase and oxidase enzymes. One characteristic that distinguishes pneumococcus is its sensitivity to optochin and bile salts. In the stationary phase of growth, it is capable of deoxyribonucleic acid (DNA) exchange and autolysis. On solid media, it appears as colorless colonies associated with alpha-hemolysis. The pneumococci are frequently found in pairs and can also be observed singly or as short-chain bacteria under light microscopy. As of 2020, there are 100 serotypes defined based on the capsule structure formed by complex polysaccharides [5]. Although various methods for determining serotypes exist, serotyping is classically based on the Quellung capsule swelling reaction, not limited to pneumococci, and can be used to identify any bacteria with a polysaccharide capsule structure [6]. Molecular methods for serotyping are now used at the USA Centers for Disease Control and Prevention (CDC) and some other leading reference laboratories worldwide.

The entire genetic material of *S. pneumoniae* serotype 4 was sequenced in 1977. Genetic sequencing was then performed on all serotypes, and a wide range of genetic diversity among serotypes was discovered [7]. However, some pneumococcal species cannot be typed based on their capsular structures [5]. The prevalence of non-serotypeable pneumococcal species, which account for 15–18% of all pneumococci, gradually increased, particularly with the widespread use of pneumococcal conjugate vaccines (PCVs) [8].

28.2.2 Virulence

The pneumococcal capsule structure has been an extensive research focus for a long time. The capsule, composed of complex carbohydrates, is a critical structure that influences virulence, the host's defense response, and serotyping. The virulence of the pneumococci is directly proportional to the capsule thickness. The host, producing antibodies against capsule polysaccharides, develops a serotype-specific defense. The capsule's function begins with the entry of pneumococcus into the host's body. Nonencapsulated pneumococci can colonize the nasal and

nasopharyngeal mucosa with significantly less intensity and shorter duration than encapsulated strains. The capsule, generally negatively charged, prevents the bacteria from being retained in the mucosa secretions, making it easier for the bacteria to reach the epithelial surface cells [9]. As the primary effect on virulence, the capsule prevents complement system elements and immunoglobulins (Igs) from adhering to the bacterial surface and reduces the impact of classical and alternative complement systems in defense. However, not the capsules of all serotypes effectively inhibit binding to the Igs of the host [10].

Again, by preventing neutrophils from recognizing Toll-like receptor (TLR) ligands on the bacterial surface, the capsule impairs the antimicrobial defense system mediated by myeloid differentiation factor 88 (MyD88) [11]. Although the capsular structure is thought to be the primary determinant of virulence, the later identified nonencapsulated pneumococci and the novel features discovered through the determination of their genetic sequences have shifted attention to the other characteristics contributing to virulence, neuraminidases, pneumolysin, hyaluronidase, choline-binding surface proteins, IgA1 protease, phase variation characteristics, and antibiotic tolerance [12, 13].

28.3 Epidemiology and Transmission

Pneumococci, spread via respiratory droplets, are human pathogens frequently found in the respiratory epithelium. In healthy individuals, pneumococcus is isolated from the nasopharynx at a rate ranging from 5% to 90%. Colonization begins early in life, peaks around 3 years, and gradually declines throughout adulthood. Pneumococcal colonization occurs in the nasopharynx of 90% of children aged 6 months to 5 years at any time [12, 14]. Asymptomatic carriage occurs at a rate of 5–10% in adults and 20–60% in school-aged children [5]. Because asymptomatic carriage does not stimulate the host's defense system or cause an inflammatory response, an individual can be recolonized with the same serotype. Asymptomatic carriage is more prevalent in nursing home residents, particularly during winter. The carriage may last for a period of up to 6 months. Transmissibility persists throughout the pneumococcal presence in the respiratory epithelium. Effective antibiotic treatment resolves the transmissibility within 24 h [5, 14, 15].

Streptococcus pneumoniae is one of the most prevalent agents of mucosal infectious diseases such as otitis media and sinusitis, not associated with bacteremia. It is also one of the most prevalent agents of invasive infectious diseases associated with bacteremia, such as pneumonia and meningitis [16]. According to data from the CDC, approximately 150,000 people with pneumococcal pneumonia are hospitalized in the USA yearly. About 1,190,000 people worldwide are estimated to die each year from pneumococcus-related lower respiratory tract infections. Considering all age groups, the morbidity and mortality rates of invasive pneumococcal disease (IPD) were 9.2 and 0.98 per 100,000 individuals in 2019, respectively. Children and adolescents accounted for 7.1% of all cases, and children under 5 years accounted for 65.9% of all patients under the age of 18 [17]. Given that these figures reflect

only those instances in which the etiologic agents can be demonstrated, the actual number of cases is likely to be much higher.

Despite widespread vaccination, IPDs continue to concern pediatric health. By the end of 2021, the pneumococcal vaccines were introduced in 154 member states of the World Health Organization (WHO) [18]. Although the causes of pneumonia vary by age, vaccination status, and the presence of concomitant diseases, *S. pneumoniae* is the most common pathogen associated with bacterial lower respiratory tract infections. Pneumococci, meningococci, *Haemophilus influenzae* type b (Hib), and *Streptococcus agalactiae* (group B streptococcus, GBS) are the most common causes of bacterial meningitis, fatal in one out of every 10 cases and causes permanent damage in one out of every 5 cases [16, 19]. According to WHO data, pneumonia is the leading cause of infection-related death in children [20]. In 2019, 740,180 children under 5 years died from lower respiratory tract infections [20]. Another reason pneumococcal infections are a serious problem is that antibiotic resistance is increasing. *Streptococcus pneumoniae* is one of the top 12 antibiotic-resistant pathogens listed by the WHO in 2017 [21].

Invasive pneumococcal diseases are more prevalent in children aged 5 years and under and have a higher mortality rate. Similarly, individuals over the age of 65 years are at risk. Compared to their peers, nursery school children have twice the rate of IPDs [22]. The male gender is another risk factor. Also, IPDs are more prevalent during the winter and following influenza infection [23]. Children with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), chronic kidney failure and nephrotic syndrome, chronic liver disease, malignancy, leukemia, lymphoma, and diseases requiring immunosuppressive drug therapy, such as Hodgkin's disease, immunosuppressive diseases requiring stem cell or solid organ transplantation, or congenital immunodeficiency, are at risk of developing IPD. The risk is increased in individuals with congenital immune system deficiencies, particularly B- and T-cell deficiencies, C1–4 complement deficiencies, and disorders of phagocytosis other than chronic granulomatous disease [12, 15].

Invasive pneumococcal diseases are more likely to occur in patients with sickle cell anemia and other hemoglobinopathies resulting in the spleen's functional or anatomical absence [14]. Children with a normally functioning immune system but have cyanotic heart disease or heart failure, chronic lung disease, asthma that requires long-term high-dose steroid therapy, diabetes, cerebrospinal fluid (CSF) leakage, or cochlear implants are also at an increased risk of developing IPDs. Older implants with cochlear electrodes pose a greater risk of IPD [12, 15]. In some ethnic groups, such as Alaska natives and native American communities, IPDs were more prevalent, but these racial disparities vanished after pneumococcal vaccination [15].

28.4 Pathogenesis

Colonization is the adhesion and proliferation of bacteria to the nasopharyngeal epithelium without causing inflammation or disease. While colonization does not always result in disease, it is a necessary precursor to developing IPD. Additionally,

colonization is the source of human-to-human transmission [24]. Pneumococci adhere to the nasopharyngeal epithelium via pili, fibrillar structures, and attachment proteins. Pneumococcus attaches to tissues via various structures; sialic acid in the nasopharynx; and the disaccharide *N*-acetylgalactosamine b1–4 galactose in the lower respiratory tract epithelium function as receptors. After attachment, if intracellular signaling pathways are activated, bacteria are taken into the cell, and the inflammatory response is triggered. Cell invasion is also influenced by pneumolysin, a cellular toxin.

28.5 Pneumococcal Vaccines

Certain serotypes are responsible for most IPDs, and current vaccines have been designed to protect against these serotypes. The pneumococcal vaccines currently in use are summarized in Table 28.1 [25, 26].

In the late 1940s, the hexavalent, in the 1970s, the 14-valent, and in the early 1980s, the 23-valent pneumococcal polysaccharide vaccines (PPVs) were introduced [25]. Polysaccharide capsule vaccines induce IgM, IgG2, and very low levels of IgG1 antibody production. The pneumococcal polysaccharide vaccine is also expected to be effective against bacterial colonization via the production of IgA by stimulated B lymphocytes stored in the mucosa [13]. However, the response induced by the polysaccharide antigens is transient and requires repeated doses because of the inability to stimulate the T-cell immune response. Also, PPV does not evoke an amnestic response.

So, polysaccharide vaccines cannot provide an adequate protective response in children younger than 2 years, as their immune systems are not mature enough, or in the elderly, as their immune response weakens with age. The pneumococcal polysaccharide vaccine's inability to elicit an adequate immune response in the most at-risk age groups for IPD, provide herd immunity, and provide sufficient protection against non-invasive infections such as otitis and conjunctivitis limits its use. These issues underscore the importance of developing PCVs.

In 2000, the first pneumococcal conjugate vaccine (PCV-7) was approved in the USA following studies demonstrating greatly improved immunogenicity in children less than 2 years of age and efficacy for preventing IPD due to the seven serotypes contained in PCV-7. In 2010, the 13-valent PCV (PCV-13) was approved in the USA. Some countries in Europe have begun using the 10-valent PCV (PVC-10). Many countries use PCV-13, some because it is part of the Global Alliance for Vaccines and Immunisation (GAVI) initiative, an international organization created in 2000 to improve access to new and underused vaccines for children living in the world's poorest countries. Finally, in 2021, 15-valent and 20-valent PCVs (PCV-15 and PCV-20) were licensed by the Food and Drug Administration (FDA) for adults aged ≥18 years but not for children [25, 27]. Recently, PCV-15 has been licensed for use in infants starting at 2 months of age in the USA, and PCV-20 will probably be licensed for use in infants starting at 2 months of age in 2023.

Table 28.1 Commonly used pneumococcal vaccines and their characteristics[a]

Type	Unconjugated capsular polysaccharide vaccines (pneumococcal polysaccharide vaccines, PPVs)	Conjugated capsular polysaccharide vaccines (pneumococcal conjugate vaccines, PCVs)		
	(PPV-23)	PCV-7	PCV-10	PCV-13[b]
Pneumococcal polysaccharides	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9F, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F	4, 6B, 9V, 14, 18C, 19F, 23F	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	1, 3, 4, 5, 6A, 6B, 7F, 9B, 14, 18C, 19A, 19F, 23F
Carrier protein		CRM197	Conjugated to protein D from non-typeable *Haemophilus influenzae* except 18C (tetanus toxoid) and 23F (diphtheria toxoid)	CRM197
Age of use	≥2 years of age	>6 weeks of age		
Mechanism	B-cell-dependent immune response	T-cell-dependent immune response—memory T-cell activation		
	It is recommended for high-risk patients with pneumococcal diseases.	Included in several national immunization programs		
Vaccination schedules		2+1 First 2 doses in the first year of life, then a booster dose in the second year of life 3+1 First 3 doses in the first year of life, then a booster dose in the second year of life		

PCV-20 (adds 22F, 33F, 8, 10A, 11A, 12F, 15B to PCV-13) is recommended for adults ≥65 years old and those 19–64 years old with certain underlying conditions in the USA
In 2023, PCV-20 is expected to be approved by the FDA and then recommended by the CDC ACIP for routine administration to infants starting at 2 months of age

[a] Adapted and modified from Refs. [25, 26]

[b] PCV-15 (adds 22F and 33F to PCV-13) is FDA-approved and is an option for administration to infants starting at 2 months of age and children

The most effective strategy for eradicating meningitis as a public health problem, one of the WHO's 2030 targets, is increasing vaccine coverage. The global population, the low coverage of the vaccines worldwide, the fact that the vaccines cover only a small subset of serotypes, and the serotype change decreased the expected benefit from the vaccines are the issues faced at the current stage of pneumococcal vaccine development.

28.6 Pneumococcal Meningitis in Children

Meningitis is caused by inflammation of the membranes that surround the brain and spinal cord. Typically, the causative agent is a virus or bacteria. Meningitis is a life-threatening medical emergency with a high rate of mortality and morbidity that should be recognized and treated promptly.

28.6.1 Vaccination and Changing Epidemiology

One of the most significant reasons for the global change in the epidemiology of bacterial meningitis over the last 25 years is the introduction of conjugate vaccines into childhood immunization practices. The etiology of bacterial meningitis is dynamic and has changed over time in response to the development of vaccines against Hib, and after 2000 with the widespread use of 7-valent, then 10- and 13-valent PCVs, the frequency of IPDs decreased significantly. However, over time, the distribution of the predominant pneumococcal serotypes circulating in the community changed, and while the serotypes covered by vaccines decreased, the non-vaccine serotypes increased. The serotype change resulted in regional differences in the prevalence of pneumococcal meningitis (PM) but did not result in the desired reduction [28–34]. One reason is that pneumococcal pneumonia is primarily caused by a few serotypes, such as 1, 3, 5, 7F, 14, and 19A, whereas meningitis is caused by a much larger number of pneumococcal serotypes [35].

The changing epidemiology may be clearly shown through the example of England and Wales: In November 2006, the PCV-7 was added to the routine childhood immunization program. In the second year following vaccination, a 93% reduction in the frequency of IPDs caused by the vaccine's serotypes was observed. However, in the fourth year, the frequency of IPDs caused by non-vaccine serotypes increased by 19%. In April 2010, PCV-13 began to be used in place of PCV-7. In addition, PPV-23 was recommended for adults aged 65 years and older and adults and children over the age of 2 years at risk. Over 90% of the target population received vaccinations. Although the frequency of IPDs caused by the vaccine serotypes decreased by up to 95% in the second year of application, the frequency of IPDs caused by non-vaccine serotypes increased by 25%, similar to PCV-7. Additionally, following the start of the PCV-13 vaccination program, the frequency of IPDs increased for the first time between 2013 and 2014, indicating that the maximum benefit point for PCV-13 administration was reached [36].

In a 2020 study based on European data, a 35.3% decrease in the frequency of IPDs was observed, attributed to the decline in the incidence of pneumonia associated with bacteremia. Throughout the study period, the prevalence of PM remained constant while the prevalence of bacteremia increased. As expected, vaccine-covered serotypes decreased in frequency while non-vaccine serotypes increased. While the most frequently observed non-vaccine serotypes were 24F, 12F, 15BC, and 10A, the prevalence of serotype 24F in PM cases increased from 2.9% to 25%. The most common vaccine serotypes were serotypes 3 and 19A. In addition, the

prevalence of penicillin-resistant strains increased from 28 to 44.8% [31]. Meningitis was more prevalent, particularly among children in the risk groups. There was no significant change in the prevalence of PM in the Cameroon data, but the serotype distribution changed [37].

Pneumococcal meningitis remains a problem for children and adults for various reasons, including serotype change following vaccination and the inability to stimulate an adequate immune response against some serotypes covered by vaccines, such as serotypes 3 and serogroup 19. The rise in antibiotic-resistant pneumococcal serotypes exacerbates this problem [38].

Between 2014 and 2019, there was no significant change in the frequency of IPDs across all European countries. Despite similar vaccination practices, epidemiology varies significantly across European countries, and the primary reason for this is thought to be serotype diversity [38, 39]. In 2018, the most frequently detected serotypes in IPD and meningitis in Swedish children aged 1–4 years were 8, 10A, 3, 19A, 24F, and 19A, and only 19A was covered by the vaccine [40]. The 24F serotype caused an increase in meningitis cases in France [41]. Another issue is that nearly half of infants worldwide lack access to vaccines [26].

Despite a relative decline in the number of cases, pneumococci and meningococci continue to be the most common causes of bacterial meningitis in children and adults after the neonatal period in low-, middle-, and high-income countries [38, 39]. Although the disease is more prevalent in children under the age of 5 years, the average age has increased due to childhood vaccinations. Despite herd immunity, pneumococcal infections continue to be a problem in adults. This situation demonstrates the critical need for vaccination programs covering children under 2 years, at-risk populations, and older children and adults [26].

Pneumococcal meningitis is associated with a high mortality rate and a high likelihood of causing permanent neurological problems. While mortality rates in high-income countries range between 20% and 37%, they can reach up to 51% in other countries [42]. Permanent neurological problems such as hearing loss (HL), cognitive dysfunction, and epilepsy can affect up to 50% of survivors [43–45]. Pneumococcal meningitis has a higher mortality rate than meningococcal and Hib meningitis, and survivors have a higher prevalence of neurological problems [26, 42, 46, 47].

28.6.2 Pathogenesis

Despite appropriate antibiotic therapy and advanced supportive care, the high prevalence of persistent complications in PM requires the development of novel treatments and protective strategies for the central nervous system (CNS), which might be possible if the pathogenesis of PM is understood at the cellular molecular level. The main PM stages are colonization of the nasopharyngeal epithelium by the pneumococci, development of bloodstream infection, bacteria entry into the subarachnoid space via barrier structures, and destruction caused by rapidly multiplying pneumococci and increasing proinflammatory cytokines. The pneumococci may

also reach the subarachnoid space via direct transport caused by breaking the bone structure following trauma leading to a CSF leak or neighborhood spread following infection of adjacent anatomical structures, such as mastoiditis, otitis, and frontal sinusitis [48].

The bone skull, meninges, blood–brain, and blood–CSF barriers isolate the brain from the rest of the body. The most challenging aspect of the pathogenesis of meningitis is how bacteria enter this specially protected structure. Molecules such as the platelet-activating factor receptor (PAFR), laminin receptor (LR), polymeric immunoglobulin receptor (pIgR), and CD31, the platelet endothelial cell adhesion molecule-1 (PECAM-1) have been implicated in various studies, either directly or indirectly. It is supported by evidence that bacterium enters brain tissue via mediated intercellular transfer [49, 50]. It is also possible for the bacterium to reach the CNS via the olfactory nerve [48, 51].

Toll-like receptors 2, 4, and 9, the primary receptors in the CNS involved in PM pathogenesis, activate nuclear factor kappa B (NF-kB), or mitogen-activated protein kinase (MAPK) signaling pathways and proinflammatory caspase enzymes. The MyD88 protein serves as an intracellular adapter molecule for TLR-2 and TLR-4. The MyD88-induced NF-kB activation increases proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-10, and transforming growth factor-beta (TGF-β), all involved in PM pathogenesis. On the other hand, bacteria that enter the CNS, an immune-privileged area, multiply exponentially in a short period. The bacterial products that emerge during this period result in the release of cytokines. Increased cytokines cause neutrophils to release large amounts of oxygen and nitrogen radicals, which cause nerve tissue damage [50, 52, 53]. Increased cytokine release and oxidative stress are the primary causes of tissue damage in meningitis. In summary, the first stage of cell destruction is caused by bacterial toxins such as pneumolysin; the second stage is by an increase in the release of proinflammatory cytokines, which occurs as the bacterial cell wall disintegrates, resulting in cell damage, destruction, and death [54].

28.6.3 Clinical Evaluation

The classic clinical manifestations of bacterial meningitis include fever, headache, vomiting, nuchal rigidity, and meningeal irritation, but not all are present in every case. Non-specific findings like fever, restlessness, drowsiness, vomiting, diarrhea, and breathing difficulties are common in newborns and infants. Unsurprisingly, viral upper respiratory tract infection symptoms and signs are observed a few days prior to the clinical manifestations of bacterial meningitis. Occasionally, symptoms manifest abruptly, and the clinical picture deteriorates within hours. Increased intracranial pressure typically results in symptoms such as headache, vomiting, and paralysis of the third, fourth, and/or sixth cranial nerves. In infants, it can manifest as fontanelle bulging or expansions of suture lines.

Papilledema may be observed, but it is not a typical finding because of the disease's acute onset. When papilledema is present, it is vital to consider possible

causes such as subdural empyema, abscess, or venous sinus occlusion. Seizures may occur throughout the disease. Early seizures are typically generalized; late-onset focal seizures are commonly due to intracranial complications. Petechiae and purpura are most frequently associated with meningococcal infections but can also occur in pneumococcal bacteremia or meningitis. In a study involving numerous pediatric cases, petechiae and/or purpura prevalence was 61% in meningococcal meningitis and 9% in PM [55]. Based on the clinical findings observed during acute meningitis, the causative agent cannot be predicted [56].

28.6.4 Complications and Long-Term Sequelae

Generally, PM has a higher mortality rate in adults; however, pediatric cases have a higher rate of permanent neurological problems [57]. Table 28.2 summarizes several PM clinical and laboratory findings associated with poor prognoses [12, 57–60]. Along with the acute complications of bacterial meningitis, a significant proportion of survivors develop permanent neurological problems. Long-term follow-up can reveal HL, cognitive function problems, spasticity, paresis, epilepsy, and behavioral issues. A study of pediatric acute bacterial meningitis cases reported that 50% of survivors experienced at least one meningitis-related problem during long-term follow-up (5 years or more) after the acute period [61]. Permanent neurological problems occur at rates that vary according to the patient's age, comorbidities, effective treatment timing, and clinical findings. Pneumococci, the leading cause of acute bacterial meningitis in children worldwide, are also the most common cause of permanent problems [62, 63].

Table 28.2 Factors associated with a poor outcome in pneumococcal meningitis[a]

Age <12 months old
Cerebrospinal fluid findings
High protein concentration
Low glucose concentration
Low cell count
Initial evaluation
Clinical findings
Unconsciousness
Septic shock
Hypotension
Need for mechanical ventilation
Focal neurological findings
Laboratory
Hyponatremia
Low serum white blood cell and neutrophil count
In hospital follow-up, the development of focal neurological signs or seizures
Delay in sterilization of cerebrospinal fluid
Presence of cochlear implant

[a] Adapted and modified from Refs. [12, 57–60]

28.6.5 Treatment

The first antibiotics used to treat pneumococcal infections were sulfonamides. However, the sulfonamide usage in treatment was brief due to the development of resistance and the demonstration of the efficacy of penicillin group antibiotics [64]. Penicillin was the favorite antibiotic in the 1940s; it was only in the 1960s that penicillin and multi-drug resistance began to occur. Pneumococcal infections resistant to antibiotics continue to be frightening [21].

Recommendations for treating meningitis, less common among pneumococcal infections but whose mortality and morbidity cannot be reduced to the desired level despite effective treatment and widespread vaccination, are also made considering the resistance problem. Ceftriaxone and cefotaxime, third-generation cephalosporins, are effective against pneumococcal infections, have a reasonable penetration rate into the CSF, and are used in empirical PM treatment. Minimal inhibitory concentrations interpretive breakpoints for pneumococcus are different for meningitis and non-meningitis infections due to the higher concentrations of penicillin or ceftriaxone/cefotaxime that can be achieved in serum, pleural, or synovial fluid compared to concentrations in the CSF [15]. Cephalosporin resistance may also be present in penicillin-resistant pneumococci. Thus, ceftriaxone and cefotaxime are not used alone empirically to treat PM; cephalosporin-resistant *S. pneumoniae strains* can be effectively treated with vancomycin. However, vancomycin is used in combination with third-generation cephalosporins in empirical treatment because it is difficult to maintain adequate CSF concentrations of vancomycin, and sufficient experience does not exist with its use as monotherapy. Even if the causative pneumococci are determined to be resistant to cephalosporins, it is recommended that vancomycin be used in combination with third-generation cephalosporins due to their synergistic effect [12].

Vancomycin is thought by some experts to be no longer needed for empiric therapy of possible penicillin-resistant pneumococci in North America, given the current exceedingly high third-generation cephalosporin susceptibility [65]. Some pneumococci strains may be resistant to penicillin but susceptible to third-generation cephalosporins and may be treated with the cephalosporin alone. If the prevalence of invasive penicillin-resistant pneumococci strains is more than 5%, the standard empirical treatment for suspected pneumococcal meningitis is concurrent administration of ceftriaxone and vancomycin [65]. The treatment dosages are listed in Table 28.3 [15, 65].

While vancomycin resistance has not been demonstrated in pneumococci, vancomycin-tolerant pneumococci exist. The increased prevalence of vancomycin-tolerant pneumococci may pose a new difficulty in treating PM. Rifampin is another effective antibiotic that may be used to treat meningitis caused by pneumococci-resistant to third-generation cephalosporins or in cases of significant allergies to beta-lactam antibiotics in combination with vancomycin. The use of rifampin alone is not recommended because resistance will rapidly develop. Carbapenems are also effective in treating PM but should not be used as first-line therapy.

Table 28.3 Drugs and dosages used to treat pneumococcal meningitis[a]

Agent	Dose/kg/day	Dose interval	
Ceftriaxone	100 mg	12–24 h	In combination with vancomycin in empirical therapy OR If the agent has been shown to be cephalosporin-susceptible, it can be used as a monotherapy.
Cefotaxime	225–300 mg	8 h	In combination with vancomycin in empirical therapy OR If the agent has been shown to be cephalosporin-susceptible, it can be used as a monotherapy.
Vancomycin	60 mg	6–8 h	In combination with ceftriaxone or cefotaxime in empirical therapy.
Penicillin G	150–240 mg	4–6 h	If the agent is shown to be penicillin-susceptible, it can be used in the treatment.
Dexamethasone	0.6 mg	6 h for 2 days	The decision to use in treatment should be made on an individual basis. If used, it should provide the most significant benefit in terms of preventing hearing loss and neurological sequelae. Either before or concurrently with antibiotic treatment.

[a] Adapted and modified from Refs. [16, 65]

There has been no significant change in antibiotic options for PM treatment over the years. Even in the best-case scenario, in which effective antibiotics are used at appropriate doses and intervals without delay, PM remains a problem due to its high mortality and frequency of causing permanent problems.

28.7 Pneumococcal Meningitis and Hearing Loss

Pneumococcal meningitis has a higher HL rate than meningitides caused by other leading agents. Particularly since the introduction of the conjugate Hib vaccine and the subsequent decline in Hib-induced meningitis cases, PM has become the primary cause of HL. In a study conducted before widespread Hib vaccination, the prevalence of HL following Hib meningitis was 34% [66]. In comparison, the prevalence of HL after PM was 30%, and in this study, PM was the leading cause of HL in children younger than 12 months. Hearing loss is a common complication of PM, occurring in up to 54% of cases [67].

The study by Worsøe et al. [67] detected some cases of HL during follow-up, in which the initial hearing tests performed at the end of PM treatment were normal. Ears may be affected unilaterally or bilaterally, ranging from mild HL to total deafness. The severity of clinical findings, the CSF characteristics, the high concentration of bacteria in CSF, the delay in initiating appropriate treatment, and the presence of concurrent otitis were determined as risk factors for developing HL [67]. However, another theory argues that effective and timely treatment cannot prevent HL since the damage that results in HL occurs early in the process [12].

28.7.1 The Architecture and Physiology of Hearing

Sound is mechanically conveyed to the inner ear by increasing intensity through the outer and middle ears. The inner ear is where sound is processed neurally. When PM impacts tissues in the inner ear, HL develops. The cochlea, the most critical inner ear component, is a tubular structure that rotates 2.75 times around the modiolus, a cone-shaped bone. Two membrane structures split it into three chambers. In the upper and lower chambers, perilymph fluid fills the scala vestibuli and scala tympani. The scala media is filled with endolymph fluid not connected directly to the chambers. The densities, electrolyte levels, and electrical charges of perilymph and endolymph fluids differ. The cochlea is tonotopically structured; the basal portion is responsive to high-frequency sounds, while the apical part is more sensitive to low-frequency sounds.

The organ of Corti is a spiral-shaped structure that extends beyond the cochlea's basal membrane, which is equipped with hearing receptors. Four rows of hair cells have hearing receptors. The first three rows are called outer hair cells, and the fourth-row inner hair cells. In particular, damage to the outer hair cells results in sensorineural HL (SNHL). Hearing loss following meningitis is most noticeable in the high-frequency ranges and is anatomically tied to the cochlea's basal region.

Although it is unknown how bacteria, proinflammatory cytokines, or bacterial products reach the inner ear during meningitis, dissemination from the CSF, through the bloodstream, or the eighth nerve may be possible [68]. Purulent labyrinthitis results from infection spreading to the cochlear canal, and over time, the structure of the membranous labyrinth becomes fibrous, resulting in HL.

28.7.2 Pneumococci and Hearing Loss

Animal studies showed that outer hair cells are more susceptible to pneumococci; their destruction increases in direct proportion to bacterial density and contact time [69]. Proinflammatory cytokines, whose levels increase in direct proportion to bacterial density, primarily affect outer hair cells and cause HL [68, 69]. Inner hair cells are more resistant to pneumococci's direct impacts. Tumor necrosis factor-alpha is the most potent ototoxic cytokine and directly attacks hair cells [69]. In CSF, TNF-α levels have been associated with the rate of long-term HL in patients with acute PM [68].

Pneumolysin toxin is directly associated with HL [69]. As demonstrated in animal studies, HL is considerably reduced in meningitis caused by pneumococci that cannot produce pneumolysin [69]. Pneumolysin has different effects on different structures depending on the dose. While it affects inner hair cells at low concentrations, it significantly affects outer hair cells at high concentrations. Its effect on outer hair cells is also dose-dependent [68]. Pneumolysin has a lesser effect on outer hair cells placed apically [68, 69]. Pneumolysin damages inner and outer hair cells; the basal region and middle part of the hair cells are more sensitive to the toxin. Being more susceptible of the regions responsible for high-frequency processing

sounds to damage explains why post-meningitis HL is more pronounced in high-frequency sounds [68].

Because nitric oxide and oxygen radicals, and the cytokines secreted or released during acute infection, are similarly ototoxic, it was postulated that the apical and basal regions are affected differently due to their varied antioxidant production capacities [68].

In summary, increased bacterial density, proinflammatory cytokines, oxygen and nitrogen radicals, and bacterial toxins contribute to an increased risk of HL in PM. Concurrent otitis is identified as a risk factor [68]. Hearing loss is believed to occur in the context of otitis due to the effect of toxins on the cochlea, not the bacteria themselves [70].

Bacteria that enter the cochlear canal via the subarachnoid space reach the perilymph fluid and produce suppurative labyrinthitis histologically [71]. Histopathology of the acute period reveals the breakdown of the labyrinth–blood barrier and the destruction of the spiral ganglion and cochlear cells. In contrast, the long-term period reveals fibrotic alterations in the perilymphatic area [72]. Hearing loss necessitating cochlear implant treatment occurs in 5% of instances following PM [73]. The implant is only helpful if sufficient healthy neurons exist in the cochlea. As a result, therapy techniques that protect spiral ganglion cells might be beneficial in the treatment of PM [72, 73].

All children diagnosed with acute bacterial meningitis should be examined for HL in the early stages. Hearing tests should be performed, ideally before hospital discharge, and follow-up should be established for cases with any documented HL.

28.7.3 Unresolved Issue

Dexamethasone is used in the treatment of bacterial meningitis to reduce inflammation because the severity of inflammation in the subarachnoid space is linked to mortality and long-term consequences [74]. Although steroids are commonly used in treatment, there is still scarce scientific evidence that they improve survival or lessen neurological damage [74, 75]. Historically, steroid usage in treating bacterial meningitis did not diminish death, HL, or the development of other irreversible neurological disorders, according to meta-analyses published in the late 1980s [76]. However, subgroup analyses revealed that when given before or simultaneously with antibiotic treatment, steroid use reduces HL, particularly in children with Hib meningitis [76, 77]. Dexamethasone treatment was not beneficial in a randomized controlled trial on the pediatric age, in which 40% of the cases were PM [46].

On the other hand, a 2015 Cochrane review concluded that dexamethasone treatment successfully reduced HL and neurological sequelae in patients with acute bacterial meningitis in high-income countries but was ineffective in others [78]. One possible explanation for this disparity is that the chances of obtaining appropriate therapy during the early stages of the disease vary significantly between countries. The effect of corticosteroids on mortality could not be established in this review.

Dexamethasone has been shown to protect against severe HL only when given early in the course of bacterial meningitis [78, 79].

Due to the subject's uncertainties, although dexamethasone is still routinely used in clinical practice, its use in compliance with recommendations is extremely low. In addition, some discrepancies exist in the recommendations of the clinical practice guides. The American Academy of Pediatrics (AAP) recommends dexamethasone for children aged 6 weeks and older after considering the benefits and risks and making a case-by-case decision, but this is not a standard recommendation [15]. Sufficient evidence does not exist to support dexamethasone use for neonatal meningitis. The Infectious Diseases Society of America (IDSA) recommends dexamethasone for adults with bacterial meningitis [80].

Regarding PM, the rise in pneumococci resistant to third-generation cephalosporins and hence the need for empiric treatment with vancomycin has given a new dimension to the problem. Vancomycin has limited penetration into the CSF, and its transmission into the CSF rises when meningeal permeability increases during meningitis [80]. Vancomycin may not reach an effective concentration in the subarachnoid space due to the decreased permeability of the meninges caused by dexamethasone. However, scientific evidence could not substantiate this hypothesis [80, 81].

Along with the unproven clinical benefit, the potential side effects of dexamethasone should be considered. More caution should be taken in the assessment of hospitalized patients treated with dexamethasone, as clinical findings may be suppressed by dexamethasone.

In summary, dexamethasone use in treating children with PM should be determined on a case-by-case basis, with careful monitoring of clinical and laboratory findings in treated cases. Table 28.3 shows the recommended dexamethasone dose and duration of use [65].

28.7.4 New Treatment Approaches: Experimental Treatments

Early and effective treatment cannot significantly reduce the frequency of HL and other neurological problems in children with PM. On the other hand, the development of cell-tissue damage resulting in HL during the early stages of meningitis is related to the host's inflammatory response rather than the bacteria itself. So, treatment research has focused on this direction. Although dexamethasone is an effective anti-inflammatory, it did not act as well as predicted, which prompted the quest for other treatments.

As known, bacterial cell wall components produced from fast bacterial death induced by antibiotic therapy exhibit antigenic features and bind to TLRs. The majority of TLRs are intracellularly attached via the MyD88 protein. The activation of NF-kB by MyD88 signals increases proinflammatory cytokine levels and cell damage [82]. New treatment approaches aim to stop or slow down this process at any point.

Numerous therapy combinations have been investigated in trials to control inflammation by lowering the elevated antigen load. In animal trials, positive results were observed when third-generation cephalosporins that cause bacterial lysis were combined with non-bacteriolytic antibiotics [83–85]. Daptomycin is the most extensively investigated antibiotic in this field, as it is efficient against cephalosporin-resistant pneumococci. A study comparing ceftriaxone and daptomycin monotherapies determined that sterilization of CSF was faster with daptomycin, caused less inflammation during the treatment phase, and caused less cortical brain damage [86]. A comparable study demonstrated that daptomycin therapy protects against cognitive and learning function damage [84]. In another experimental study, when daptomycin and anti-inflammatory doxycycline were added to ceftriaxone treatment, cortical necrosis was reduced, inflammatory cytokines decreased significantly in CSF, and HL was also reduced in the evaluation at the end of third weeks [85].

When matrix metalloproteinase inhibitors were administered in conjunction with non-bacteriolytic antibiotics, TNF-a, IL-1, IL-6, and IL-10 levels decreased significantly in the groups receiving adjuvant medication, while learning and cognitive abilities improved and HL decreased [87]. Additionally, it is well established that HL is reduced when antioxidant medication is used with conventional antibiotic therapy to counteract the harmful action of oxygen and nitrogen radicals [88]. However, this strategy is still in its infancy and has not yet found a home in clinical practice [88].

Animal trials have examined various anti-inflammatory therapeutic alternatives, such as antioxidant medicines [89]. Metformin was the subject of one of the most recent investigations. In a mouse experiment, metformin administration decreased inflammatory cytokine and nitric oxide levels in CSF and astroglial cell cultures [88]. Mice treated with metformin plus ceftriaxone had reduced cortical necrosis and HL on a follow-up hearing test. Another property of metformin is that it is neuroprotective for inner ear ganglion cells [89].

Neurotrophins (NTs) are proteins that ensure the growth and maintenance of neurons. Neurotrophins in the cochlea are known as NT-3 and brain-derived neurotrophic factor (BNDF). Animal experiments have shown systemic NT-3 treatment effectively protects neurons in PM. The discovery that permanent pathological abnormalities are significantly more pronounced when therapy is administered after the 24th hour reaffirms that early-stage damage is related to neurological complications and HL [70].

28.8 Conclusion

Pneumococcal meningitis and associated complications continue to be a problem despite the introduction of PCVs in childhood immunization practices over the past 25 years and the expansion of treatment options. Although new treatment options are promising, increasing vaccination rates and updating national immunization programs in light of evolving epidemiological data appear to be the most efficient strategies for preventing pneumococcal infections under current conditions.

Monitoring all cases with a meningitis diagnosis in terms of HL will allow for early detection and proper management of the disorder before concerns such as HL-related learning difficulties and developmental delays occur.

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Meningococcal Infections in Children and Hearing Loss

29

Ener Çağrı Dinleyici, Emin Sami Arısoy, and Sheldon L. Kaplan

29.1 Introduction

Invasive meningococcal disease (IMD) is one of the leading causes of infectious disease morbidity and mortality worldwide [1]. With over 1.2 million cases reported annually, IMD is a foremost global public health concern [2]. Despite improvements in intensive care facilities, 10% of patients die (case fatality rates range from 5% to 20%) and 20% have serious sequelae that can affect their life [1, 3–5]. Factors such as the host characteristics, the invasiveness of the causative serogroup, availability of treatment, intensive care facilities, and disease follow-up all play a role in the prognosis and mortality of IMD [3, 4, 6]. Due to the disease's high mortality, severe and lifelong sequelae in surviving patients, the sudden onset of the disease, and its rapid course, it has been highlighted as a vaccine-preventable disease, and vaccination studies have been recommended [1].

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29.2 Etiology and Epidemiology

Humans are the only reservoir for *Neisseria meningitidis*. Infection is transmitted through respiratory droplets. The meningococci are colonized on the nasopharyngeal mucosa and then can enter the bloodstream and spread to the meninges (meningitis), the entire body (meningococcemia), or both. The symptoms vary from moderate nonspecific ones to multi-organ failure [7]. Although *N. meningitidis* has 12 serogroups based on its capsular polysaccharide antigenic structure, the most common serogroups are A, B, C, Y, W, and X [1]. Over the years, the serogroup epidemiology of IMD may differ from country to country and even from region to region within the same country. The routine use of meningococcal vaccines is another factor influencing seroepidemiology [1, 8, 9].

29.3 Risk Factors

The patient's age has been recognized as the most critical risk factor for IMD. According to reports, 35–40% of meningococcal disease is seen in children under the age of 5 years old (particularly <1 year), mainly due to low serum bactericidal antibodies [4, 9]. Adolescents and young adults between the ages of 15 and 24 years old are the second age group at risk for IMD, primarily due to school and social habits [4]. Although several conditions have been linked to an increased risk of IMD, in more than 90% of cases, no underlying disease or risk factor exists [10, 11].

The incidence of IMD (250–600 times higher) and recurrence probability is increased in people with complement (C)-5-C9 and properdin deficiencies in the complement pathway [12]. In recent years, it has been shown that eculizumab treatment, used to treat many diseases in children and adults, especially in treating atypical hemolytic syndrome and paroxysmal nocturnal hemoglobinuria, causes a significant increase in the risk of IMD [1]. Human immunodeficiency virus (HIV) infection increases the IMD risk 10 times [1]. Anatomical or functional asplenia is another important risk factor for IMD, as it is for all encapsulated bacteria [7]. Staying in dormitories for the first year at universities, spending time in public areas such as camps, festivals, and military units, traveling to places where the disease is endemic, such as Hajj and Umrah, crowded home environments, active or passive smoking, preceding respiratory tract infections, such as influenza, respiratory syncytial virus (RSV), and mycoplasma, are among the other risk factors [1, 8, 9, 13].

29.4 Clinical Manifestations

Meningococcal meningitis, meningococcemia, and meningococcemia with meningitis are the most typical clinical presentations of IMD. It is challenging to diagnose the illness at the initial stage since the early symptoms, including sudden onset of fever, nausea, vomiting, headache, and muscular aches, are nonspecific and may

resemble those of an upper respiratory tract infection. In some studies, patients have been admitted to the hospital within less than 22 h when symptoms first appeared; in children under 5 years, this was 13–14 h [7, 14, 15].

Meningococcal meningitis is characterized by abrupt onset of fever, nausea, vomiting, headache, changes in consciousness, and myalgia as presenting symptoms. The early clinical signs may be mistaken for an influenza infection if symptoms occur in the final months of the winter season. Non-blanching rashes may be present in two-thirds of patients. Fever, headaches, photophobia, nausea, vomiting, confusion, lethargic behavior, and changes in consciousness are the most typical symptoms in older children. Twenty percent of cases have been reported to have had seizures. Most times, there is no history of contact with the meningococcal illness. Meningococcemia may accompany meningitis.

Meningococcal meningitis and meningococcemia are characterized by a rapid progression of symptoms, a decline in general health, and the potential for shock. Leg pain, numbness in the hands and feet, abrupt changes in skin color, and the appearance of a rash are all considered warning signs of meningococcemia in children with meningococcal meningitis [7, 14, 16].

Fever and a non-blanching rash are the most typical meningococcemia presenting symptoms in children. Although the rash initially looks like maculopapular rashes, it has the potential to develop into petechiae and ecchymosis within minutes to hours. It has been seen that initially, sparse petechiae quickly increase in number within minutes or hours to become ecchymoses. The degree of thrombocytopenia and the emergence of disseminated intravascular coagulation are directly correlated with petechiae occurrence. Additionally, the conjunctiva and soft palate may bleed. Initial clinical symptoms of meningococcemia include leg pain, numbness in the hands and feet, and skin discoloration (mottled appearance with signs of circulatory dysfunction). The patient may experience nonspecific symptoms at the onset of the illness, such as fever, headache, myalgia, and signs of an upper respiratory infection that looks like the flu; shock could occur within hours.

Patients with IMD due to serogroup W present gastrointestinal symptoms, particularly diarrhea, abdominal pain, and in some cases, an acute abdomen. Rapidly developing symptoms are commonly reported, including tachypnea, sweating, tachycardia, hypotension, extended capillary filling time, and oliguria related to shock. Unconsciousness and coma might be seen depending on the decline in cerebral perfusion. The development of hypotension not responsive to fluids or vasoactive agents and multiple organ failure are risk factors for mortality.

Purpura fulminans occurs in 15–25% of patients with meningococcemia. Necrosis may spread to the deep tissues and then to the muscles and bones, resulting in significant loss of tissue and organs. Most fatality occurrences have been reported to occur within the first 12–48 h after the onset of illness [7, 14, 17, 18].

Pneumonia, arthritis, purulent pericarditis, endophthalmitis, primary peritonitis, urethritis, and osteomyelitis are other illnesses linked to meningococcal infections. Ten percent of meningococcal infections result in meningococcal arthritis, which frequently affects the knee joint. Immune complex arthritis brought on by

meningococcal infection typically affects multiple joints and has onset later in the course of illness compared with true septic arthritis caused by *N. meningitidis* [7].

29.5 Diagnosis and Laboratory Findings

Early diagnosis of IMD is attainable with suspicion based on the history and clinical findings. Because of the disease's potential effects on the general public's health, detection or isolation of *N. meningitidis* is also crucial. Leukopenia or leukocytosis, anemia, thrombocytopenia, proteinuria, and hematuria might be detected in IMD with routine laboratory testing. Even when the disease progresses quickly in the beginning, the erythrocyte sedimentation rate and serum C-reactive protein levels may be high. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, metabolic acidosis, and lactate elevation might be observed. The majority of cases have coagulation problems related to disseminated intravascular coagulation. Computed cranial tomography can detect cerebral bleeding and/or high intracranial pressure syndrome in meningococcal infections, followed by loss of consciousness [7, 14, 16, 18].

The gold standard for diagnosis of IMD is the presence of the *N. meningitidis* in blood, cerebrospinal fluid (CSF), or other sterile bodily fluids, such as joint fluid, pleural or pericardial fluid, or samples taken from petechiae or purpura lesions. Gram staining in samples collected from skin lesions or buffy-coat can show gram-negative diplococci. Patients who have taken antibiotics have a lesser chance of the agent being isolated in blood culture samples, and negative findings are frequently obtained. In these situations, a polymerase chain reaction (PCR) test can be used to demonstrate *N. meningitidis* within 4–8 h and determine the serogroup. Syndromic test panels (meningitis or sepsis) have been popular in recent years as tools for the early detection of disease [7, 19]. Analysis and culture of CSF are required to confirm the diagnosis of meningococcal meningitis. Thus, lumbar puncture (LP) should be performed in patients for whom a diagnosis of meningococcal meningitis is suspected as long as there are no contraindications for this procedure. Gram staining of the CSF may reveal gram-negative diplococci along with cytochemical results (increased neutrophil count in CSF, increased CSF protein concentration, and reduced CSF glucose concentration), supporting the diagnosis of bacterial meningitis. Cerebrospinal fluid Gram staining yields a positive result in 75–80% of untreated cases; the test's specificity is 97%. Rarely, CSF results are within normal limits in a patient with meningococcal meningitis; in such instances, CSF cultures may be positive, or diplococci might be found on CSF Gram stain in cases where CSF culture is negative [7, 15].

29.6 Treatment

In cases with clinical suspicion of IMD, if possible, empirical third generation cephalosporin treatment, primarily ceftriaxone or cefotaxime, should be initiated after culture samples are taken. Considering that *N. meningitidis* is transmitted by droplets, it is crucial to take isolation precautions. In regions where pneumococcal meningitis cannot be excluded, and penicillin and ceftriaxone resistance have been reported in regional pneumococcal isolates, it is recommended to add vancomycin to the treatment. Antibiotic treatment is usually recommended for 7 days. Vancomycin therapy should be discontinued in proven cases with *N. meningitidis* [7, 15, 18].

Rapid evaluation of shock in meningococcemia cases, follow-up, and treatment in the intensive care unit are required. Intubation should be planned for follow-up on mechanical ventilators in necessary cases. Fluid support treatments and inotropic support should be provided quickly for the shock treatment. Hematological, coagulation, blood gas, and biochemical parameters should be closely monitored. Anticoagulant or fibrinolytic treatments, plasmapheresis, and extracorporeal membranous oxygenation (ECMO) treatment approaches can be applied on a case-by-case basis. No data exists on steroid use's benefit in meningococcal meningitis cases. In meningococcemia, steroid treatment may be beneficial in patients with severe septic shock with resistant hypotension or secondary adrenal insufficiency (Waterhouse–Friderichsen syndrome) [7, 14, 18].

29.7 Prognosis

Invasive meningococcal disease is still a significant public health concern worldwide, not only because of its high mortality rate but also because of its severe disabling sequelae, such as hearing loss (HL). Despite being relatively uncommon, IMD is a serious public health problem because of its rapid onset and potentially severe and sometimes lifelong sequelae, including neurologic, physical, and psychological complications [5, 20, 21]. Disabling long-term sequelae in survivors have potentially devastating effects on survivors' quality of life (QoL), particularly in children and adolescents [22].

29.8 Bacterial Meningitis, Invasive Meningococcal Disease, and Hearing Loss

Acute bacterial meningitis (ABM) is the most prevalent bacterial central nervous system (CNS) infection, with a high case-fatality rate and potential neurological complications [23, 24]. Children with ABM had a 3.1-fold higher risk of disabilities, and 8.5% had serious sequelae such as severe HL, mental retardation, and epilepsy in some studies [25, 26]. Outcomes are highly dependent on the patient's age (significantly below 1 year), the infecting organism (sequelae are higher in

ABM due to *Streptococcus pneumoniae* than *Haemophilus influenzae* type b and *N. meningitidis*), and the time it takes to start antibiotics [27, 28]. Hearing loss is a typical complication of ABM, ranging from mild to severe [23, 28–32]. According to a retrospective database research in Spain, the total deafness rate was 2.6%; however, the rate was 6.1% among meningitis survivors compared to 1% in the general pediatric population [22].

Hearing loss may be conductive or sensorineural, and it is characterized as mild (hearing threshold 20–40 decibels [dB]), moderate (40–70 dB), severe (70–90 dB), or profound (deep) (>90 dB) based on severity [33]. The most common cause of acquired sensorineural HL (SNHL) in children is ABM, which accounts for 60–90% of all cases [34]. Sensorineural HL can be unilateral after ABM, but a bilateral HL is significantly more likely [29]. The frequency of some degree of HL after ABM ranges from 2% to 33.6%; 5% to 25% of children experience bilateral severe or profound HL [31, 35].

Edmond et al. [31] evaluated the chances of major and minor sequelae induced by ABM, with HL being the most prevalent major sequelae (33.6%). The most prevalent combination of multiple impairments was cognitive deficit plus HL (39.1%). Changes in hearing testing methodology, parameters used to define hearing impairment, and interpretation of results account for most of the variation in reported HL [33]. In high-income countries, improved immunization practices, a consequent fall in susceptibility to fatal disease, better health-seeking habits, and early hospital admission could all contribute to the large discrepancy in prevalence rates [32].

Late-onset HL has always been a concern, although it is usually recognized promptly after infection [24]. Hearing loss is most common in the first 48 h of illness, and many children have reversible HL in the first 2 days of illness [33]. According to Smyth et al. [36], the frequency decreased from 44% (48 h after diagnosis) to 29% (6 weeks post-admission) and 21% (12 weeks post-admission). Patients with normal hearing initially kept their normal hearing after meningitis. On the other hand, meningitis-related HL may improve or deteriorate with time. The average rate of deterioration of a first-time HL is 14% [24].

The frequency and severity of HL linked with IMD and/or meningococcal meningitis have been studied extensively. Strifler et al. [37] systematically reviewed health outcomes in IMD cases and found that the most common sequelae related to IMD were hearing and cognitive impairments and psychosocial difficulties. While meningococcal meningitis was associated with a lower rate of HL than pneumococcal meningitis, HL was the most common long-term outcome of meningococcal meningitis in particular [33]. According to a meta-analysis of long-term consequences of meningococcal meningitis, unilateral or bilateral SNHL is the most common complication, necessitating cochlear implantation in just 0.4% of patients [20, 30].

The incidence of HL associated with meningococcal meningitis varies [22, 30]. In a large nationwide cohort study in the Netherlands, HL occurred in 20 of 495 children (4%) after meningococcal meningitis among 578 children who survived ABM [38]. A retrospective examination of Dutch IMD hospital cases from 1999 to 2011 revealed 5.6% of HL events, with 2.5% occurring in children aged 0–4, 1.3%

in children aged 5–19, and 1.7% in adults aged 20–64 years [39]. At 21 months, 11.9% of adolescent IMD survivors (73% meningitis with or without septicemia) experienced hearing impairments, compared to 4% (1/25) of college students [40, 41]. Thirteen percent of meningococcal meningitis patients (68% serogroup B) had neurologic deficits at discharge, with 8% having HL [42].

In 159 occurrences of IMD treated in 10 pediatric hospitals in the United States of America (USA) between 2001 and 2005, unilateral or bilateral HL occurred in 12.5% of 112 children with meningitis, a proportion quite similar to in studies from over 25 years ago [43]. Another study in the USA found that 11% of children with meningococcal meningitis had severe HL at discharge, whereas 13% had mild or moderate HL [44]. A follow-up study in the United Kingdom (UK) reported SNHL in 15 of 232 survivors with serogroup B meningococcal disease (32% with meningitis with or without septicemia), with 2% having severe bilateral SNHL and 5% having moderately severe bilateral SNHL [45]. A retrospective assessment of national IMD cases in Canada from 2002 to 2011 found 46 HL occurrences out of 868 cases (58% with meningitis with or without septicemia), with 7.4% in children and 3.3% in adults [27].

Davis et al. [46] analyzed healthcare use and expenses between individuals with and without IMD-related complications. They found 173 individuals with IMD; 41.0% had one or more sequelae during the follow-up, and 9.3% had HL. Hearing loss was more prevalent following meningococcal meningitis in two African studies [30]. Hearing loss was found in 19% of 351 meningococcal meningitis patients in an Angolan research on day 7 of hospitalization [47]. An investigation on HL in children with meningococcal meningitis in Malawi revealed that 23% of the 67 children who participated in the study had HL [48].

Gil Prieto et al. [49] examined medical data from 1997 to 2008 in Spain for all 11,611 meningococcal infections (median age 5 years) linked to hospital discharges and deaths (846 deaths for IMD, 235 for meningococcal meningitis, and 605 for meningococcemia). In the 30 days after discharge, they reported that 3% of the subjects were readmitted, with HL being one of the causes for readmission.

Children with more severe IMD are more likely to develop serious neurological sequelae and HL. On follow-up 4–10 years after being discharged from the pediatric intensive care unit, 35% of 120 children who survived meningococcal septic shock showed neurological impairments in one study [50]. Two to four percent of IMD survivors, including those who have experienced meningococcal septic shock and those who have experienced meningitis, are found to suffer HL [50].

Also, a difference between the meningococcal serogroups exists. A matched-cohort study of adolescent survivors of IMD in the UK found that 57% had severe physical sequelae, such as mobility, speech, and hearing impairments. These sequelae were more severe in meningococcal serogroup C (MenC) disease survivors than in meningococcal serogroup B (MenB) disease [13]. The MOSAIC study enlisted children who had MenB disease in the UK between May 2008 and September 2010 and evaluated their physical, psychological, and neurocognitive outcomes 3 years later [45]. The majority of children with MenB disease recovered without serious complications. Approximately a tenth of those with significant

sequelae had major physical or neurological disabilities, such as HL. Compared to controls, children with MenB disease had a 4.8-fold higher incidence of bilateral SNHL of 40 dB or more. This research demonstrated a higher prevalence of SNHL in IMD than previously reported, both in terms of profound HL requiring a cochlear implant and less severe HL [45].

Richardson et al. [23] aimed to find out more about the natural history and pathophysiology of HL in 124 children with ABM in England and Wales (74% of whom had meningococcal meningitis). Children were subjected to audiological examinations, the first of which, otoacoustic emissions, was done within 6 h after diagnosis. Children who had been sick for more than 24 h were more likely to have HL. This study adds to the growing body of evidence showing HL occurs early in the course of ABM, with a reversible HL rate of 10.5%, with most instances resolving within 48 h. The absence of otoacoustic emissions and normal tympanogram in all of these children indicated cochlear dysfunction. The cochlea was identified as the source of the lesion in both permanent and reversible sensorineural deficits. The administration of dexamethasone did not appear to impact the audiological outcome in this investigation [23].

In Canada, with proven IMD among children and adults (55% MenB), Sadaranghi et al. [27] discovered risk factors related to mortality and the development of sequelae. There were 73 deaths (8.4%) and 157 complications (18%) among the 868 people admitted to the hospital with IMD (21% in children and 15%in adults). Hearing loss (5.4%) was the most prevalent complication. Children under the age of 1 year were most likely to suffer from HL and seizures, while children between the ages of 1 and 4 years were most likely to suffer from skin scarring and amputation. Monitoring of the circulatory condition and early and vigorous shock care are critical since shock is the most significant predictor of death in adults and children and a major predictor of complication rates.

The etiology of HL after ABM is linked to abnormalities in the cochlea and auditory nerve that develop during ABM. Hearing loss can occur as a result of both direct bacterial product dissemination and the host's inflammatory reaction to the invasion of the meninges and CSF. The auditory lesion in meningitis occurs in the inner ear. Severe labyrinthitis develops when bacteria migrate from the subarachnoid area to the cochlear aqueduct, resulting in blood–labyrinth barrier breakdown and, eventually, meningitis-associated HL. Serofibrinous exudate, inflammatory cell infiltration, and granulation cell formation are all indicators of cochlear disease. In untreated labyrinthitis ossificans, the infectious process in the cochlea creates an endosteal response, most typically involving the basal scala tympani. It could also be caused by bacterial toxins or inflammatory mediators acting on the hair cells of the Corti organ. Alternatively, the same mechanisms could disturb the endocochlear potential.

According to growing data, toll-like receptors (TLRs) appear to mediate cochlear damage in meningitis. A metabolic deficiency caused by insufficient CSF fluid glucose and the influence of variations in intracranial pressure conveyed by the cochlear aqueduct are further possibilities. Other reasons include cochlear nerve injury or vascular damage caused by septic emboli or thrombotic occlusions of the cochlear

artery and/or vein. Although retrocochlear disease is uncommon, bacterial meningitis can cause direct injury to the auditory nerve and central brain circuits. The absence of otoacoustic emissions has been observed in children with bacterial meningitis and SNHL, and this observation shows that the cochlea is the site of the damage in deafness after ABM since emission production is independent of the nervous system [23]. Indeed, the fact that the aqueduct is more likely to be patent in childhood than in maturity could explain why HL after ABM is more common in children. For *H. influenzae* type b, pneumococcus, and meningococcus, the distribution of different sequelae appeared similar, implying that the organisms may produce similar cerebral pathogenic processes [23, 30, 32–34, 51].

Genetic diversity in innate immune response genes influences interindividual disparities in illness appearance and infection consequences. Some associations between TLR single nucleotide polymorphisms (SNPs) and HL exist in patients with ABM. The immune response to ABM and subsequent neuronal damage, as well as cochlear inflammation, appear to be mediated by the TLR system. Toll-like receptor-9 SNPs have previously been associated with meningococcal meningitis risk. Toll-like receptor-4+896 mutant alleles were found to be strongly linked to HL after ABM, particularly meningococcal meningitis. According to a multigene analysis, combining the TLR2+2477 wild type (WT) and TLR4+896 mutant alleles enhances the likelihood of HL. Genetic markers may be utilized to identify high-risk patients by developing prediction criteria for HL after ABM and other complications and a better understanding of the complicated immune response in the CNS, perhaps leading to new treatment options [51].

29.9 Meningococcal Meningitis Follow-Up for Hearing Loss

In infants and toddlers, a critical period exists in which language and speech developments occur. To avoid long-term repercussions such as speech and language delays, poor academic performance, behavioral difficulties, and poorer psychosocial integration, early identification of SNHL in children is crucial. Serious language development and academic achievement impairments arise even when only a mild-to-moderate bilateral SNHL is present in neonates and young children [24, 30, 34]. Compared to children with SNHL discovered later, those identified earlier showed more remarkable development in language and vocal skills, age-appropriate language retention, and superior language skills [34]. Children who survive meningococcal meningitis have a greater rate of behavioral and psychiatric issues and lower academic achievement, which may be linked to HL. Hearing loss and other neurological sequelae can have long-term effects on the development of children and on their ability to reintegrate into society [30].

As a result, all surviving patients should have their hearing tested as part of the usual follow-up after ABM. Hearing tests are performed on all people with bacterial meningitis after the acute phase has passed. Testing during the acute phase is ineffective: even in the case of severe HL and cochlear ossification, the patient's physical condition must be addressed before a cochlear implant may be implanted [24].

Even if HL is not clinically suspected, all children afflicted with meningitis should have their hearing tested before release or 4–6 weeks after discharge. Because up to 90% of children's cochleae with HL due to meningitis can ossify, preventing effective treatment with cochlear implants, it is crucial to get an audiology evaluation a month following diagnosis, or sooner if possible. The chance of developing HL in people who do not have HL immediately after infection is extremely low, and audiological follow-up is not required. Patients who incur an HL during ABM require long-term and detailed audiological monitoring [24, 28].

Bozzola et al. [33] looked for factors that could predict long-term audiological difficulties in children with meningitis, including meningococcal meningitis, between 2017 and 2019. If the results were normal, the tests were redone at discharge, and if the results were normal again, the patients were dropped from the follow-up program. Regular hearing tests were performed if a unilateral SNHL was found. If bilateral SNHL was found, high-resolution temporal computed tomography (CT) scans and magnetic resonance (MR) imaging with gadolinium for the inner ear were conducted quickly to look for signs of labyrinthine fibrosis or ossification. In severe or substantial SNHL, immediate bilateral simultaneous cochlear implantation was recommended if ossification was discovered. Otherwise, imaging and audiological tests were repeated after 15 days; if no progress was seen, the patient received appropriate therapy with cochlear implantation or hearing aid fitting within 6 weeks [33].

No uniform recommendation exists for follow-up for children with ABM for HL [24]. The UK's National Health System (NHS) states that little evidence exists to support the need for additional testing if the initial hearing test after meningitis is satisfactory. In the USA and Australia, ABM is recognized as a risk factor for late-onset HL, albeit the timing and frequency of hearing reevaluations are not specified [24]. The French Infectious Diseases Society published the most recent recommendations for pediatric ABM follow-up. According to these recommendations, follow-up appointments should be scheduled at the end of treatment or within 15 days (neurological exam and hearing test based on the patient's age), 1 month after diagnosis (neurological exam, head circumference measurement, hearing test), and then every 3 months for the next year (clinical monitoring of the patient's hearing abilities, school adjustment monitoring). An otorhinolaryngology visit is advised for severe HL to assess for early cochlear ossification [26].

Cochlear implantation surgery should be considered in children as young as 1 year old who have severe or profound bilateral deafness (hearing threshold >75 dB HL) as evidenced by both subjective and objective audiometric techniques and cases where hearing and communication skills have not improved after 3–6 months of hearing aids and speech therapy, according to Italian guidelines [33]. Even if the patient is under the age of 12 months, bilateral simultaneous cochlear implantation surgery is essential in cases of profound SNHL caused by meningitis [33].

In addition to HL, IMD survivors should be tested for cognitive abnormalities and developmental delays on a regular basis. In order to reintegrate an IMD survivor back into society, extensive follow-up treatment and adaptive measures may be required. Hearing aids, physiotherapy, and specialized schooling are among the

adaptation procedures necessary to return a survivor to a quality of life as close to normal as feasible [13, 35].

29.10 Health-Related Quality of Life and Cost of IMD Complicating with Hearing Loss

Invasive meningococcal disease negatively influences patients' health-related quality of life (HRQoL) and their family and close caregiver network in the short and long term. After several years, even IMD survivors who had no sequelae had a negative influence on HRQoL, hurting self-esteem and physical, mental, and psychosocial health. Health-related quality of life was worse in those with cognitive and behavioral sequelae. A large percentage of IMD survivors experience a variety of sequelae and a reduction in HRQoL that lasts years after infection.

Compared to adults, childhood IMD survivors experience a greater number and more severe sequelae [22]. In a high-income country, the estimated burden of IMD sequelae in terms of quality-adjusted life-years lost varies by type and degree of sequelae. Hearing loss, blindness, motor deficits, neurological sequelae, convulsions, scarring, mental retardation, and attention deficit hyperactivity disorder (ADHD) are all associated with significant financial costs [3]. Quality-adjusted life-years lost for most to least severe sequelae were calculated to be 0.19 for HL if 1.0 represents 1 year in ideal health. The longer the interval between birth and the projected occurrences, the lower the current value of expenses will be [35].

Invasive meningococcal disease can cost the healthcare system and society a lot of money. The high expenditures per IMD case reflect the disease's severity in each patient, mainly due to the development of sequelae. In the study by Ivanova-Markova et al. [52], psychological impairment was the costliest outcome in most age groups, followed by renal failure, HL, and neurological damage. Indirect expenses and long-term repercussions, such as HL, should be considered when calculating the economic impact of IMD [52]. Davis et al. [46] compared healthcare utilization and costs in IMD patients with and without linked sequelae to understand better the economic impact these sequelae have. They found that predicted healthcare costs for patients with complicated IMD were three times higher than those with uncomplicated IMD. Patients with severe IMD were more likely than those with uncomplicated IMD to require rehospitalization after their initial IMD admission.

Huang et al. [53] evaluated the economic impact of IMD in Germany in a sample population of 164 IMD cases between 2009 and 2015, highlighting significant expenses and increased healthcare resource consumption, notably in the first year following diagnosis and due to IMD-related hospitalization. In the cost-effectiveness study by Ivanova-Markova et al. [52] in Spain, sequelae costs accounted for 62.5% of the total cost [52]. Another study looked at the expenditures incurred by all IMD patients in France over 6 years, finding that the majority of the extra costs were due to the care of sequelae in most cases [54]. Amputation, skin scarring, mental

retardation, and bilateral HL were the most expensive of these sequelae in the year following the index hospitalization, all costing more than €20,000 in the first year.

As a result, policymakers and scientists may find these findings helpful in creating and conducting cost-effectiveness studies of vaccination programs.

29.11 Prevention

Invasive meningococcal disease must be recognized quickly and aggressively treated as soon as possible to reduce mortality. To help improve patient outcomes, early detection and delivery of effective antibiotic treatment, as well as proper management of IMD consequences such as circulatory shock and elevated intracranial pressure, are crucial [50].

Vaccination is the most effective way to avoid ABM and its associated consequences. Highly effective vaccinations are available for the three most common ABM causes. Over the last three decades, the introduction of conjugated vaccines against *H. influenzae* type b, *S. pneumoniae*, and *N. meningitidis* has resulted in a significant reduction in the incidence rate of ABM in countries where these vaccines are included in routine infant and child immunization programs. Routine immunization can lead to the formation of community protection by preventing transmission within a population in an indirect way [55]. The frequency of acquired SNHL in children living in high-income countries has been reduced over the last three to four decades as a result of improved newborn care and the widespread implementation of immunization programs [29].

Vaccination is the only sensible way to prevent IMD and related morbidity and mortality. In spite of the fact that the primary goal of the meningococcal vaccines is to avoid severe and, in many cases, deadly complications, a secondary benefit would be a reduction in disease-related consequences such as HL, which can lead to long-term handicaps in survivors. After meningitis, the onset of SNHL might be unpredictable. Hearing loss and seizures are most common in children under the age of 1 year, while skin scarring and amputation are most common in children between 1 and 4 years. These consequences are all likely to have a long-term influence on health and healthcare expenses, so they are crucial to consider when weighing the benefits of routine meningococcal immunization.

Immunization is provided in certain countries through national immunization programs (NIPs), whereas in others, vaccination is only offered to high-risk populations or for outbreak control. To maximize coverage, it is best to include vaccination using NIPs. The country- and serogroup-specific incidence of *N. meningitidis* by age group is the most critical component in vaccination recommendations. It underscores the significance of ongoing surveillance to ensure vaccines available to those who need them most quickly. Immunizing children and high-risk patient populations with existing meningococcal vaccines may minimize disease among vaccines, prevent outbreaks, and drastically limit *N. meningitidis* transmission. To reduce IMD-related morbidity and death, global coordinated, sustained, and long-term policies and active surveillance are urgently needed in all nations.

29.12 Conclusion

Invasive meningococcal disease is still a significant public health concern worldwide, not only because of its high mortality rate but also because of its severe disabling sequelae, such as HL. Vaccination of children and high-risk patient populations may minimize *N. meningitidis* transmission, IMD burden, and IMD-related complications. It is best to implement meningococcal vaccines into NIPs to reduce the rates of IMD-related mortality and morbidity, including HL.

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Haemophilus influenzae Type b Meningitis in Children and Hearing Loss

30

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30.1 Introduction

Haemophilus influenzae was discovered in 1889 by Richard Pfeiffer during the influenza pandemic and was named influenza bacillus [1]. Since it requires blood factors for growing, the bacterium was renamed *Haemophilus*, meaning "*blood loving*." This gram-negative coccobacillus colonizes the nasopharynx and upper respiratory tract in humans. Depending on the presence of a polysaccharide capsule, isolates of *H. influenzae* can be encapsulated (typeable) or nonencapsulated (nontypeable) strains. *Haemophilus influenzae* has six encapsulated serotypes, a–f [1, 2]. *Haemophilus influenzae* capsular serotype type b (Hib) is a significant cause of invasive diseases in nonimmunized populations, accounting for 95% of all strains [2, 3].

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30.2 Epidemiology

Haemophilus influenzae type b is a human pathogen, and no known host exists other than humans [4]. Nasopharyngeal colonization, especially by nonencapsulated strains, is common. The transmission mode is mainly by droplet inhalation or direct contact with secretions from the respiratory tract. During the pre-vaccine era, most young children were colonized with Hib, the commonest cause of bacterial meningitis and other invasive diseases [3]. After the first Hib vaccine was accredited in 1989, there has been a dramatic decrease in the incidence of Hib invasive disease in countries with high vaccination rates [5]. The incidence of Hib invasive disease decreased by nearly 99% in children under 5 years in the United States of America (USA) [6]. Children below 18 months have the highest risk for invasive Hib disease, with a peak incidence between 6 and 9 months; the risk decreases gradually after 2 years of age [2].

Due to maternal antibodies passed through the placenta and breastfeeding during the first 6 months, some infants have protection against Hib [3]. Antibodies to the polysaccharide capsule, composed of polyribosyl-ribitol-phosphate (PRP), confer protection against invasive Hib infections. Systemic Hib disease is rare after 6 years of age because of naturally acquired antibodies to PRP [4]. Invasive Hib diseases currently occur in unimmunized children. After the extensive usage of the conjugate vaccine, invasive *H. influenzae* disease in the USA is predominantly caused by non-type b serotypes and non-typeable strains [7]. *Haemophilus influenzae* type b is still one of the leading causes of invasive infections in low-income countries where vaccines are unavailable [2, 8].

30.3 Microbiology

Haemophilus influenzae type b is a nonmotile, nonspore-forming, pleomorphic gram-negative coccobacillus that can grow in aerobic or anaerobic conditions. The organism requires two supplements for in vitro growth; X factor (hemin), heat-stable, and V factor (nicotinamide-adenine-dinucleotide), heat-labile. *Haemophilus influenzae* type b can be cultured in most media enriched with X and V factors. These factors are present in erythrocytes and permit the organism to grow on chocolate agar. The need for these factors differentiates Hib from other *Haemophilus* species under laboratory conditions. Clinical samples should be immediately inoculated onto appropriate media because Hib is a fastidious microorganism, and its viability is lost rapidly. Some strains benefit from incubation with 5–10% carbon dioxide [4, 8].

Haemophilus influenzae type b has several virulence factors. The polysaccharide capsule, the most important virulence factor, prevents phagocytosis and complement-mediated lysis. Other virulence factors are noncapsular cell wall proteins, immunoglobulin A (IgA) proteases, and lipooligosaccharide (LOS) [2, 8]. Additionally, the binding of Hib to mucus and the respiratory epithelium is mediated by pilus and non-pilus adherence factors. Variation of bacterial antigen, entrance into host cells,

penetration between host cells (paracytosis), LOS changes, and formation of biofilm influence persistence on mucosal surfaces [1].

Determining the capsular type expressed by Hib is essential for clinical and epidemiological purposes. Polymerase chain reaction (PCR) techniques targeting the capsular gene locus (*cap* locus) have been developed to accurately identify strains expressing the six recognized capsular types. These techniques benefit patients whose cultures are negative because of previous antibiotic use [2, 6]. Due to their low sensitivity and specificity, antigen detection methods are not recommended.

30.4 Pathogenesis

Haemophilus influenzae type b infection begins with colonizing respiratory mucosal membranes with microorganisms. Otitis media, sinusitis, conjunctivitis, bronchitis, and pneumonia may develop after colonization. Anatomic factors, antecedent viral respiratory tract infections, especially influenza virus infection, immunodeficiencies, and exposure to cigarette smoke are among predisposing factors for respiratory tract disease. *Haemophilus influenzae* type b can penetrate the nasopharyngeal epithelium from the upper respiratory tract mucosa and spread to the bloodstream. Bacteremia precedes nearly all invasive Hib diseases, but direct extension from adjacent sinusitis, otitis media, or conjunctivitis may occur in some situations. The polysaccharide capsule protects Hib from phagocytosis, and the bacterium can survive and disseminate to distant sites, more commonly to the meninges [1, 2, 4].

30.5 Clinical Manifestations

Haemophilus influenzae type b usually causes severe diseases and requires hospitalization, especially in infants. The most typical clinical presentations of Hib infection are epiglottitis, otitis media, pneumonia, bacteremia, meningitis, cellulitis, septic arthritis, and purulent pericarditis [6].

30.5.1 Meningitis

Meningitis is the most familiar and gravest clinical presentation of invasive Hib disease, accounting for 40–75% of invasive cases [8]. The signs and symptoms are usually nonspecific and may include fever, vomiting, irritability, and lethargy, particularly in young infants. Classic findings of bacterial meningitis, including headache, photophobia, and meningismus, are seen in older children. Infants often do not have nuchal rigidity. Occasionally, fulminant Hib meningitis may occur with seizures, coma, and respiratory arrest. Cranial nerve palsy indicates increased intracranial pressure. In addition, petechial or purpuric rash and shock may occur [1]. Between 10% and 20% of children with meningitis have cellulitis, arthritis, or pneumonia concomitantly [2, 6]. Subdural effusion is a common complication. Clinicians

should be alert if seizures, mainly focal, hemiparesis, or neurologic deterioration, occur [4].

30.6 Diagnosis

Blood cultures are important in any febrile child at risk of Hib disease. The focal illness may develop in 30–50% of patients with occult Hib bacteremia, so these children should be reevaluated carefully [2, 8]. Collected body fluids such as blood, cerebrospinal fluid (CSF), pleural fluid, or synovial fluid should be cultured on appropriate media [3, 8]. Cerebrospinal fluid analysis is necessary to identify the causative organism and antibiotic test sensitivity. Pleocytosis with a predominance of polymorphonuclear leukocytes is typically seen in CSF analysis. Most patients with meningitis have hypoglycorrhachia and an elevated CSF protein concentration. Cerebrospinal fluid lactate may distinguish bacterial meningitis from aseptic meningitis, except in patients who received antimicrobial treatment before the lumbar puncture [5]. Approximately 70–80% of patients with Hib meningitis have a positive CSF gram stain [1, 2]. Positive CSF culture is the gold standard for diagnosing Hib meningitis [2]. All isolates of *H. influenzae* are supposed to be serotyped. A slide agglutination test may detect capsular polysaccharide antigens in CSF but has low sensitivity and specificity [3]. Serotype-specific real-time PCR assays can detect each serotype and be used to diagnose Hib meningitis, especially when antibiotics were previously administered [3, 9].

30.7 Treatment

30.7.1 Antibiotic Therapy

Since mortality reaches nearly 100% without treatment, Hib meningitis should be diagnosed and treated promptly. Antimicrobial therapy should be initiated swiftly for a good prognosis. The treatment of choice for Hib meningitis is third-generation cephalosporins. Cefotaxime (200–225 mg/kg/day, every 6 h) or ceftriaxone (100 mg/kg/day, every 12 h) are potential bactericidal drugs against Hib [10]. An intravenous administration of antimicrobials should be considered to achieve high CSF levels [1]. Treatment usually takes 7–10 days for noncomplicated cases [8].

30.7.2 Corticosteroids

Administration of dexamethasone with antibiotics is recommended in children older than 6 weeks with Hib meningitis, decreasing the rate of neurological sequelae and sensorineural hearing loss (SNHL) [11]. Dexamethasone (0.15 mg/kg every 6 h) should be started just before or concurrently with the first dose of antibiotics in the first 4 days of treatment [1, 2, 8]. Dexamethasone can still be administered up to

4 h after starting the first dose of antibiotics [12]. However, dexamethasone should be used carefully in bacterial meningitis as it may lead to low penetration of antibiotics (e.g., vancomycin) into the CSF. Dexamethasone may cause fever recurrence and change the clinical and bacteriological response to antimicrobial treatment [9].

30.8 Complications

Subdural effusion or empyema, cerebritis, ventriculitis, intracerebral abscess, cortical infarction, cerebral herniation, and hydrocephalus are among the most common complications of Hib meningitis [2]. The leading neurologic sequelae are seizures, SNHL, vision impairment, and behavior abnormalities. *Haemophilus influenzae* type b meningitis has a mortality rate of 3–6% [8].

30.9 *Haemophilus influenzae* Type b Meningitis and Hearing Loss

Bacterial meningitis is the commonest cause of acquired SNHL in children [13]. Although Hib meningitis was the most common type in the pre-vaccine era, SNHL occurred most often in children with pneumococcal meningitis. Despite adequate treatment regimens, SNHL is a significant neurological sequela of Hib meningitis. In a study about acute-phase neurologic complications of Hib meningitis, 42% (53/126) of patients had at least one acute-phase complication on neurologic examination, while 12% (15/126) had SNHL [14]. In another study, where 185 infants and children with acute bacterial meningitis (64% with Hib meningitis) were followed up for 15.5 years (mean duration was 8.9 years) for neurological abnormalities, persistent SNHL was detected in 18 (10%) patients [15]. Several reports reported SNHL in 5–10% of the patients with Hib meningitis [1, 16, 17]. In Africa, the risk of SNHL in Hib meningitis may be up to 26% [18].

Predictors of SNHL include delayed presentation, delayed initiation of antibiotics, young age, severe illness, raised intracranial pressure at admission, reduced CSF glucose, and elevated CSF protein [17–20]. In a prospective study involving 44 infants and children with Hib meningitis, patients were grouped according to their pretreatment concentrations of bacteria in CSF [21]. The study revealed that patients with greater than or equal to 10^7 colony-forming units (CFUs) of Hib/ml in CSF before treatment were more likely to have neurologic sequelae, including SNHL, than those with less than 10^7 CFUs of Hib/ml in CSF. The authors concluded that the concentration of bacteria in CSF predicts SNHL in Hib meningitis. High endotoxin concentrations at the time of diagnosis in CSF correlated with permanent neurologic complications, including SNHL, in patients with Hib meningitis was also demonstrated [22].

The main pathogenic steps required for initiating Hib meningitis include bacterial colonizing the mucosa, spreading to the surrounding tissue, into the bloodstream, invading the meninges, replicating, and inflammation of the subarachnoid

space. Corticosteroids have known potent activities in limiting inflammation. Corticosteroids were used to manage bacterial meningitis to minimize the subarachnoid space inflammation and decrease several manifestations such as vasogenic brain edema, increased intracranial pressure, cerebral blood flow changes, cerebral vasculitis, and neuronal injury [23–25]. The effect of corticosteroids on mortality rate, HL, and other neurologic sequelae has been evaluated. Proof of clinical advantage was most prominent for audiologic results.

Numerous clinical trials focused on the impacts of corticosteroids on audiologic outcomes in patients with Hib meningitis. In a double-blind, placebo-controlled research, patients were given cefuroxime or ceftriaxone in addition to either dexamethasone or placebo, 13 of 84 placebo group patients (15%), and 3 of 92 patients in the dexamethasone group (3.3%) had moderate or more severe bilateral HL. The efficacy of dexamethasone on SNHL was documented only for patients having Hib meningitis. In this study, there were too few patients with meningitis by other organisms to assess whether dexamethasone has the same effect in these cases [26]. One prospective, multicenter, placebo-controlled clinical trial with 143 children with bacterial meningitis demonstrated no significant overall difference between patients given dexamethasone and those given a placebo for SNHL. The only subgroup where a benefit was observed with dexamethasone was that of patients with Hib meningitis [27]. In the following years, several reviews of the studies advocated the benefit of supplementary dexamethasone in hearing outcomes of infants and children suspected or proven to have Hib meningitis [28–30].

In 2010, a meta-analysis of 24 studies involving 4041 participants showed that corticosteroids obviated severe HL and any HL in children with bacterial meningitis. Analysis of subgroups for causative organisms indicated that corticosteroids minimized severe HL in Hib meningitis [31]. A recent meta-analysis of 25 studies involving 4121 participants (2511 pediatric patients, most children had meningitis due to Hib) showed that corticosteroids minimized severe HL in children with Hib meningitis but not in children with meningitis of non-*Haemophilus* species. Further analysis of the country's income level where the individual studies were conducted indicated that dexamethasone decreased the severe HL rate among children in high-income countries but not in low and middle-income countries [11].

In experimentally induced Hib meningitis, a single ceftriaxone dose given intravenously resulted in a significant increase in LOS and tumor necrosis factor-alpha (TNF-α) concentrations in CSF 2 h later, as compared with the levels in untreated animals. Dexamethasone significantly reduced TNF-α concentrations and indexes of meningeal inflammation in CSF when administered with antibiotic simultaneously, but not if it was given 1 h later [32]. Similarly, concentrations of free endotoxin and TNF-α in CSF increased 2–6 h after the first dose of ceftriaxone in infants with Hib meningitis [33]. In another placebo-controlled, double-blind trial of dexamethasone treatment in Hib meningitis, including 101 infants and children, patients received either dexamethasone or a placebo with cefotaxime. When dexamethasone was administered before the initiation of cefotaxime treatment (15–20 min before), the indexes of meningeal inflammation and concentrations of cytokines in CSF improved rapidly and significantly compared with the patients given only

cefotaxime [34]. It is generally recommended that adjunctive dexamethasone be beneficial if given just before or concurrently with the first antimicrobial agent(s) dose in Hib meningitis [28]. It can be explained by the rapid killing of bacteria in the CSF, which releases toxic cell products and can lead to additional neurologic injury [35].

In the early stages of bacterial meningitis, SNHL typically develops and progresses within 48 h [36–38]. Histopathologic studies in animals with Hib meningitis indicate that labyrinthitis is a probable cause of SNHL [36, 39]. The pathophysiology of labyrinthitis associated with bacterial meningitis was investigated by histopathologically examining the inner ears of 114 rats with Hib meningitis [36]. Except for the endolymphatic space, cochlear nerve fibers, and middle ear, the perilymphatic spaces of the cochlea and semicircular canals were inflamed. The inflammation reached a peak 48 h after inoculation. Immunofluorescent staining of cochleae demonstrated the presence of bacteria in the inflamed areas and the endolymphatic space and organ of Corti. In a histopathology study of 41 human temporal bones after death from acute bacterial meningitis, 20 (41%) temporal bones had suppurative labyrinthitis, and the cochlea was affected [40]. While the cochlear aqueduct was the sole pathway for spreading infection in the rabbit, in humans, the modiolus and the aqueduct were potential pathways suggested. It is mainly accepted that the transmission of infection from the subarachnoid space to the labyrinth is the cause of HL, and both the cochlear aqueduct and the cochlear nerve in the modiolus are the potential pathways of the infection extension [41]. Inflammatory cell infiltration, serofibrinous exudate formation, and granulation cells also indicate cochlear pathology [41–43]. Vascular events such as septic emboli and thrombotic occlusion of the cochlear artery and vein result in cochlear hypoxia, ischemia, and neural damage [44]. Inflammatory products such as nitric oxide and superoxide induce cytotoxic injury on the cochlea by destroying the blood–labyrinth barrier [9].

Diagnostic techniques of SNHL are complementary and vary according to the patient's developmental age (cooperative or uncooperative). As soon as SNHL is identified through the screening, age-appropriate testing will be implemented. If a child cannot complete behavioral audiometric tests, otoacoustic emission (OAE) and brainstem auditory evoked response (BAER) testing should be performed, which requires more time and expertise to interpret but elicits more detailed information [45]. Otoacoustic emission tests are rapid and easy to perform. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, OAE is used for screening children with bacterial meningitis [12]. In case of failure, children are referred for a further hearing evaluation, such as BAER testing or speech tone audiometry, according to the patient's age [12].

Imaging the temporal bone and cochlea are needed for profound SNHL after meningitis before cochlear implantation [46]. Computed tomography (CT) or magnetic resonance (MR) imaging may be done depending on the decision of the otolaryngologist. Magnetic resonance imaging can visualize the detailed inner ear anatomy and allows for rapid cochlear implantation if a risk of cochlear obliteration presents itself [47]. Gadolinium-enhanced MR imaging effectively predicted SNHL by detecting labyrinthitis in the early phase of bacterial meningitis in children [48].

Sensorineural HL rehabilitation is vital for normal speech and language and the child's educational and social development. Cochlear implantation is a treatment option in patients with bilateral SNHL after bacterial meningitis [47]. A cochlear implant is a neuroprosthetic device surgically implanted to stimulate the auditory nerve. Cochlear implantation is approved by the USA Food and Drug Administration (FDA) for children aged 12–24 months with profound bilateral SNHL and those older than 24 months with bilateral severe to profound SNHL. No FDA approval exists for implantation in children below 12 months of age. Implantation candidates are also determined through comprehensive audiologic and developmental evaluation [49]. Since any delay decreases the success rates of cochlear implantation because of cochlear fibrosis and calcification, early determination of SNHL secondary to meningitis is crucial [44].

There is a consensus that SNHL should be detected early, and if detected, it should be monitored regularly. Various suggestions exist for the long-term audiologic follow-up of patients with no SNHL at the initial assessment [50–53]. Some countries do not recommend further testing in case of a normal initial hearing test after meningitis [50]. Conversely, several hearing evaluations are recommended after bacterial meningitis in other countries [51]. The ESCMID guideline recommends follow-up testing in patients with no SNHL during the initial hospitalization [12]. Spontaneous SNHL regressions, fluctuations, or progressions may also be observed after recovery from meningitis [41, 42]. A study reported that 8% (5 of 64) and 10% (7 of 71) of children with Hib meningitis had profound SNHL in short- and long-term follow-ups [16]. Another study described progressive HL over 11 years following Hib meningitis [52]. Close monitoring seems helpful for SNHL in patients with Hib meningitis.

30.10 Postexposure Chemoprophylaxis

Postexposure prophylaxis is important for preventing secondary cases. High-risk groups for secondary infection are unimmunized or incompletely immunized children exposed to invasive Hib disease in childcare or household settings [8]. Children below the age of 4 years are at higher risk for Hib disease following household contact [2]. Chemoprophylaxis can eliminate nasopharyngeal colonization and reduce invasive Hib disease risk in susceptible people [1].

Rifampin has been reported to eradicate Hib from the nasopharynx in nearly 95% of carriers. Studies have also demonstrated its effectiveness in preventing secondary invasive Hib cases [6]. A dose of rifampin at 20 mg/kg once daily orally (600 mg maximum) for 4 days, administered for Hib prophylaxis, should be initiated as soon as possible [6]. Prophylaxis with rifampin is to be used for all household contacts in the following conditions: in households having at least one infant below 12 months with incomplete primary Hib vaccine series, in households with at least one child below 4 years that are not fully vaccinated, and in families with an immunocompromised child regardless of their Hib immunization status or age. In addition, prophylaxis is recommended for all contacts if two or more invasive Hib

disease cases happen within 60 days in attendees of a childcare facility and incompletely vaccinated children attend the facility. If the index patient is below 2 years old or a household member with susceptible contact and was treated with a regimen other than cefotaxime or ceftriaxone, prophylaxis will be given at the end of the treatment. As per the immunization schedule, unimmunized or incompletely immunized children are supposed to receive the Hib vaccine.

30.11 Prevention

Routine use of Hib vaccines in infants and children is the most effective prevention method for meningitis. The Hib conjugate vaccine is produced with the conjugation of the Hib capsular polysaccharide PRP to carrier proteins. Conjugate vaccines are highly effective for invasive Hib infections in infants and children. Besides their preventive effects, these vaccines prevent nasopharyngeal colonization with Hib and provide herd immunity [4]. The Hib conjugate vaccine doses are administered at 8 weeks intervals (a minimum of 4 weeks) [8]. The primary series of Hib vaccines have either three doses, administered at 2, 4, and 6 months of age, or two doses at 2 and 4 months, depending on the vaccine products. The first dose may also be administered at 6 weeks of age. A booster dose is administered between 12 and 15 months of age. High-risk groups for invasive Hib disease include children with sickle cell disease, functional or anatomic asplenia, human immunodeficiency virus (HIV) infection, certain immunodeficiency syndromes, bone marrow transplants, and patients receiving chemotherapy [6].

30.12 Conclusion

In children, bacterial meningitis is the leading cause of acquired SNHL [44]. The administration of conjugate vaccines has led to a dramatic decrease in the incidence of Hib meningitis. Despite effective antimicrobial treatment and timely administration of dexamethasone, SNHL may occur in patients with Hib meningitis, so the increased effort for vaccination is essential in preventing the disease. Sensorineural HL has several long-term complications, including speech and language difficulties and intellectual and behavioral disabilities. So, the early determination of HL is critical. Sensorineural HL caused by meningitis can be subtle, especially in infants. Routine follow-up after bacterial meningitis should include a hearing evaluation. There should be a prompt referral of children recovering from bacterial meningitis for audiologic assessment. When SNHL is detected, the child is evaluated for cochlear implantation, the current surgical management of children with SNHL. If there is no HL in initial hearing tests, it is unclear whether follow-up testing is needed. Because fluctuations or progressions of SNHL are reported after bacterial meningitis, close follow-up is required.

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Gram-Negative Bacterial Meningitis in Children and Hearing Loss

31

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31.1 Introduction

The leading gram-negative bacteria causing acute bacterial meningitis (ABM) are *Neisseria meningitidis* (meningococcus), *Haemophilus influenzae* type b (Hib), *Salmonella* spp., *Acinetobacter* spp., *Pseudomonas* spp., and enteric gram-negative bacilli, including mainly *Escherichia coli*, and *Klebsiella* spp. This chapter primarily focuses on ABM caused by gram-negative bacteria, with neurological complications, especially hearing loss (HL), and its evaluation. In addition, the general characteristics of ABM will also be briefly discussed to highlight the distinctive features of ABM caused by different pathogens.

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31.2 Etiology

Gram-negative bacteria, mainly *N. meningitidis*, Hib, and *E. coli*, are the significant agents of ABM. Gram-negative bacilli are among the common causes of ABM, especially in newborns and infants younger than 3 months [1]. Gram-negative bacilli are a common cause of healthcare-associated meningitis but rare as community-acquired meningitis causes in older children and adults [2]. Gram-negative bacteria may cause infection in immunocompromised children and children with a ventriculoperitoneal shunt (VPS).

Pseudomonas species meningitis may occur following chronic cranial osteomyelitis, a rare complication of mastoiditis or trauma, and may also be seen in children with immunodeficiencies. *Citrobacter diversus* is a rare cause of meningitis in newborn infants but is associated with significant morbidity and mortality. One-third of newborns with *Citrobacter* meningitis die, and most survivors have significant neurological sequelae. Brain abscess is a common complication in neonatal *C. diversus* meningitis [3]. *Citrobacter freundii* and *C. diversus* are rare causes of meningitis in children and adults [2].

31.3 Epidemiology

In a surveillance study conducted in the United States of America (USA) between 2006 and 2007, the annual incidence of ABM was 81/100,000 in children <2 months, 7/100,000 between 2 months and 2 years, 0.6/100,000 in 2–10 years, and 0.4/100,000 in 11–17 years [4]. After the immunization programs for Hib and pneumococci with conjugate vaccines, the incidence of ABM decreased in all age groups. However, the incidence remains high in infants under 2 months of age, where the effects of vaccines have not yet been seen [2].

Infants less than 3 months (≤90 days) are more vulnerable to infections than the other age groups. Causative pathogens of meningitis may vary according to age [5–8]:

- Newborn (0–28 days): Group B streptococcus (GBS), *E. coli*, and other gram-negative bacilli are the primary causative pathogens in neonatal ABM.
- Infants <3 months (29–90 days): Group B streptococcus, *E. coli*, other enteric gram-negative bacilli, *Streptococcus pneumoniae* (pneumococcus), *N. meningitidis*, more rarely *Enterococcus* spp., *Staphylococcus aureus*, *Listeria monocytogenes*, group A streptococcus (GAS), and Hib may be seen [3, 5].
- Infants >3 months (≥90 days) and children: *Streptococcus pneumoniae* and *N. meningitidis* are common pathogens. Group A streptococcus, GBS, Hib, and other gram-negative microorganisms are less commonly seen.
- In adolescents: *Neisseria meningitidis* is the most common pathogen [3, 5].

Escherichia coli, *Klebsiella* spp., and *Pseudomonas* spp. cause %14 cases of gram-negative ABM in infants worldwide [9].

According to geographical regions, pneumococci in North America and meningococci in Europe and sub-Saharan Africa are the most common causes of ABM [3, 5]. Meningococcal serogroup B and A meningitis are more common in Europe and Africa, respectively [3, 5]. However, meningococcal serogroup distribution may change over the years, even in the same geographical area. So, the actual epidemiology-based variations of different countries or regions should be checked for pretravel vaccination [3, 5].

Gram-negative bacillary meningitis primarily occurs in specific situations, including neonatal, post-traumatic, healthcare-associated, post-brain surgery, and spontaneous gram-negative meningitis in adults and VPS infections [3, 5]. Most neonates with meningitis are infected with *E. coli* strains containing K1 capsular polysaccharides, which can help the organism to be saved from host defense [3, 5]. In newborns and infants, gram-negative bacillary meningitis may be associated with neural tube defects and urinary tract anomalies. Any condition that disrupts the dura mater integrity, such as neurosurgery or trauma, may predispose to meningeal infection and cause gram-negative bacterial meningitis. This probability is relatively increased when antimicrobial prophylaxis is given predominantly for gram-positive coverage to prevent surgical site infection [2, 5].

31.4 Pathogenesis and Pathophysiology

The most common mechanism in the invasion of the causative agent to the central nervous system (CNS) is the nasopharyngeal colonization of the pathogen, such as Hib, meningococcus, and pneumococcus, usually acquired by droplets first, then passing through the blood circulation and penetrating the subarachnoid space from the capillary endothelium.

The second way is the direct entry of the microorganism to the CNS by contiguous infections, such as complicated sinusitis, mastoiditis, septic cerebral venous thrombus, or by direct spread from a congenital neural tube defect or cerebrospinal fluid (CSF)-related pilonidal sinus, trauma, neurosurgery, CSF leakage, or through medical devices such as VPSs, and cochlear implants. This pathogenetic mechanism is more likely for gram-negative bacillary meningitis. However, in cases of dural tear and/or CSF leakage secondary to head trauma, pathogens that tend to colonize the mucosa and skin, such as pneumococci and staphylococci, may also be seen.

Thirdly, meningitis may develop with the invasion of the CNS following bacteremia from a different localized source, such as a catheter infection, infective endocarditis, or complicated urinary tract infection [5]. This mechanism is more common in patients with immunodeficiencies, such as meningococcal meningitis in terminal complement deficiencies.

Most significant meningitis pathogens have surface components such as fimbriae or pili that increase mucosal colonization. Meningococci use a variety of receptors, including the platelet-activating factor receptor, beta-2 adrenergic receptors, and CD147, for adhesion through type IV pili. Outer membrane proteins (OpC and OpA) also contribute to establishing and maintaining adhesion [10, 11]. Also,

bacterial encapsulation is a significant virulence factor for nasopharyngeal colonization and systemic invasion of pathogens [12]. The polysaccharide capsules of the primary meningitis pathogens, including *S. pneumoniae*, *N. meningitidis*, Hib, GBS, and *E. coli*, inhibit phagocytosis by preventing the accumulation of adhesins such as complement factors [12].

Bacterial entry into the subarachnoid space is facilitated by the intensity and duration of circulating bacteria, the virulence of the microorganisms, and the degree of host defense deficiency, such as immunodeficiency. Also, it occurs through the interaction of bacteria with endothelial cells forming the blood–brain barrier (BBB). In Hib and *S. pneumoniae* meningitis, evidence exists that the initial bacterial entry site into the ventricle and spread to the CSF may be the choroid plexus [12–14].

Although some structural differences exist between the lipooligosaccharide (LOS) of *N. meningitidis* and the lipopolysaccharide (LPS) of gram-negative bacilli, both generally contribute to infection by a similar pathogenetic mechanism. Lipooligosaccharide is commonly found in gram-negative pathogens such as pathogenic *Neisseria* spp., *H. influenzae* types, *Haemophilus ducreyi*, *Moraxella* spp., and *Bordetella* spp. that infect non-enteric surfaces. The oligosaccharide portions of the LOS contain structures that mimic human tissue antigens (e.g., paragloboside, pk, i antigen, Lewis X, and sialyl-Lewis X) [15]. Lipooligosaccharide interacts with various cells, including neutrophils, macrophages, and endothelium, to initiate the release of inflammatory mediators of shock state, mainly tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, and interferon-gamma (IFN-γ). Symptoms of meningococcal sepsis are caused by LOS, which acts as an endotoxin and activates proinflammatory cytokine pathways of the host [16].

The highest plasma levels of endotoxin measured in sepsis have been demonstrated in patients with meningococcemia. The ability of the organism's outer membrane to scatter heavily into bubbles or vesicle-like structures is a significant factor in producing these high endotoxin levels. Although the endotoxin release in the membrane bleb form is highest in meningococci, it was also documented in several other gram-negative bacteria, including *Salmonella*, *Shigella*, *E. coli*, *Citrobacter*, and *Haemophilus* spp. [16].

Immunoglobulin and complement are at very low levels in CSF, at concentrations nearly 1000 times lower than in serum, resulting in poor opsonic activity in CSF. After the invasion of CSF, bacteria can multiply to high concentrations (up to 10^7 organisms/mL) within hours due to insufficient humoral immunity in CSF [12]. When inflammation begins, cerebrovascular autoregulation and vasogenic edema occur; intracranial pressure increases due to the separation of tight junctions between cells in the BBB endothelium [12, 17].

31.5 Clinical Features

In many children with ABM, fever and meningeal inflammation symptoms develop. Some children with ABM present fulminant meningitis symptoms and signs rapidly within a few hours. The fulminant course is often complicated by severe cerebral

edema. If meningitis develops after VPS, pilonidal sinus, or adjacent tissue infections, such as mastoiditis, initial respiratory tract infection findings may not be prominent.

The clinical features and treatment of ABM show significant differences in newborns, preterm infants, postneonatal infants, and children.

31.5.1 Clinical Features in Newborns and Premature Infants

Clinical findings of ABM in newborns and preterm infants may not differ from sepsis without meningitis and may be very similar. Therefore, the possibility of ABM should be kept in mind in every neonatal sepsis case. Decreased activity, poor feeding, difficulty in sucking, respiratory distress, temperature irregularities, fever (rectal temperature >38 °C more common in term infants), hypothermia (rectal temperature <36 °C more common in preterm infants), neurological findings such as decreased tone, irritability, sleeplessness, inclination, and convulsions are the most common clinical findings [17].

Neonatal meningitis is also more likely to have other intracranial and neurological complications, such as hydrocephalus, than other age groups. However, even in newborns with neurological complications, symptoms and physical examination findings may be very ambiguous, so these babies should be evaluated frequently and carefully by experienced pediatricians. If necessary, imaging studies should be performed for complications in suspected cases.

Laboratory findings may accompany sepsis-related laboratory findings such as blood culture positivity, leukocytosis, leukopenia, neutrophilia, neutropenia, increased immature/total white blood cell ratio, thrombocytopenia, and elevated c-reactive protein (CRP) and procalcitonin levels. In addition, abnormal CSF findings may be seen, including pleocytosis, increased neutrophil count, increased protein and low glucose concentrations, bacteria on Gram stain, and CSF culture positivity. Transfontanel ultrasonography (US), contrast-enhanced computed tomography (CT), or contrast-enhanced magnetic resonance (MR) imaging are recommended for neurological complications.

31.5.2 Clinical Features in Postneonatal Infants and Children

Infants with ABM mainly present clinical findings such as fever or hypothermia, irritability, lethargy, poor feeding, vomiting, bulging fontanel, and seizures. Children and adolescents may present clinical findings, including fever, headache, vomiting, irritability, confusion, lethargy, neck stiffness, and photophobia [5]. Fever, seizures, and vomiting are the most common findings in children with ABM [18, 19]. Also, in the study of Amorilyo et al. [19], photophobia was highly specific (88%) but lowly sensitive (22%) for meningitis.

Generally, upper respiratory tract infection symptoms and signs begin before meningeal symptoms. Previous oral antimicrobials do not change the clinical

manifestations of meningitis. Children with ABM often appear restless and sick. Vital sign anomalies such as tachycardia and tachypnea may be seen, especially in young children. Meningeal symptoms, including neck stiffness, and Kernig's and Brudzinski's signs, are present in many children with ABM at presentation [5].

In physical examination, signs of increased intracranial pressure (IIP), seizures, and other focal neurological findings may be seen in addition to irritability, confusion, and lethargy. The level of consciousness at presentation may range from irritability, confusion, and lethargy to coma associated with poor prognosis and adverse neurological outcomes [5]. While symptoms have been occurring, the signs of meningitis may not be fully established yet; however, pleocytosis and other CSF findings compatible with ABM may exist.

Seizures mainly occur before or within the first 48 h of hospital admission in about 20–30% of patients with ABM [20]. Usually, generalized seizures are seen. Later, focal seizures indicating cerebral damage may occur [5]. In a study, seizures were present in 92.5% of 361 children with ABM [18].

Bulging fontanelle and diastasis of the cranial sutures may occur in infants with IIP. Other clinical IIP signs may not be apparent in infants with open fontanelles. In a study on children with suspected meningitis, bulging fontanelle was present in 50% of children with meningitis and had a positive predictive value of 38% [19]. On the other hand, in older children with closed fontanelles, vomiting, headache, and consciousness changes may be seen earlier with IIP. Cushing's triad, composed of bradycardia, hypertension, and respiratory irregularity, indicating cerebral herniation, is a late manifestation. Involvement of the third, fourth, and sixth cranial nerves and papilledema, a rare finding in ABM, also suggest IIP. If papilledema occurs, complications such as sinus vein occlusion, subdural empyema, or brain abscess should be investigated [5].

Motor abnormalities, including asymmetrical or absent tendon reflexes, hemiparesis, quadriparesis, and consequences of cranial nerve injuries such as facial asymmetry, eye deviation, extraocular movements, abnormal pupillary light reflexes, and visual field defects, may be seen as focal neurological findings, generally as late complications of meningitis [5]. A study involving 235 children with ABM, aged 4 days to 18 years, mean 26 months, followed for 1 year, reported that 10% of the cases had focal neurologic findings at presentation. Focal neurologic findings at admission were associated with an increased risk of permanent neurologic and cognitive abnormalities 1 year after discharge [21].

In children with ABM, serious complications such as disseminated intravascular coagulation (DIC), septic shock, pericardial effusion, acute respiratory distress syndrome, septic arthritis, and reactive arthritis may accompany the clinical picture, primarily due to bacteremia. Skin eruptions like petechiae and purpura may occur mostly in ABM caused by *N. meningitidis*. Lesions are more prominent on the extremities following an erythematous maculopapular rash [5]. Patients may also have continuing infections such as sinusitis, facial cellulitis, otitis media, pneumonia, or arthritis [2, 5].

31.6 Laboratory and Radiological Evaluation

31.6.1 Blood Tests

In cases with suspected ABM, complete blood count, glucose, serum electrolytes, creatinine, blood urea nitrogen, inflammatory markers such as CRP and procalcitonin, coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) should be analyzed. Blood cultures are positive in approximately 67–86% of cases with ABM [22, 23]. About 50% of adult patients with gram-negative bacillary meningitis may have bacteremia before the clinical manifestation of meningitis [5, 24].

31.6.2 Cerebrospinal Fluid Evaluation

The definitive diagnosis of meningitis is made by CSF evaluation. In practice, lumbar puncture (LP) indication arises when meningitis is considered clinically. If CSF findings suggest ABM, empiric antibiotics should be started immediately [5].

31.6.2.1 Contraindications for Lumbar Puncture

Cardiopulmonary failure, gushing vomiting episodes, IIP, papilledema, cranial nerve involvements suggesting IIP, and skin infection over the LP region are the primary contraindications for LP. Clinical findings related to IIP should be investigated before performing LP. And especially in older children with closed fontanelles, CT is an appropriate method to exclude pre-LP IIP or an intracranial space-occupying mass such as a brain abscess or tumor. Lumbar puncture should be performed immediately after imaging if an IIP finding or an intracranial mass lesion is not visualized [5].

Antimicrobial treatment should not be delayed because of the need for cranial imaging and contraindication for LP. Blood samples for tests and cultures should be taken immediately, and empirical antibiotics administered. A single dose of antibiotics administered before LP does not significantly alter CSF leukocyte count, protein, or glucose and may slightly reduce rates but generally does not affect CSF Gram-staining and culture results [5, 25].

The probability of detecting bacteria in Gram-staining may be pathogen related. In pneumococcal meningitis, approximately 80–90%, and in meningococcal meningitis, 70–80% of pediatric patients have positive CSF Gram-staining. But, CSF Gram-staining is positive for half and one-third of the patients with gram-negative bacillary and *Listeria* spp. meningitis, respectively [5]. O Gram-stained smears, gram-positive diplococci suggest *S. pneumoniae*, small pleomorphic gram-positive cocci, and coccobacilli GBS, gram-positive bacilli and coccobacilli *L. monocytogenes*, gram-negative diplococci *N. meningitidis*, and gram-negative coccobacilli *H. influenzae*. Although Gram-staining helps estimate the causative pathogen, broad-spectrum antibacterial treatment should be continued until CSF culture results are obtained [5].

More than 50% of adult patients with gram-negative bacillus meningitis have the bacilli on Gram-staining [24]. In a study of 66 patients with culture-proven gram-negative meningitis in children, CSF Gram-staining was positive in 61% of the cases [1]. Gram-staining was negative in all patients with sterile CSF cultures in the same case series. In rare cases, CSF Gram-staining results may be false-negative or false-positive; therefore, a negative or positive Gram-staining result, although important, should not be the only guide for empirical treatment [2, 24].

31.6.2.2 Cerebrospinal Fluid Examination

In CSF examination, cell count, cell distribution, glucose and protein concentrations, Gram stain, and culture should be seen. Typically in ABM, increased CSF pressure (>25 cm H_2O), neutrophilic pleocytosis (>100/cubic millimeter [mm^3; microliter, μL] usually thousands, usually >50–70% polymorphonuclear leukocyte [PMN]), low glucose (<40 mg/dL or CSF/serum glucose ratio <40%), elevated protein (>45 mg/dL, usually >100 mg/dL) is detected. In CSF Gram-staining, bacteria and PMN-weighted leukocytes may be seen, and bacteria can be detected by CSF culture or polymerase chain reaction (PCR) test. Cerebrospinal fluid lactate (usually >30 mg/dL) and lactic dehydrogenase (LDH) levels (usually >20 U/L) may be measured in ABM. Cerebrospinal fluid lactate level may be helpful when CSF is bloody or routine tests show unsatisfactory results [5].

Normally, leukocytes are not expected to be found in CSF. Generally, >5/mm^3 leukocytes and >1/mm^3 PMNs are considered abnormal. In cases where the CSF is traumatized, the "corrected" CSF leukocytes are calculated. Accordingly, roughly 1 leukocyte/mm^3 is subtracted for every 1000 red blood cells (RBCs)/mm^3. Cerebrospinal fluid protein concentration in children with traumatic LP may be increased due to increased protein concentration in plasma and protein secretion from lysed erythrocytes. The “corrected” CSF protein concentration is roughly calculated by subtracting 1 mg/dL for every 1000/mm^3 RBCs [5].

The use of oral antibiotics before the diagnosis of ABM may change the results of CSF biochemistry, although it does not significantly affect cytology [5].

Cerebrospinal fluid culture positivity confirms the diagnosis. A CSF culture should be obtained in all suspected cases of ABM. Cerebrospinal fluid culture may be positive without pleocytosis at the onset of infection [5].

Cerebrospinal fluid culture may not be positive in children treated with antibiotics before LP, especially in meningococcal meningitis. In meningococcal meningitis, CSF rapidly becomes sterile after the parenteral administration of antibiotics. In such cases, nucleic acid amplification tests or PCR-based molecular methods are used to confirm the diagnosis of CNS infections [5]. Cerebrospinal fluid cultures are also negative in epidural or subdural abscesses [5].

A blood culture should also be obtained in a child with suspected meningitis. Blood culture positivity strongly supports the diagnosis of ABM. Nasopharyngeal or throat cultures do not help determine the etiology.

31.6.2.3 Cerebrospinal Fluid Examination in Newborns and Premature Babies

Some differences exist in CSF evaluation in newborns and preterm infants compared to older children. In general, the number of CSF cells is higher (usually up to 10/mm^3), glucose levels are lower (may be as low as 30 mg/dL in term newborns, 20 mg/dL in premature newborns), protein levels are slightly higher (100 mg/dL in term newborns, may be up to 120–160 mg/dL in premature babies). Cerebrospinal fluid leukocyte count >9/mm^3 in infants <3 months and >6/mm^3 in infants ≥3 months of age are generally considered abnormal. Therefore, the combined evaluation of findings in newborns and premature babies becomes more important. The cell count in neonatal gram-negative meningitis was generally higher than in group B streptococcal meningitis [26, 27].

31.6.3 Cranial Imaging

Computed tomography or contrast-enhanced MR imaging in case of mental status change (coma), papilledema, focal neurological deficit (except sixth or seventh cranial nerve palsy), presence of CSF shunt, history of hydrocephalus, recent head injury, or neurosurgery operation is recommended [5]. In addition, contrast-enhanced cranial imaging is recommended in all neonatal meningitis, gram-negative ABM, and all meningitis with a complicated clinical course. Magnetic resonance imaging is advantageous because it does not contain radiation and shows soft tissues better. However, it can be counted among the disadvantages of being expensive, not being available everywhere, and requiring anesthesia in small babies and children due to the extended shooting time.

Neuroimaging (transfontanellar cranial ultrasonography, CT, MR) is recommended routinely in newborn ABM because of a more complicated course compared to older infants and children. Cranial ultrasonography is the most commonly performed examination, especially in the early stages of infection. It is beneficial for detecting intraventricular hemorrhage and measuring ventricular size. It can also show ventriculitis, echogenicity, abnormal parenchyma, and extracerebral fluid collections. It also provides bedside imaging in clinically unstable patients and allows for follow-up. In the early period, CT and MR imaging may show cerebral edema, ventricular obstruction, infarction, abscess, and subdural fluid collections. Later in treatment, contrast-enhanced MR imaging or CT helps detect cerebral abscesses, areas of persistent cerebritis, infarction, or encephalomalacia, and the degree of cerebral cortical and white matter atrophy. Contrast-enhanced neuroimaging should be performed in all neonates with meningitis caused by organisms prone to intracranial abscess formation, including *Citrobacter koseri*, *Serratia marcescens*, *Proteus mirabilis*, and *Enterobacter sakazakii* [28].

31.7 Differential Diagnosis

Acute bacterial meningitis should be suspected if there are signs of meningeal irritation on physical examination of a child who presents with fever, headache, vomiting, and/or changes in consciousness. In addition, ABM should be considered in a child with any (serious) signs of infection accompanied by neurological signs. The diagnosis of ABM is confirmed by CSF culture positivity, blood culture positivity with CSF pleocytosis, and detection of bacteria in CSF by molecular methods [5].

31.8 Treatment

Children with suspected ABM require prompt administration of appropriate antimicrobial therapy, immediate evaluation, and treatment (Table 31.1). Mortality in untreated ABM is close to 100%. Even with optimal treatment, morbidity and mortality can occur, and neurological abnormalities are common among survivors [5].

31.8.1 General Principles

31.8.1.1 Supportive Measures

The basic supportive measures include appropriate respiratory support, venous access for patients with hypoxia or respiratory distress, and appropriate hemodynamic support for children presenting with signs of shock. Supportive measures include treating metabolic problems such as hypoglycemia, electrolyte abnormalities, and acidosis, and treating seizures if present [29].

Table 31.1 Commonly used antimicrobial agents for acute bacterial meningitis in children

Antimicrobial agents	Doses
Penicillin G	300,000 units/kg/day, IV, in 4 doses
Ampicillin	300–400 mg/kg/day, IV, in 4–6 doses, max. 12 g/day
Cefotaxime	225–300 mg/kg/day, IV, in 3–4 doses, max. 12 g/day
Ceftriaxone	100 mg/kg/day, IV, in 2 doses, max. 4 g/day
Ceftazidime	150 mg/kg/day, IV, 3–4 doses, max. 6 g/day
Cefepime	150 mg/kg/day, IV, 3–4 doses, max. 6 g/day
Gentamicin	5–7.5 mg/kg/day, IV, in 3 doses
Meropenem	120 mg/kg/day, IV, 3 doses, max. 6 g/day
Aztreonam	120 mg/kg/day, IV, 3–4 doses, max. 8 g/day
Vancomycin	40–60 mg/kg/day, IV, in 4 doses
Ciprofloxacin	10 mg/kg/dose, IV, 3 doses/day, max. 400 mg/dose
Chloramphenicol	25 mg/kg/dose, IV, 4 doses/day, max. 4 g/day
Trimethoprim-sulfamethoxazole (cotrimoxazole)	10–20 mg/kg/day, IV, in 2–4 doses

IV intravenous, *max* maximum

31.8.1.2 Fluid Management

Avoiding over- or under-hydration is an essential aspect of supportive therapy. Fluid–electrolyte balance is vital for management. Hypotonic fluids (e.g., 1/2–1/4 normal saline) should be avoided as they may increase the risks of hyponatremia and cerebral edema. Optimal hydration should be maintained, considering the patient's volume status, hemodynamics, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH; e.g., serum sodium <130 mEq/L). Children in shock should be given adequate isotonic fluids to maintain cerebral perfusion and blood pressure. In case of hypovolemia without shock, daily weight, serum electrolytes, and urine output should be monitored and supplemented with isotonic fluids. In children with ABM, SIADH is common. For children without shock or hypovolemia and suspected SIADH, the fluid restriction should be given to 2/3 to 3/4 normal saline maintenance. Daily weight, urine output, serum electrolytes, and serum and urine osmolality should be monitored. Fluid administration can be normalized when serum sodium is >135 mEq/L. In a study of children with pneumococcal meningitis, 10% had serum sodium values <130 mEq/L at admission [29]. Children without shock, hypovolemia, or signs of SIADH (normal perfusion, normal serum sodium ≥135 mEq/L) may receive isotonic fluids as a maintenance fluid. Volume status and serum electrolytes should be monitored regularly, as SIADH may develop during follow-up [29].

31.8.1.3 Follow-Up

Complications, such as seizures, IIP signs, and development of subdural effusion, are most common in children treated for ABM during the first 3 days of treatment. Vital signs and a complete neurological examination should be monitored at regular periods every day [29].

31.8.1.4 Hospital Infection Control

All patients with meningitis should be hospitalized in separate rooms, if possible, and standard precautions for infection control should be taken. Droplet precautions are recommended for *N. meningitidis* and Hib meningitis until the patients receive effective 24-h therapy [29].

31.8.2 Antibiotic Treatment

Two basic principles should be considered in selecting antibacterial therapy for ABM. The first is that the antibiotic chosen should have a bactericidal effect, and the second should have an excellent transition to CSF. Because the CSF is a region of weaker humoral immunity, patients receiving bacteriostatic antibiotics (e.g., clindamycin or tetracycline) have a poor response to therapy [29]. For the treatment of ABM, a sufficient concentration of antibiotics should be present in the CSF. Most drugs achieve only 10–20% of the peak concentrations of serum in the CSF. Macromolecular antibiotics cannot adequately cross the BBB; small molecular weight and lipophilic molecules cross more easily. Inflammation increases

the permeability of the BBB, which facilitates the peak concentration of drugs in the CSF. In a study of children with ABM, 2 h after intravenous penicillin administration, the mean CSF/serum ratio was 42% on the first day of treatment and decreased to less than 10% on the 10th day when the inflammatory findings regressed [29, 30].

31.8.2.1 Treatment Selection Based on the Bacteria

Neisseria meningitidis
Third-generation cephalosporins for meningococcal meningitis are preferred:

Ceftriaxone 100 mg/kg/day, maximum 4 g/day, in two equal doses, intravenous (IV), or
Cefotaxime 225–300 mg/kg/day, maximum 12 g/day, in three or four equal doses, IV

High-dose penicillin G (300,000 units/kg/day, in four equal doses) is an alternative low-cost option. However, this treatment for non-beta-lactamase-producing *N. meningitidis* isolates is preferred in cases with documented penicillin susceptibility.

The course of treatment is 5–7 days. Patients should receive antimicrobial therapy to eliminate nasopharyngeal carriage treated with penicillin [29].

Haemophilus influenzae
Third-generation cephalosporins for *H. influenzae* meningitis are preferred:

Ceftriaxone 100 mg/kg/day, maximum 4 g/day, in two equal doses, IV, or
Cefotaxime 225–300 mg/kg/day, maximum 12 g/day, in three or four equal doses, IV

Ampicillin is used only in the presence of a non-beta-lactamase-producing pathogen [29].

The course of treatment is 7–10 days.

Gram-Negative Bacilli
The optimal treatment combination may vary depending on the growth pathogen and antibiotic susceptibility/resistance characteristics. If possible, a pediatric infectious disease specialist consultation is recommended for children with gram-negative bacillus meningitis.

Enteric Gram-Negative Bacilli
As a treatment regimen for susceptible isolates, a broad-spectrum cephalosporin, primarily ceftriaxone (100 mg/kg/day, maximum 4 g/day, in two equal doses, IV) or cefotaxime (225–300 mg/kg/day, maximum 12 g/day, in three or four equal doses, IV) plus an aminoglycoside (e.g., gentamicin 7.5 mg/kg/day, in three equal doses, IV) are preferred. Aminoglycoside may be discontinued, usually after the first 5–7 days, once the CSF has been documented to be sterile [29].

Pseudomonas aeruginosa

In treating *P. aeruginosa* infections susceptible to ceftazidime (150 mg/kg/day, maximum 6 g/day, in three or four equal doses, IV) or cefepime (150 mg/kg/day, in three or four equal doses, IV) are effective cephalosporins. For *P. aeruginosa* isolates resistant to ceftazidime, meropenem (120 mg/kg/day, maximum dose 6 g/day, in three or four equal doses, IV) is an effective alternative.

Extended-Spectrum Beta-Lactamase (ESBL) Producing Organisms

Meropenem (120 mg/kg/day, maximum dose 6 g/day, in three or four equal doses, IV) is the agent for treating meningitis caused by susceptible isolates [29].

31.8.2.2 Other Antibiotics

The role of tigecycline in the treatment of gram-negative bacterial meningitis is limited because tigecycline CSF penetration is only 11% of serum levels, and CSF concentrations after intravenous administration have been shown not to exceed the minimum inhibitory concentration (MIC) of most *Acinetobacter baumannii* strains [31].

Aztreonam has excellent CSF penetration through inflamed and non-inflamed meninges. It crosses into CSF at 17–38% of serum levels sufficient for treating meningitis [31].

Meropenem and imipenem penetrate CSF well. The use of imipenem is not the primary choice in pediatric patients because it may cause seizures. A study showed seizures developed in 33% of 21 pediatric cases using imipenem/cilastatin [31, 32].

Trimethoprim-sulfamethoxazole is well absorbed into the CSF; although it is not a preferred agent, it can be added to the treatment when necessary.

Aminoglycosides cross the BBB poorly and usually do not reach sufficient concentrations in the CSF to kill pathogens causing meningitis when used parenterally. Parenteral aminoglycosides are helpful only when given with another bactericidal drug with good CSF penetration [31, 32]. Therefore, aminoglycosides are often combined with a third-generation cephalosporin to treat gram-negative microorganisms. Although gentamicin is used more frequently, tobramycin or amikacin may be used where they are susceptible. In the case of resistance to cephalosporins, aminoglycosides may be used intrathecally and intravenously simultaneously to treat resistant gram-negative bacillary meningitis [31].

The concentration of ciprofloxacin in the CSF of inflamed and non-inflamed meninges was 8% and 37%, respectively [33]. In another study, ciprofloxacin and ofloxacin reached 11–50% of their serum concentrations in CSF [34]. Moxifloxacin has been reported to achieve CSF concentrations of up to 80% of serum levels based on data from patients with tuberculous meningitis [35]. Due to the lack of sufficient clinical data, it should be used for treating multiresistant isolates. Physicians should only use it with knowledge of its pharmacokinetics, dosage, and in vitro activity [36].

Like most third-generation cephalosporins, cefepime has adequate CSF penetration (5–20% of serum levels). Cefpirome passes into the CSF at 5–20% of its serum concentration [31].

In gram-negative bacillus meningitis, repeat LP should be performed 2–3 days after treatment initiation to assess therapy efficacy [29].

31.8.3 Treatment in Newborns and Prematures

In cases where clinical and CSF findings, such as CSF pleocytosis, increased protein level, decreased glucose level, and microorganisms seen in Gram-stained CSF suggest ABM, empirical antimicrobial therapy should be started immediately. Treatment for possible pathogens, mostly GBS, *E. coli*, and other gram-negative enteric bacilli, is chosen empirically. Ampicillin plus an aminoglycoside (usually gentamicin) or a (spectrum cephalosporin (e.g., cefotaxime, ceftazidime, or cefepime) plus an aminoglycoside (usually gentamicin) is recommended for most newborns. If *L. monocytogenes* or enterococci are suspected, ampicillin should be included or added to the treatment. These regimens are suitable for early-onset (first 72 h) and late-onset (>72 h) neonatal meningitis. Vancomycin plus an aminoglycoside (usually gentamicin) plus a broad-spectrum cephalosporin (such as cefotaxime, ceftazidime, or cefepime) is started for the treatment of late-onset meningitis in hospitalized neonates from birth. The treatment may change according to the reproducing factor and the responses. If multidrug-resistant (MDR) gram-negative bacilli are suspected based on the current flora of the neonatal intensive care unit (NICU), meropenem should be used instead of a broad-spectrum cephalosporin.

Acyclovir (60 mg/kg/day, divided into three doses, IV) may be added for herpes simplex virus (HSV) infection to empirical treatment in cases clinically thought to have neonatal meningitis with CSF pleocytosis, and no microorganism was detected on Gram-staining. Treatment is given for at least 21 days in HSV meningitis, and oral suppressive acyclovir (900 mg/m^2/day, divided into three doses, oral) treatment is continued for 6 months after the newborn is discharged [37].

Empirical broad-spectrum antimicrobial treatment should be continued until the causative organism and susceptibility of the organism are identified. Treatment coverage should be altered based on antimicrobial susceptibility when the causative agent is detected.

Ampicillin is used for ampicillin-susceptible strains to treat *E. coli* and other gram-negative bacteria. In ampicillin-resistant organisms, a combination of a broad-spectrum cephalosporin and an aminoglycoside (such as gentamicin) is used in most cases. Multidrug-resistant gram-negative bacteria are treated with meropenem. The duration of treatment is at least 21 days [28].

Ceftazidime or cefepime may be preferred when cefotaxime is unavailable. In the neonatal period, ceftriaxone should not be used in neonates, as it may inhibit bilirubin–albumin binding and cause kernicterus. When used with intravenous calcium, it may precipitate and cause severe reactions [28].

Newborns with ABM should undergo serial neurological examination, evaluation of the general clinical condition, repeated blood cultures, and LP in bacteremic patients. In neonates with meningitis, repeat LP should be performed 24–48 h after initiation of antimicrobial therapy to confirm CSF sterilization. Repeat LP is

primarily recommended in neonatal meningitis caused by GBS, gram-negative bacteria, such as *E. coli*, and *Listeria* spp., or with a complicated course; most patients with neonatal meningitis. With the sterilization of CSF, combination therapy may be discontinued in some patients with GBS or *Listeria* meningitis [28].

Most newborns with uncomplicated ABM show clinical improvement within 24–48 h after receiving appropriate antibiotic therapy. The absence of expected improvement or clinical deterioration in this time interval should suggest a complication such as obstructive ventriculitis, subdural effusion, brain abscess, intraventricular hemorrhage, or inadequate antimicrobial therapy. In this situation, neuroimaging should be performed, and pediatric infectious diseases and neurosurgery consultation should be requested. In newborns with ABM, neurological complications may present with ambiguous findings. Therefore, MR imaging can be performed 48–72 h before the cessation of treatment, even if there are no obvious neurological findings in responding cases. Neonatal neuroimaging with neurological signs should be performed earlier [28]. In addition, delay in CSF sterilization is associated with neurological sequelae and requires a detailed evaluation of the patient [28].

Hearing, vision, and developmental stages should be followed for a duration of time for all newborns with ABM. Hearing should be evaluated by auditory brainstem response (ABR) test within 4–6 weeks of completion of therapy [28].

31.8.4 Adjuvant Therapy

Permanent neurological sequelae, such as focal neurological deficits and HL, are common in ABM survivors, especially with pneumococcal and Hib meningitis. These complications depend on the inflammatory state, host response, and bacterial pathogen. Animal studies show that neurological complications are associated with the severity of the inflammatory process. Therefore, in treating ABM, anti-inflammatory agents, such as dexamethasone, have come to the fore in addition to antimicrobial therapy. Anti-inflammatory agents can potentially prevent neurological complications of ABM by reducing intracranial pressure and cytokine production. There is less research on other treatments aimed at inhibiting vasogenic edema (glycerol) and inflammatory mediators (e.g., nitric oxide synthase inhibitors), and they are currently not recommended for routine treatment [38].

In a meta-analysis of 2511 pediatric patients from 18 randomized controlled trials, the mortality rate in children treated with dexamethasone ($n = 1269$) was similar compared to placebo ($n = 1242$); 13.2% and 14.6%, respectively [39]. However, the rate of severe HL (usually defined as ≥60 decibels bilateral HL or requiring bilateral hearing aids) was lower in patients treated with dexamethasone (7% vs. 11.4%) [39]. The positive effect of dexamethasone was limited to children with Hib meningitis, 3.9% and 11.9% of patients who did and did not receive the drug, respectively. In comparison, the rates of severe HL for other bacteria were similar in the dexamethasone and placebo groups; 9.6% and 10.2%, respectively. The incidence of neurological sequelae other than HL was similar (18% vs. 20%) in both groups, regardless of the causative organism [38, 39].

The results obtained in another meta-analysis (n = 2029 pediatric patients) included five studies; dexamethasone was found to reduce HL (24.1% vs. 29.5%) [40]. However, mortality rates (26.5% vs. 27.2%) and other complications, such as severe neurological sequelae or bilateral HL, were similar [40]. Variables, such as the etiologic pathogen, duration of pretreatment symptoms, state of consciousness at admission, the timing of dexamethasone administration, and human immunodeficiency virus (HIV) infection status, did not differ with any of the subgroups evaluated [38, 40].

The benefits of dexamethasone therapy vary depending on the etiologic agent. Dexamethasone is primarily used to prevent HL complications related to meningitis caused by Hib. Its effects in pneumococcal or meningococcal meningitis have not been demonstrated, and dexamethasone is not generally recommended, although there is no consensus among experts.

However, in clinical practice, the causative organism is not known initially. If CSF Gram-staining or other rapid diagnostic test results suggest Hib meningitis or if the distinction cannot be made clear, adjuvant treatment with dexamethasone may be recommended. The initiation time of dexamethasone therapy should be before or concurrently with empirical antibiotic therapy. The benefit of dexamethasone therapy started 1 h after antibiotic treatment has not been demonstrated [38]. Therefore, in practice, the administration of dexamethasone will probably not be beneficial after 1 h of the first dose of antimicrobial therapy. Dexamethasone is not indicated for treating aseptic, nonbacterial, or suspected gram-negative meningitis. In this respect, if it is started before the definitive diagnosis, it should be discontinued when it is confirmed [38]. Dexamethasone is not indicated in infants under 6 weeks of age or those with congenital or acquired abnormalities of the CNS and VPS meningitis. Dexamethasone is not recommended in gram-negative bacterial meningitis because of insufficient evidence for a benefit–harm relationship in treating IIP and inflammation [31, 41].

Dexamethasone 0.15 mg/kg/dose may be given intravenously every 6 h for 2–4 days. Two-day treatment is as effective as longer-term treatment and has a lower risk of toxicity [38].

As a corticosteroid, dexamethasone reduces vomiting and edema and can ameliorate fever. Therefore, it is challenging for the clinician to monitor the patient's response to treatment. It may increase the risk of gastrointestinal bleeding in approximately 1–2% of children [38]. After discontinuing dexamethasone therapy, secondary fever after a 24-h period without fever may occur. In patients receiving dexamethasone for pneumococcal meningitis requiring vancomycin treatment, increased BBB permeability due to inflammation may decrease the transmission of vancomycin to CSF. However, there is no delay in CSF sterilization in patients receiving dexamethasone treatment as an adjuvant. So, children with *S. pneumoniae* meningitis who receive dexamethasone at admission should be carefully monitored during treatment. The effects of dexamethasone on viral meningitis are not fully known; there is not enough scientific data on this subject [38].

The use of therapeutic hypothermia is not recommended in children with ABM at risk for neurological sequelae [38]. Glycerol may be used within its indications if

it is indicated for the treatment of cerebral edema. There is no other proven adjuvant therapy, and its use is not recommended [38].

31.8.5 Duration of Therapy

The duration of therapy for ABM varies according to the type of causative pathogen. Treatment may also vary and be prolonged by risk factors, complications, and response to treatment. The duration of treatment in meningitis cases with optimal response to treatment is 10–14 days for *S. pneumoniae*, 5–7 days for *N. meningitidis*, 7–10 days for *H. influenzae*, 21 days for *L. monocytogenes*, at least 2 weeks for *S. aureus*, and 3 weeks or a minimum of 2 weeks after CSF sterilization, whichever is longer for gram-negative bacilli [29, 42]. In inadequate response to treatment or complications, treatment periods may be prolonged. If sterilization in the CSF (presence of CSF culture positivity at 24–48 h and later) is delayed, the treatment durations are recommended to be longer.

31.9 Prognosis

Acute bacterial meningitis can cause significant morbidity and mortality despite effective antimicrobial therapy. The risk of complications or death is related to the causative pathogen, patient's age, underlying disease, duration and severity, and sometimes delays in initiating antibiotic therapy [43].

Mortality in children with ABM ranges from 0% to 15% [29]. However, it has been higher in some low- and middle-income countries. An ABM study conducted in Angola of 723 children aged 2 months to 13 years in 2005–2008 reported that the patients were generally severely ill at hospital admission, and 38% had died [44]. In another study conducted in the USA of 2780 children between 2001 and 2006, the mortality rate was 4.2% [45]. A meta-analysis of 4920 children between 1955 and 1993 showed that mortality was 4.8% in high-income countries and 8.1% in low-and middle-income countries [46]. The mortality rate in high-income countries was 3.8% for Hib meningitis, 7.5% for meningococcal meningitis, and 15.3% for pneumococcal meningitis [46]. In a multicenter study of pneumococcal meningitis in the USA from 2007 to 2013, the mortality rate was 7% [29, 47]. Generally, pneumococcal meningitis has a higher risk of death or neurologic sequelae than meningococcal or Hib meningitis [29].

Gram-negative bacillary meningitis is less common but has a worse prognosis, and the mortality rate in adults and children ranges from 40% to 80% [2]. Patients with spontaneous ABM typically have a higher risk of shock, bacteremia, and death [2]. In an ABM study of 654 children, the Glasgow Coma Score (GCS) at presentation was the strongest independent predictor of severe neurological sequelae or death. The risk of death was approximately 10 times higher in the GCS 7–9 range, and mortality was about 30 times higher if GCS $\leq$6 [29, 48].

The prognosis of ABM in children is related to the level of consciousness at hospital admission, etiologic pathogen, CSF glucose concentration, presence of

seizures, delayed sterilization of CSF, and underlying diseases [29]. Seizures after 72 h from the start of treatment have been associated with neurological sequelae, especially in pneumococcal and Hib meningitis [29]. Likewise, children with underlying immunodeficiency, malnutrition, malignancy, or preexisting neurological disease are at higher risk of death or neurological sequelae [29]. Cases with baseline CSF glucose concentration <20 mg/dL are associated with adverse outcomes such as delayed sterilization of CSF (continuing positive culture after 16–18 h of initiation of therapy), abnormal neurological findings, seizures, moderate to severe sensorineural HL (SNHL), and hemiparesis [29].

Worldwide, 12–35% of survivors of ABM have sequelae. In Africa, this figure may double [49]. Permanent neurological sequelae are common in children with ABM. The most common sequelae are HL, seizures, intellectual disability, spasticity, and paresis [29]. Hearing loss occurs in 31% of children with *S. pneumoniae* meningitis, 10.5% with *N. meningitidis* meningitis, and 6% with Hib meningitis [50].

In young children treated for meningitis, developmental steps should be followed throughout the growth and development process [29]. The hearing examination should be done at the hospital or immediately after discharge. Hearing can be evaluated with pure tone audiometry. The ABR test can be used in young children or children who cannot cooperate with pure tone audiometry. The hearing evaluation should be repeated if the initial assessment results show more than a mild HL [29].

31.9.1 Neonatal Meningitis Prognosis

Neonatal meningitis is a devastating disease. Neonatal intensive care follow-up decreases mortality, but morbidity remains high. Neonatal ABM mortality is approximately 10%, which may cause moderate to severe disability in about 15–20% of survivors and mild disability in 30–35% [28]. Long-term hearing, vision, and developmental stages should be followed-up in infants with neonatal meningitis.

Poor prognostic factors in newborns with ABM are low-birth-weight (LBW, <2500 g), preterm birth (<37 weeks of gestation), history of clinical signs more than 24 h before hospitalization, leukopenia (white blood cell, <5000/mm^3) and neutropenia, very high CSF protein level (>3 g/dL) and/or very low CSF glucose (<10% of blood glucose value), seizures occurring 72 h after hospitalization, focal neurological disorders recorded during acute illness, need for mechanical ventilation or inotropes, and delayed sterilization of CSF [28].

In neuroimaging findings of meningeal inflammation, the presence and size of parenchymal lesions, such as thrombus, and encephalomalacia, have prognostic importance. Mainly, abscess formation is associated with neurological sequelae that may develop in the future. The overall prognosis is worse, especially in preterms compared to term neonates [28].

In neonatal meningitis, the causative GBS mortality is around 6–11%, and the long-term sequelae rate is about 20–40% [28]. The mean mortality in *E. coli* meningitis in newborns is 9%, and mortality in preterms is 3 times higher than in term

neonates. The most common short-term morbidities among newborns are seizures, empyema, intraventricular hemorrhage, hydrocephalus, cerebral venous thrombosis, and stroke [28].

Between 1977 and 1995, in 64 very-low-birth-weight (VLBW <1500 g) newborns with 67 culture-positive meningitis, etiologically, 43% coagulase-negative staphylococci, 19% other gram-positive bacteria, 17% gram-negative bacteria, and 20% *Candida* spp. were observed. In surviving cases, culture-proven meningitis compared without meningitis (sepsis); the rate of major neurologic sequelae (41% vs. 11%, respectively) and subnormal Mental Development Index (<70) (38% vs. 14%, respectively) were higher. However, no difference was found between neurological sequelae according to the pathogen [51].

31.10 Prevention

The best way to eliminate the neurological complications of ABM is to prevent infections. Acute bacterial meningitis can be controlled mainly by vaccines, such as conjugate Hib, 13-valent pneumococcal, 4-valent meningococcal, and meningococcal B vaccines, and antibiotic chemoprophylaxis in risky exposure situations [38]. Vaccination is more effective, long-lasting, and reliable.

Antibiotic prophylaxis may be required for close and risky contact with patients with Hib and invasive meningococcal diseases. Antibiotic prophylaxis against other bacterial pathogens of meningitis is not recommended.

31.10.1 Meningococcal Chemoprophylaxis

The infection rate in close contact with patients with meningococcal disease is 0.4%, which is 500–800 times higher than the general population. Close contacts should be given chemoprophylaxis. Close contact refers to persons with exposure less than 1 meter close to the patient and >8 h of direct exposure to the patient's oral secretions. The chemoprophylactic agent should be administered before 7 days and up to 24 h after the appropriate antibiotic therapy onset of the patient's symptoms [42]. All household contacts, contacts staying in the same room with the index case for more than 8 h, or traveling or sleeping in the same room are considered in this group [52].

Nasopharyngeal or oropharyngeal cultures are not recommended and have no place in deciding the need for chemoprophylaxis as they may unduly delay administration [42]. Antimicrobial chemoprophylaxis should ideally be administered within 24 h after the index case diagnosis. After 14 days of exposure to the index case, chemoprophylaxis is not recommended by the USA Centers for Disease Control and Prevention (CDC) because its efficacy is controversial [42, 53]. Postexposure infection is usually seen in the first 10 days on contact persons; however, cases occurring in a more extended period have also been reported rarely.

The preferred agents for antimicrobial chemoprophylaxis against meningococcal infection are rifampin, ceftriaxone, ciprofloxacin, and azithromycin [45, 52]. For meningococcal prophylaxis, rifampin (20 mg/kg/day, maximum 600 mg/day, in neonates 10 mg/kg/day, in equal 2 doses, orally, 2 days), ceftriaxone (125 mg for <15-year-old, 250 mg for >15-year-old, intramuscular [IM], as a single dose), ciprofloxacin (20 mg/kg for >1 month-old, maximum 500 mg, orally, as a single dose) or azithromycin (10 mg/kg, maximum 500 mg, orally, as a single dose) may be administered [52]. However, rifampin and ciprofloxacin are not given to pregnant women [52].

If treated with an antibiotic other than a third-generation cephalosporin, the nasopharyngeal carriage of *N. meningitidis* may not be resolved in patients with invasive meningococcal disease. Therefore, these patients should receive appropriate chemoprophylaxis for the eradication of nasopharyngeal carriage before discharge from the hospital. Chemoprophylaxis regimens for such patients are the same as postexposure prophylaxis [29, 42].

31.10.2 *Haemophilus influenzae* Type b Chemoprophylaxis

Rifampin is recommended for Hib prophylaxis. Rifampin is given once daily (20 mg/kg, maximum 600 mg, in newborns 10 mg/kg, orally) for 4 days [54]. Prophylaxis is given to household contacts of children with Hib meningitis if an unvaccinated or incompletely vaccinated child exists under 4 years of age at home or an immunocompromised child regardless of age. In addition, chemoprophylaxis is applied to children in preschool nurseries or nursing homes if there are ≥2 children with invasive Hib disease. Chemoprophylaxis is also used for a sick child receiving treatment other than cefotaxime or ceftriaxone if there is contact with a child younger than 2 years old or immunocompromised at home [54].

31.11 Complications

Complications of ABM may be classified as neurological and non-neurological complications. Non-neurological systemic complications such as fluid–electrolyte disturbances, cerebral edema, septic shock, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and septic or reactive arthritis are usually the results of bacteremia, which often accompanies meningitis [43]. Neurological complications, however, are sequela-related complications that tend to be longer-lasting. Complications of meningitis are usually neurological.

31.11.1 Non-Neurological Complications

In ABM, septicemia in children and organ failure such as kidneys, liver, lungs, and heart failure may be seen depending on the severity of septicemia. As in meningococcemia, extremity losses due to purpura fulminans may be seen.

31.11.2 Neurological Complications

General neurological complications are mainly mental status changes, brain edema, seizures, IIP, HL, quadriparesis, hemiparesis, ataxia, cranial nerve palsies, cerebrovascular abnormalities, developmental disorder, neuropsychological disorders, hydrocephalus, subdural effusion or empyema, rarely brain abscess and hypothalamic dysfunction. Neurological complications of meningitis can occur any time after the onset of symptoms. Impaired mental status is seen in most patients at the presentation time, and seizures are mostly seen in the acute period. These are also counted among the clinical findings of the disease. Complications may also be of an acute or chronic nature [43]. Although many neurological complications are readily and severely apparent, such as HL, they may occur in the early stages of infection. Although SNHL occurs early, it may not be noticed in young children until a hearing assessment is performed [43].

31.11.2.1 Cerebral Edema

Cerebral edema occurs due to cytotoxic, vasogenic, or interstitial mechanisms and leads to IIP. Vasogenic cerebral edema is usually caused by increased permeability of the BBB, particularly in the choroid plexus and cerebral microvascular endothelia. Cytotoxic factors released from neutrophils, microglia, and astrocytes can cause brain edema. Inflammation due to infection may interfere with the normal absorption of CSF from the subarachnoid space through the arachnoid villi. Cerebral edema and IIP are initially manifested by headache, confusion, irritability, nausea, and vomiting. Papilledema may be detected on physical examination. More severe intracranial hypertension is characterized by severe impairment of consciousness; coma. In addition, cranial nerve palsies, primarily the sixth nerve, hypertension, bradycardia, Cushing's reflex, or triad may occur. In severe cases, cerebral edema can cause death by cerebellar herniation. In critically ill patients with meningitis, the possibility of cerebral edema should be kept in mind, particularly those with severely impaired consciousness, asymmetric pupillary reflexes, or other cranial nerve palsies. Neuroimaging confirms the diagnosis, but urgent empirical treatment may be required if there is high clinical suspicion. In children with ABM, fluid volume balance should be carefully adjusted, considering cerebral edema [43].

31.11.2.2 Subdural Effusion

Subdural effusion occurs in 10–33% of children with ABM [43]. In young children, the bulging fontanel may signify subdural effusion, whereas, in older children, subdural effusions may rarely cause IIP and shift in intracranial structures. Most children are asymptomatic and do not require treatment. However, drainage is required if a compression-related neurologic finding or subdural empyema exists [43].

31.11.2.3 Seizures

Seizures occur in 20–30% of children with ABM. The pathogenesis of seizures in meningitis is not clear. Although fever can be a risk factor in very young children, most seizures are likely caused by cerebrovascular inflammation or secondary

neurochemical changes [43]. Seizures occurring before or at admission are usually generalized, but seizures occurring after 72 h are generally focal. Early and easily controlled seizures are rarely associated with permanent neurological sequelae. In contrast, seizures that begin more than 72 h after hospitalization are challenging to manage or are prolonged and more likely associated with neurological sequelae, suggesting that a cerebrovascular complication may have occurred [43].

31.11.2.4 Cranial Nerve Palsy

Cranial nerve palsies may result from nerve compression due to cerebral edema or perineuritis due to adjacent meningeal inflammation. The sixth cranial nerve is the cranial nerve most affected by IIP due to the length of its intracranial part. The third, fourth, and seventh cranial nerves may also be affected. Cranial nerve disorders due to meningitis are usually temporary. Acute bacterial meningitis can cause arachnoiditis around the optic nerve, resulting in temporary or permanent vision loss. Irreversible complete blindness is a rare complication of severe meningitis due to optic atrophy [55].

In a literature review covering 1970–2010, approximately half of 1433 postneonatal ABM survivors had at least one neurologic sequela at ≥5 years of follow-up [56]. Of the reported sequelae, 78% were mental/behavioral defects, such as academic difficulties, cognitive impairment, and attention deficit hyperactivity disorder; 14% were neurological defects, including seizures, motor defects, and cerebral palsy, 7% were HL, and 3% were visual impairment. Considering the bacterial agents of children with sequelae, 37% were *H. influenzae*, 4% were *S. pneumoniae*, and 3% were *N. meningitidis.*

Risk factors for neurological complications of ABM in children vary according to the following characteristics [43]:

- Patient age: The younger the child, the worsening the prognosis.
- The type of etiologic pathogen: *Streptococcus pneumoniae* infection has a worse prognosis than others.
- The disease duration before effective antibiotic therapy: ≥2 days post-symptom hospital admission.
- Severe CSF findings at admission: Very low CSF glucose concentration, bacterial growth; $\geq 10^7$ (colony-forming unit [CFU]/mL), delayed CSF sterilization.
- Seizures starting 72 h after admission.
- Focal neurologic deficit in non-postictal patients.
- Inadequate host response to infection.

Gram-negative bacillus meningitis has a worse prognostic outcome than other bacterial pathogens in all age groups [43].

31.11.2.5 Ataxia

Among all neurological sequelae, ataxia is considered a minor complication. Ataxia was observed in 1–5% of patients with *H. influenzae* or meningococcal meningitis and 18% with *S. pneumoniae* meningitis [44]. It is usually transient, but cases of

ataxia lasting for months have rarely been identified. This finding suggested that ataxia may be of vestibular origin, rather than cerebellar origin, as in most cases of acquired postinfectious ataxia in childhood.

31.11.2.6 Motor Deficits

Hemiparesis, quadriparesis, and other motor deficits may be seen as complications of ABM. Most motor deficits are temporary with successful treatment, but long-term sequelae may occur. The paresis is typically caused by an intracranial abnormality such as a cerebral artery spasm, cortical or sagittal vein thrombosis, subdural effusion or empyema, cerebral infarction or abscess, hydrocephalus, or cerebral edema. Paralysis from meningitis usually resolves over time. In a study of 235 children with ABM, quadriparesis or hemiparesis was found in 12% of patients immediately after discharge [20]. However, paresis persisted in only 2% of cases at follow-up, 1 year after discharge.

31.11.2.7 Cerebrovascular Complications

Thrombosis, vasculitis, intracranial hemorrhage, acute infarction, and aneurysm formation are potential complications of ABM. These findings may present as focal abnormalities such as hemiparesis or focal seizures [43].

31.11.2.8 Mental and Behavioral Disabilities

Survivors of ABM are at increased risk for learning difficulties, developmental delays, and behavioral problems [43]. This is true even for those who do not have acute neurological complications during the acute illness. Caregivers and teachers should be aware of possible language problems and problems understanding language-based materials. Early diagnosis and intervention can help to alter the long-term effect of these problems.

31.11.2.9 Intellectual Disability

Intellectual disability is a well-known complication of ABM in children and can range from mild to severe. A meta-analysis of 19 prospective studies of ABM in children in developed countries reported that 4% of survivors had intellectual disability (intelligence level IQ $\leq$70) [43, 46]. Compared with the healthy control group, children with ABM in infancy were found to have lower school performance and were about four times more likely to attend special needs schools [57].

31.11.2.10 Behavioral Problems

Survivors of childhood ABM may have behavioral problems such as increasing somatic complaints, mood disorders, social problems, and thought and attention disorders. It is unclear whether behavioral problems vary by the pathogen.

31.11.2.11 Hearing Loss

The most common cause of acquired HL in childhood is ABM. Hearing loss after meningitis can be temporary or permanent. In many affected patients, transient HL may occur due to conduction disturbance. However, SNHL (temporary or

permanent) may result because of damage to the eighth cranial nerve, labyrinth, or cochlea or direct bacterial invasion and the inflammatory response caused by infection. Permanent SNHL has been reported in 2–18% of children with ABM [17, 43]. Those with pneumococcal meningitis were higher (up to 30%). In addition, 10% of children have temporary HL. Another study reported 22% of overall HL complications in *S. pneumoniae* meningitis and 8% in *N. meningitidis* meningitis [58]. The reported frequency of permanent HL varies between 2.5% and 18%.

In a cohort study conducted in 2003, it was reported that 7% of children with ABM developed HL, and 25% showed signs of HL at the end of the routine follow-up period [49]. Hearing loss in children with *S. pneumoniae* meningitis is two to three times higher than from other ABM pathogens [43, 49]. In a multicenter study of 161 children with pneumococcal meningitis treated between 2007 and 2013 in the USA (3 years before and after the administration of the 13-valent pneumococcal conjugate vaccine [PCV-13]), HL developed in 31% of cases [47]. As HL and ataxia are associated with bacterial labyrinthitis, both are commonly associated with each other [43, 49].

31.12 Gram-Negative Ventriculo-Peritoneal Shunt Meningitis

Meningitis may be acquired in a community setting and associated with an invasive device like a VPS. Because of the device, shunt meningitis may be classified as healthcare-associated meningitis. Gram-negative bacilli and *Staphylococcus* spp. mainly cause meningitis related to VPS, in which fever, headache, nausea, and mental status changes are also common. Sometimes just fever or abdominal tenderness/peritonitis may be a symptom of VPS meningitis. Fever and increased CSF white blood cell count in patients could suggest infection. In CSF culture, microorganisms such as *Staphylococcus* spp. (especially coagulase-negative staphylococci, *Staphylococcus epidermidis*), *Propionibacterium acnes*, gram-negative bacilli, including *Pseudomonas* spp., *E. coli*, *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and *Candida* spp., *Aspergillus* spp., and *Exserohilum* spp. could be seen [59]. In this section, shunt meningitis will not be discussed in detail.

31.13 Hearing Loss

In this section, early and late HL caused by gram-negative ABM due to *N. meningitidis*, Hib, and other gram-negative bacteria will be discussed in detail. On the other hand, the literature on HL in gram-positive ABM will also be mentioned in terms of comparison.

Hearing loss is the most common congenital disorder in high-income countries, 1–3 per 1000 children are born with SNHL, and 1–2 per 1000 children develop HL later [60]. About 60% of patients with HL have bilateral HL [41].

Hearing loss can develop in different ways [61].

31.13.1 Conductive Hearing Loss

Conductive HL (CHL) is caused by a problem in the outer or middle ear that prevents sound from being transmitted to the inner ear. It can occur anywhere from the external auditory canal or auricle to the stapes and oval window. Conductive HL in children is mostly temporary, as in otitis media with effusion, but may be permanent due to permanent damage to the osseous structures of the tympanic membrane and middle ear because of aural atresia or chronic suppurative otitis media.

31.13.2 Sensorineural Hearing Loss

Sensorineural hearing loss is caused by damage, disease, or other disorders affecting the inner ear (e.g., cochlea) and/or the auditory nerve (eighth cranial nerve) [17]. Hearing loss after ABM is mainly the sensorineural type. Hearing loss of at least 16 decibels (dB) in the low- or high-frequency range is normally seen in approximately 15% of children aged 6–19 years [61].

31.13.3 Auditory Neuropathy Spectrum Disorder

In auditory neuropathy spectrum disorder (ANSD), also called auditory neuropathy, neural asynchrony, neural dissonance, and paradoxical HL, the cochlea can detect sound, but signals are not properly transmitted from the inner ear to the brain. The ANSD is characterized by normal otoacoustic emissions (OAEs), indicating normal outer hair cell function. However, the ABR test is abnormal, indicating an abnormality of the inner hair cells of the cochlea or the cochlear branch of the cranial nerve.

31.13.4 Retrocochlear Hearing Loss

Retrocochlear term refers to lesions close to the cochlea. Abnormalities of the eighth cranial nerve cause retrocochlear HL. The most common retrocochlear lesion is vestibular schwannoma. However, similarities between retrocochlear HL and ANSD in tests exist.

31.13.5 Mixed Hearing Loss

Mixed HL refers to the combination of CHL and SNHL.

31.14 Gram-Negative Bacterial Meningitis and Hearing Loss

Bacterial meningitis is the most common cause of acquired HL. In ABM, SNHL develops mainly if no accompanying complicated otitis media exists. Hearing loss related to ABM may primarily be a neurological complication of meningitis or be due to the drugs used in the treatment, ototoxic drugs such as aminoglycosides. Hearing loss may be temporary or permanent, unilateral or bilateral, and mild or severe enough to require a cochlear implant.

As a complication of ABM, SNHL generally develops in the first 48 h of ABM. It progresses by showing improvement or worsening in the first 2 weeks of the disease. Permanent HL may result from damage to the labyrinth, cochlea, or eighth cranial nerve due to bacterial invasion and inflammatory response caused by infection. Labyrinthitis detected by MR imaging may herald the development of SNHL [17]. Therefore, children with ABM should initially undergo a rapid and complete hearing assessment and should be followed up regularly if the assessment is abnormal. These children may be candidates for early cochlear implantation.

Some studies reported that early dexamethasone adjuvant therapy in the treatment of ABM reduces the likelihood of HL and neurological sequelae, especially when the causative pathogen is Hib. However, it is unclear whether dexamethasone reduces the risk of HL in other ABM pathogens [17]. Therefore, dexamethasone is not routinely recommended in non-Hib ABM.

31.14.1 Ototoxic Drugs

Ototoxic drugs such as aminoglycosides, high-dose intravenous loop diuretics, and chemotherapeutic agents such as cisplatin can cause significant HL. Aminoglycosides are given mainly in the treatment of neonatal ABM. Hearing loss caused by antibiotics or chemotherapeutic agents usually begins at high frequencies. With continued use, HL becomes more pronounced and may worsen after the drug is discontinued. Sensorineural HL associated with most of these drugs is persistent [17].

All aminoglycosides are ototoxic; however, some are vestibulotoxic rather than cochleotoxic. In addition, the risk of ototoxicity may be greater if there is preexisting or secondary renal failure. The most toxic aminoglycoside is gentamicin; next come tobramycin, amikacin, and netilmicin. Individuals with mutations in certain mitochondrial genes have a genetic predisposition to develop ototoxicity when exposed to small doses of aminoglycosides. Otoacoustic emissions reflecting the functional state of outer hair cells in the cochlea are a sensitive measure of the early effects of aminoglycoside-induced damage on the peripheral auditory system and may help monitor cochlear function during therapy with ototoxic drugs.

Vancomycin is among the antibiotics used in ABM, which may cause ototoxicity, albeit less.

31.14.2 Hearing Loss and Epidemiology in Acute Bacterial Meningitis

Hearing loss is a common neurological sequela of ABM. Hearing loss due to ABM is related to all pathogens, but the highest incidence of HL is seen after *S. pneumoniae* infection. It is usually detected immediately after infection; however, late-onset HL can also be seen. Also, meningitis can cause obliteration of the cochlea. If cochlear fibrosis occurs, the implant should be placed before progressive obliteration develops. Early diagnosis of HL in children prevents language and speech development disorders [41].

Permanent SNHL develops in 5–35% of patients with ABM. Hearing loss is severe and bilateral in approximately 4% of patients [62]. The precise mechanism of HL in ABM is not clearly understood but is likely due to many factors, including cochlear neuroepithelial injury, vascular injury, and direct labyrinth involvement. Early diagnosis and rehabilitation can reduce long-term adverse outcomes by identifying children at risk for developing HL [62].

In a study evaluating 122 children with severe HL, aged 1–17 years, who required single/or bilateral cochlear implants, perinatal, such as hypoxia, prematurity, sepsis, LBW, ototoxicity, hyperbilirubinemia, and meningitis, and postnatal, such as meningitis, risk factors were found to be 13.1% and 3.3%, respectively [60]. In addition, cytomegalovirus (CMV) deoxyribonucleic acid (DNA) was detected in 9.8% of the cases.

In a systematic review examining the risk factors, incidence, or course of post-meningitis HL from 1985 to March 2015, 14% of cases had HL >25 ± 5 dB and 5% severe HL (>90 dB) [41]. Hearing loss after ABM usually has an early onset. Patients with normal hearing immediately after meningitis showed stable normal hearing, and the initial HL that develops in the first period of meningitis may improve or worsen over time. For this reason, audiological tests are recommended for all patients with ABM, especially in the early period. Patients with normal hearing at the onset of meningitis do not require extended follow-up; it is necessary for patients with early-onset HL. The course of patients with HL requiring audiological follow-up (>25 ± 5 dB) varies considerably. The authors recommended that all patients with ABM be audiologically tested as soon as possible before or immediately after hospital discharge and long-term audiological follow-up only in patients who develop HL during meningitis [41].

Between 2005 and 2008, 723 patients with ABM, aged between 2 months and 13 years, were followed up for hearing [63]. The hearing was evaluated with ABR test performed within 24 h of admission, 7 ± 1 days of treatment, and ≥1 month after admission. The ears with purulent discharge or with perforated tympanic membranes were excluded. The study reported that significant HL changes existed during childhood ABM in almost half of the ears after admission. During recovery from bacterial meningitis, a very early ABR test result has less prognostic value, and significant improvement may occur in addition to a severe deterioration in the future. Therefore, the authors recommended that a definitive hearing assessment be performed at least 1 month after admission and in all children regardless of previous findings [63].

In another study, severe bilateral HL as a complication of ABM was diagnosed in 4 of 5 (80%) patients, on average 33.5 days after the meningitis episode. Bilateral deafness can occur immediately or several months after bacterial meningitis. Therefore, the physician monitoring the patient should be aware of this potential risk and request a consultation from the ear, nose, and throat specialist, audiology, and phonology team in suspected cases [58].

In a study to examine the possibility that microorganisms that cause meningitis can cause labyrinthitis ossificans and severe HL, 1568 meningitis patients from the New South Wales Health Department between 1995 and 2005 and meningitis-related hearing data from the Sydney Cochlear Implant Center between 1984 and 2005 were examined. The data of 59 patients (70 ears) who used cochlear implants due to HL were analyzed. Patients were compared in terms of etiological pathogens of meningitis cases and 11.4% of severe HL cases resulting in cochlear implants. *Streptococcus pneumoniae* was found to cause 41.1% of meningitis and 85.7% of cochlear implantation, and *H. influenzae* caused 2% of meningitis and 2.9% of implants. Although labyrinthitis ossificans was more common after *S. pneumoniae* meningitis, there was no statistically significant difference between *S. pneumoniae*, *H. influenzae*, or *N. meningitidis*. As a result, *S. pneumoniae* meningitis has a higher risk of severe HL necessitating cochlear implants than *N. meningitidis* or *H. influenzae* [64].

In a cohort study conducted in 2003, it was reported that 7% of children with ABM developed HL, and 25% showed signs of HL at the end of the routine follow-up period. It was stated that all children with HL had symptoms ≥2 days before admission, low CSF glucose concentration (≤10 mg/dL), absence of petechiae, and at least 1 or more risk factors such as *S. pneumoniae* infection and ataxia [49].

Hearing loss in children with pneumococcal meningitis is two to three times higher for severe HL, cochlear ossification, and cochlear implant risks. *Neisseria meningitidis* accounts for 56.9% of other ABM pathogens [43, 49]. In a multicenter study of 161 children with pneumococcal meningitis treated between 2007 and 2013 in the USA (3 years before and after the administration of PCV-13), HL developed in 31% of cases [47].

In Angola, 244 ears of 124 children with ABM were evaluated with auditory brainstem audiometry 3 months after admission. Unilateral HL was detected in 5% of children and bilateral HL in 11%. Especially in children with HL of ≥80 dB, seizures before hospital admission or during hospitalization and the severity of the disease were significant prognostic factors [65].

Roine et al. [63] found that half of all ears were evaluated as possible profound or permanent HL after ABM; this finding was already present at the presentation. It has been shown that the other half presents with normal or only moderate HL and then develops severe/very severe impairment. On the other hand, it was observed that the severe HL at the time of presentation was usually temporary and resolved at least 1 month later in the follow-up. Significant fluctuations in hearing occurred in <41% of ears evaluated. It was also observed that 76% of initially severely affected ears (22% of all ears tested) subsequently recovered. Hearing loss detected at baseline was similarly resolved in other studies by 50–81% at follow-up [63, 66–68].

31.14.3 Pathogenesis of Hearing Loss in Acute Bacterial Meningitis

Acute bacterial meningitis can cause peripheral or central HL and also leads to intracranial pathologies through immune, inflammatory, and ischemic mediators or cerebral edema.

In an experimental study, rabbits were injected with 10^5 pneumococci intracisternal; CSF findings and auditory evoked potentials were recorded every 4 h and hourly, respectively [69]. Progression to SNHL and severe HL were observed in all rabbits at 12 h postinfection. A CSF leukocytosis of >2000 cells/mm^3 was observed before the onset of HL, with CSF protein and lactate increasing to >1 mg/mL. In this study, hypoglycorrhachia was not observed to be associated with HL. The probability of developing HL was directly proportional to the duration of infection. In histopathology of the temporal bone, pneumococci and leukocytes were found from the CSF to the perilymph via the cochlear aqueduct. There may be sudden inflammatory changes in the CSF before HL develops in meningitis. Hearing loss progresses from the cochlear base to the apex in parallel with the degree of inflammation [69].

Hearing loss due to meningitis is most likely because of cochlear pathology. The severity of the HL that develops is proportional to the severity of the inflammation in the perilymph. As the inflammation progresses from the cochlear base to the apex, the HL spreads from high frequency to low. When the HL progresses to advanced levels, the degree of inflammation within the perilymph is more severe than mild HL. If inflammation occurs around the cochlear nerve, HL can be seen; however, the integrity of neurons and progression of HL from high frequencies to low frequencies do not support this on histological examination [70].

A 10-year study was conducted to detect the presence of SNHL in 171 children with ABM [62]. At least unilateral mild SNHL was found in 30.6% of 134 patients who underwent audiological testing during their first hospitalization. The incidence was higher in pneumococci than in *N. meningitidis* meningitis, 5.9% and 23.9%, respectively. Length of hospital stay, seizures, high CSF protein, and low CSF glucose levels were detected as significant risk factors for HL in children with ABM. These factors were not considered strong predictors for HL in patients with meningococcal meningitis. In this study, the hearing was followed by audiometry [62].

When meningitis develops, treating and reducing the inflammation immediately is important. Richardson et al. [67] found that late diagnosis and treatment of meningitis for more than 24 h predicts HL. In this perspective, dexamethasone may reduce inflammatory mediators such as tumor necrosis factor-α (TNF-α), which has been found to play an essential role in cochlear damage after bacterial invasion [67]. In an experimental study, TNF-α blockade was shown to reduce postmeningitis cochlear damage and HL in gerbils with experimental pneumococcal meningitis [71].

When ABM develops, it is crucial to detect HL early. Bacterial meningitis causes HL as a result of labyrinthitis, nerve damage, or a central lesion. Acute bacterial

meningitis triggers a series of reactions that damage the organ of Corti and destroy spiral ganglion cells [58]. Inflammation, acute damage, fibrosis, and ossification develop in the organ of Corti in patients with ABM, and the organ of Corti has become damaged. The ossification of the organ of Corti is one of the most serious complications of ABM. As HL and ataxia are associated with bacterial labyrinthitis, both are commonly associated with each other [43, 49].

Ossification can occur 2 months after meningitis in CT scans. Animal studies also show that ossification in the cochlea occurs 3 weeks after intrathecal injection of pneumococci [64]. Cochlear fibrosis/ossification was detected by MR imaging in 80% of the cases who underwent cochlear implants after ABM, and surgical implant difficulty was observed in all patients with fibrosis. Ossification can make cochlear implant placement difficult or even impossible, depending on the time elapsed from the onset of meningitis and its increased capacity. When ossification is observed after ABM, it is necessary to quickly diagnose HL and assess the need for cochlear implants [58].

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommends using dexamethasone for Hib meningitis [54]. It also recommends dexamethasone for pneumococcal meningitis, noting that it has not been proven effective [72].

31.14.4 Clinical Evaluation and Diagnosis of Hearing Loss in Acute Bacterial Meningitis

Some questions may be asked for screening purposes that can be easily done to determine the HL roughly [59, 61]. These help identify hearing problems, especially in older children and adolescents:

- Do you have hearing problems when talking on the phone?
- Do you have trouble following the conversation when more than two people are speaking?
- Do you have trouble understanding conversations?
- Do you have hearing problems in a noisy or crowded background?
- Do you ask other people to repeat what they said?
- Are many people you talk to mumbling or not speaking clearly?
- Do you misunderstand what other people are saying and react inappropriately?
- Do people get angry because they misunderstand what you're saying?

31.14.5 Laboratory Diagnosis and Evaluation of Hearing Loss

Audiological evaluation is necessary for the objective review of HL. The formal audiological assessment is performed by an audiologist in a soundproof environment, providing detailed information about the environment and hearing ability. Audiological evaluation includes pure tone audiometry, speech audiometry,

behavioral observation audiometry, tympanometry, and/or tests such as otoacoustic emission (OAE) and electrophysiological ABR test. Which tests are administered will depend on the child's developmental age, the reason for referral, the testing environment, available equipment, and the skill of the test administrator. No child is too young to have their hearing evaluated [61].

31.14.5.1 Brainstem Response

The auditory brainstem response (ABR) test is also known as brainstem evoked response audiometry (BERA), auditory brainstem evoked response (ABER), or brainstem auditory evoked response (BAER) test. The ABR test converts click and tonal burst stimuli from high (80 or 90 dB) to low (0–20 dB) into an auditory response. These responses are recorded using electrodes placed on the child's head and ears. A computer records the responses and the generated waveforms compared with normal data. Delayed or absent waves suggest cochlear or neurological deficits. Patterns of normal hearing or conductive HL may also be recognized. The diagnostic ABR test differs from the automated ABR (AABR), commonly applied to screen newborns. The AABR is a screening tool with an automatic pass/fail response, while the diagnostic ABR test provides quantitative data such as waveforms interpreted by trained audiologists. Sedation may be required for the ABR test because excessive movement may impair the results [61].

31.14.5.2 Otoacoustic Emissions

Otoacoustic emissions are weak sounds produced by the normal movement of the cochlea's outer hair cells in a healthy ear. These sounds are transmitted retrogradely through the middle ear and tympanic membrane, which can be measured by a microphone placed in the external auditory canal. The test is rapid and noninvasive. The presence of OAEs suggests normal cochlear function. Sedation is not required for OAE testing [61].

Behavioral observation is a subjective measure of hearing ability and does not provide ear-specific or frequency-specific information. It is best used in conjunction with objective methods [61].

31.14.6 Follow-up and Management of Hearing Loss

Late determined and untreated HL can cause language, speech, and cognitive delays, especially in the first year of life, and this is usually preventable. Early diagnosis and appropriate treatment improve communication, language, and cognitive skills. Children with permanent HL should be managed by a multidisciplinary team of otolaryngologists, audiologists, speech pathologists, genetic counselors, and education specialists. They should be referred to a pediatric ophthalmologist, as their communication and learning are based on vision [73].

Although the frequency of bilateral HL varies according to the pathogen, disease severity, and treatment, it may occur immediately after ABM or a few months later, regardless of the microorganism. Therefore, after ABM, audiometric monitoring

appropriate to the patient's age is required for 2 years. Before discharge, an appointment is made for pure tone and speech behavioral audiometry appropriate for the patient's age and concentration level. It is recommended that audiometry be repeated every 4 months for 2 years. When audiometry shows SNHL, it should be confirmed with ABR and auditory steady-state response (ASSR) tests. Once HL is confirmed, MR imaging should be performed as soon as possible, especially within 10 days. If HL is suspected based on the child's behavior, an audiophonology team should evaluate the patient. If the patient is still hospitalized, evaluations, including ABR and ASSR tests, should be made. When these examinations show SNHL, audiometry and MR imaging should be performed immediately. Thus, severe or profound bilateral HL can be quickly recognized. Once cochlear implantation is decided upon, the operation should be performed quickly before the onset of cochlear ossification [58].

Cochlear implants electrically stimulate the cochlear nerve to provide hearing. Cochlear implants are recommended for patients with severe bilateral SNHL who experience little or no benefit after 6 months of hearing aid use. Bilateral rather than unilateral implantation is recommended, minimizing the time between implants [74]. Patients with severe HL after meningitis should be implanted as early as possible before labyrinth ossification develops [61]. Care should be taken to ensure that patients with cochlear implants have complete conjugate pneumococcal vaccines, and a single dose of 23-valent pneumococcal polysaccharide vaccine should be administered 8 weeks after the last PCV-13 [72].

31.15 Conclusion

Acute bacterial meningitis can cause neurological complications such as HL, especially in low- and middle-income countries. Hearing loss should be evaluated and treated immediately after ABM. Early identification of HL, whether temporary, usually conductive, or permanent, typically sensorineural, and determining the etiology is necessary for good outcomes and counseling families.

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Extraintestinal Pathogenic Escherichia coli Infections in Children and Hearing Loss

32

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32.1 Introduction

Escherichia coli is a gram-negative, facultatively anaerobic, motile, nonspore-forming bacterium in the Enterobacteriaceae family [1]. In general, *E. coli* is a normal part of the gut microbiota of healthy people. Although intestinal infections are the most common, some strains can cause extraintestinal infections.

Extraintestinal pathogenic *E. coli* (ExPEC) has been becoming more common worldwide. The ExPEC group has three main characteristics: (1) they can present as commensals in their hosts' gastrointestinal tracts without causing disease, (2) once they escape their host's gastrointestinal tract, they can colonize other parts of the body, resulting in an infection, and (3) their virulence genes are encoded on large mobile genetic elements called pathogenicity islands (PAIs) [2, 3]. Many virulence-associated factors in ExPEC include adhesins, toxins, iron acquisition factors, lipopolysaccharides, polysaccharide capsules, and invasins [4].

Extraintestinal *E. coli* mainly causes three diseases in children: urinary tract infection (UTI), meningitis, and bacteremia/sepsis. They are also associated with infections related to immunocompromised hosts [5]. Avian pathogenic *E. coli* (APEC), uropathogenic *E. coli* (UPEC), septicemic pathogenic *E. coli* (SEPEC), and neonatal meningitis-causing *E. coli* (NEMEC) are common classifications for

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ExPEC [5]. This group now includes two new animal pathogens: mammary pathogenic *E. coli* (MPEC) and endometrial pathogenic *E. coli* (EnPEC) [6]. Furthermore, ExPEC can cause pneumonia, spontaneous bacterial peritonitis, surgical wound infection, osteomyelitis, and myositis [7].

The emergence of antimicrobial resistance has complicated the management of ExPEC infections. Extraintestinal pathogenic *E. coli* was relatively susceptible to first-line antibiotics until the late 1990s. However, several surveillance studies conducted worldwide in the 2000s revealed increasing resistance to first-line antibiotics such as cephalosporins, fluoroquinolones, and trimethoprim-sulfamethoxazole [8]. The "newer-lactamases," which include plasmid-mediated AmpC-lactamases (e.g., CMY types), extended-spectrum beta-lactamases (ESBL; e.g., CTX-M types), and carbapenemases (e.g., NDM), are important causes of resistance to beta (β) -lactam antibiotic resistance among ExPEC [8].

32.2 Infections Involving Extraintestinal Pathogenic *Escherichia coli*

32.2.1 Avian Pathogenic *Escherichia coli* (APEC)

Avian pathogenic *E. coli* causes systemic infection in poultry, resulting in avian colibacillosis [9]. Respiratory infections, septicemia, polyserositis, coligranuloma, cellulitis, yolk sac infection, omphalitis, and swollen head syndrome are among the diseases that affect poultry [10]. It causes worldwide economic losses to poultry farms by increasing mortality and reducing poultry production [9]. Multiple studies have identified APEC as a potential foodborne zoonotic pathogen and a source or reservoir of human extraintestinal infections [11]. Furthermore, antibiotic use in the poultry industry and increases in poultry product consumption may have resulted in antibiotic resistance's emergence, spread, and persistence, a serious health concern for animals and humans.

32.2.2 Uropathogenic *Escherichia coli* (UPEC)

Urinary tract infection is one of the most common bacterial infections in children, characterized by fever and urinary symptoms such as dysuria and frequency. Urinary tract infections affect about 10% of the pediatric population and are diagnosed in about 1% of boys and 3–8% of girls [12]. The infection is more common in boys during the neonatal period (approximately 60%), but this tendency reverses after 2–3 months [10]. Uropathogenic *E. coli* is the most common pathogen responsible for UTIs [13]. Extraintestinal pathogenic *E. coli* bacilli are the most commonly implicated urinary tract pathogens, accounting for up to 90% of uncomplicated community-acquired UTI and pyelonephritis cases [14]. The host's intestinal flora is a potential source of UPEC, but the infection can also be transmitted via the fecal–oral route or through sexual contact [15].

The ability of UPEC to cause UTIs is associated with virulence factors such as hemolysin and pili-mediated adherence to uroepithelial cells [16]. Uropathogenic *E. coli* colonizes the perineum, overcomes natural host defenses, travels through the urethra, and then infects the bladder, causing cystitis. Some *E. coli* strains can infect the kidneys, causing organ damage with severe pyelonephritis and also causing sepsis in infants [16].

The rise in antibiotic resistance is a public health emergency in treating UTIs. Beta-lactams are one of the most commonly used antibiotics for treating UTIs. Extended-spectrum beta-lactamases are enzymes that can hydrolyze penicillins, first–third-generation cephalosporins, and monobactams (aztreonam) produced by certain bacteria, including some strains of *E. coli* [17]. Resistance patterns vary according to geographical location, so that treatment may differ depending on the patient, hospital, and country.

32.2.3 Septicemic Pathogenic *Escherichia coli* (SEPEC)

Bacteremia is the invasion of bacteria into the bloodstream. It may occur through wounds, infections, surgical procedures, or injections. *Escherichia coli* is the most common cause of bacteremia among gram-negative bacteria, accounting for more than 30% of all cases [18]. Septicemic pathogenic *E. coli* emerged as a distinct *E. coli* group. It possesses virulence characteristics shared by other groups of *E. coli*, such as diarrheagenic *E. coli* and other ExPEC groups [19]. Isolates of *E. coli* that infect the bloodstream frequently contain virulence factors that allow the organisms to bypass normal clearance mechanisms and evade the host immune response [20].

32.2.4 Neonatal Meningitis-Causing *Escherichia coli* (NMEC)

Because their immune systems are still developing, newborns are especially vulnerable to ExPEC infections. One of the most common causes of neonatal bacterial meningitis is caused by *E. coli* (NMEC) [21]. The mortality rate from neonatal meningitis is estimated to be 10% in industrialized countries and 40%–58% in low-middle-income countries [22]. Despite advances in intensive care, survivors experience neurologic sequelae like hearing loss (HL), developmental delay, and cognitive impairment [23]. In early-onset infection, *E. coli* is acquired from the maternal genital tract in utero or through the birth canal. Infants with late-onset infection, on the other hand, can get *E. coli* from various sources, including their mother, the hospital, or community contacts [24].

Neonatal meningitis-associated *E. coli* has a set of virulence factors for adhesion, invasion, and fitness to cause neonatal meningitis, with 80% of them possessing the capsule K1, and the majority of these K1 isolates being related to a small number of O serotypes (e.g., O1, O7, O16, O18, O45) [25]. Bacteremia, adhesion and invasion of human brain microvascular endothelial cells, and traversal of the blood–brain

barrier to produce inflammation in the central nervous system, leading to meningitis, are the different processes of NMEC infection [26].

Cerebritis, infarction, brain abscess, subdural effusions or empyema, sinus thrombosis, and ventriculitis are well-known neurological sequelae following *E. coli* meningitis. Chronic complications include cerebral atrophy, hydrocephalus, and HL [27].

32.3 Extraintestinal Pathogenic *Escherichia Coli* Infections in Children and Hearing Loss

Hearing loss is the most common neurological disorder globally, affecting over half a billion people [28]. Sensorineural HL (SNHL) is estimated to affect 1–3 of every 1000 children born in industrialized countries [29]. In low and middle-income countries, this rate is expected to be higher [30]. Klinger et al. [31] reported HL as a long-standing sequela in a neonatal meningitis group where *E. coli* and other pathogens were included. However, the impact and mechanism of ExPEC groups are unknown.

32.3.1 Otitis Caused by Extraintestinal *Escherichia coli* and Hearing Loss

Hearing loss related to otitis media caused by *E. coli* is unknown. The most common cause of HL in children, especially in low-middle-income countries, is chronic suppurative otitis media (CSOM) [32]. Chronic suppurative otitis media is a common ear infection characterized by persistent or recurrent purulent drainage from the middle ear through a non-intact tympanic membrane. Rates of *E. coli* isolation in CSOM have been reported between 10% and 20% [33–36].

Conductive HL, a common finding in CSOM, can be caused by a perforated tympanic membrane, ossicular chain discontinuity or fixation, middle ear effusion, tympanic membrane atelectasis, the presence of granulation tissue in the middle ear, or cholesteatoma [37]. Its severity is proportional to the perforation size and the extent of ossicular chain destruction. Possible mechanisms for HL in CSOM include direct damage to inner ear structures as a result of bacterial toxins and inflammatory mediators penetrating the round-window membrane [38], disease-related destruction of the inner ear bony framework, such as a semicircular canal fistula exposing the inner ear to the environment of the diseased middle ear and resulting in labyrinthitis [39], or mechanical and acoustic trauma to inner ear structures as a result of intraoperative drilling and manipulation of the ossicular chain or disease removal [40].

Otitis media is an important cause of SNHL [41]. Many factors associated with otitis media have been proposed, including pathogens, specifically bacterial toxins, topical drugs, and inflammatory chemical substances. Endotoxin has been detected in small amounts in the middle ear effusions of various types of otitis media [42].

Furthermore, endotoxin has been shown to damage the mucosal lining of the middle ear [43]. According to a 1990 study, instilling 100 pg of *E. coli* endotoxin into the middle ear cavity causes HL at low frequencies 48 h later [44]. However, when the pathological condition of the middle ear had resolved 30 days after application, no significant HL was found. Spandow et al. [45] reported that SNHL at 31.5 kHz persisted 14 days after 1 mg/mL *E. coli* endotoxin was applied to the round window membrane.

32.3.2 Meningitis Caused by Extraintestinal *Escherichia coli* and Hearing Loss

Hearing loss is a well-known complication of bacterial meningitis. A 2010 systematic review and meta-analysis of 132 articles from around the world published between 1980 and 2008 reported a 33.6% incidence of HL due to bacterial meningitis from all causes [46]. Bacterial meningitis-related HL typically manifests early in the course of the disease, and no specific antibiotic regimen has been shown to reduce the incidence. The mechanism of meningitic HL can be explained in various ways. Hearing loss can be caused by bacterial invasion of the inner ear leading to suppurative labyrinthitis. Permanent HL can be caused by subsequent fibroblastic proliferation and ossification [47]. Serous or toxic labyrinthitis is another mechanism by which meningitis leads to HL. The damage to the labyrinth is caused by toxic materials diffusing through the cochlear aqueduct [48].

Other mechanisms for HL include vascular occlusion caused by a septic embolus, common in bacterial meningitis [31]. Other mechanisms include meningeal irritation, which results in auditory nerve neuritis. In meningitic cases, the resolution of labyrinthitis and transient neuritis is thought to be the cause of complete or partial improvement of HL [49].

Escherichia coli is one of the most common gram-negative bacillary organisms causing meningitis, and *E. coli* meningitis remains a significant cause of mortality and morbidity worldwide. In resource-rich countries, *E. coli*, in particular, remains the primary causative organism of neonatal meningitis [50]. There are few publications on *E coli* meningitis and HL, and they are generally limited to case reports and animal studies. In a case report, *E. coli* meningitis in a newborn was complicated by central permanent diabetes insipidus, bilateral deafness, partial blindness, and neurodevelopmental disorder [51]. In a study evaluating 10 patients with HL after meningitis or meningoencephalitis, one patient was found to have neonatal *E. coli* meningitis [52]. In the infant, at 9 months of age, the left ear's hearing improved noticeably in the low and middle frequencies up to 1500 Hz, and the right ear initially recovered as well; however, after 2 years, the hearing began to deteriorate. In another study of 40 children with post-meningitic SNHL, *E. coli* meningitis was detected in 3 patients, and while all had HL in the acute phase, HL persisted in 2 patients in the third and sixth months [49]. In animal experiments, it was observed that HL developed after the administration of *E. coli* endotoxin [53, 54].

32.3.3 Hearing Loss Induced by Drugs Used in the Treatment of Extraintestinal *Escherichia coli* Infection

Escherichia coli is a leading cause of UTIs, and systemic infections, including bacteremia, neonatal meningitis, nosocomial pneumonia, cholecystitis, cholangitis, peritonitis, cellulitis, osteomyelitis, and arthritis [8]. Amikacin is an important aminoglycoside antibiotic in treating *E. coli* infections in pediatric patients and is commonly used in neonatal intensive care units [55]. Aminoglycosides can provide excellent coverage for UTIs, and a meta-analysis of available randomized evidence suggests that once-daily dosing should be used in children [56]. Low amikacin resistance in urinary isolates of ESBL-producing *E. coli* has been reported in children and adults [57].

The most serious issues with using aminoglycoside antibiotics are nephrotoxicity and ototoxicity. Ototoxicity related to aminoglycosides can be caused by vestibular or cochlear damage. However, the precise mechanisms underlying aminoglycoside ototoxicity are unknown. Many cellular processes have been implicated, which remains an active area of investigation [58]. Aminoglycoside agents must enter hair cells to cause cell death [59]. Many cellular mechanisms and processes may be involved after entry into hair cells. Mitochondrial protein synthesis may be disrupted, free oxygen radicals will be formed, c-Jun N-terminal kinase (JNK) will be activated, and caspases and nucleases will be activated [59]. Through interactions with potassium channels, aminoglycosides have also been shown to affect cellular membrane potentials directly [60]. Furthermore, the interaction of aminoglycosides with transition metals such as iron and copper promotes the formation of free radicals and further cell damage. Eventually, some interaction of these numerous processes results in the permanent loss of sensory hair cells in the cochlea and the vestibular apparatus, resulting in permanent HL or balance dysfunction [61].

Aminoglycoside ototoxicity is more likely with higher doses, blood levels, or prolonged treatment duration. Patients at increased risk include the elderly, those with renal insufficiency, preexisting hearing problems, a family history of ototoxicity, and those taking loop diuretics or other ototoxic or nephrotoxic medications [61]. There is a genetic predisposition in mitochondrial ribonucleic acid (RNA) mutation 1555A>G, which has been linked to nonsyndromic and aminoglycoside-induced HL [62]. To prevent aminoglycoside ototoxicity, serum drug levels and renal function should be monitored, and hearing tests performed before, during, and after therapy.

32.4 Conclusion

Hearing loss is the most common neurological illness globally, and various factors can cause it. The proportion of *E. coli* isolates in CSOM has been estimated to be between 10% and 20%. Hearing loss associated with *E. coli* endotoxin was shown in case reports and animal models. Hearing loss was observed in animals following

E. coli endotoxin injection. Although numerous processes and conditions have been proposed for HL in children associated with ExPEC infections, there is still a lack of knowledge.

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Citrobacter Infections in Children and Hearing Loss

33

Melike Emiroğlu, Mehmet Turgut, and Tobias Tenenbaum

33.1 Introduction

Citrobacter species are typically found in water, soil, and food and colonize the gastrointestinal tract of humans and animals. Although these species present low virulence, *Citrobacter* infections have been increasingly reported in human diseases. These infections are primarily healthcare-associated, particularly in newborns and immunocompromised hosts. *Citrobacter* species primarily cause urinary tract, bone, lung, and intra-abdominal infections. In addition, they are among the etiological agents of sepsis, meningitis, and brain abscess, particularly in newborns [1–3].

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33.2 Microbiology

The genus *Citrobacter*, a member of the Enterobacteriaceae family, was described in 1931 [4]. Well-known *Citrobacter* species include *Citrobacter freundii*, *Citrobacter koseri* (formerly *Citrobacter diversus*), *Citrobacter youngae*, *Citrobacter farmeri* (formerly *Citrobacter amalonaticus*), *Citrobacter braakii*, *Citrobacter werkmanii*, *Citrobacter sedlakii*, *Citrobacter gillenii*, *Citrobacter murliniae*, and *Citrobacter rodentium* [5]. Among these, *C. freundii*, *C. koseri*, and *C. farmeri* are distinct, while *C. koseri* alone is genetically homogeneous. A few other species, challenging to distinguish biochemically, form a closely related group called the *C. freundii* complex [6]. Recently, *Citrobacter pasteurii* was isolated from a patient with diarrhea [7], *Citrobacter europaeus* from human stool and water [8], *Citrobacter cronae* from human rectal swab and stool [9], and *Citrobacter telavivum* from human rectal swab [10]. *Citrobacter rodentium* specifically infects mice, while all other species have been detected in human clinical specimens. However, most *Citrobacter* infections in humans are caused by *C. koseri* and *C. freundii*.

Citrobacter species are gram-negative, facultatively anaerobic, motile, and nonspore-forming bacilli. Their sizes are 1.0 μm × 2.0–6.0 μm. The colonies are solitary or in pairs. *Citrobacter* bacilli use citrate only as a carbon source and ferment glucose and other carbohydrates [11, 12]. They are catalase-positive and can reduce nitrate, but lack oxidase, urease, and lysine decarboxylase activities [2, 5, 8].

33.3 Epidemiology

Citrobacter species are commensals in the intestines of humans and animals. *Citrobacter* bacilli are dispersed into the environment through fecal excretion and retransmitted to humans via water, sewage, and soil [5]. *Citrobacter* species rarely colonize the human perineum. Deoxyribonucleic acid (DNA) typing has revealed that newborns may be colonized while passing through the birth canal [13]. In addition, transmission from colonized healthcare personnel is an important route, particularly during epidemics in neonatal wards [14, 15].

Citrobacter species are rarely described as infectious agents in humans. They are commonly detected in feces as a part of gastrointestinal flora. *Citrobacter* species have been detected in the blood, urine, cerebrospinal fluid (CSF), respiratory tract secretions, bones, joint fluid, wounds, and rarely other infection-related samples during infections [2, 16–19]. *Citrobacter freundii* and *C. koseri* have been isolated from several regions where infections were identified, while *C. koseri* has mostly been isolated from CSF and brain samples. *Citrobacter farmeri* has been isolated from all regions except CSF. Meanwhile, *C. braakii* and *C. youngae* have mainly been detected in feces [6].

Citrobacter species account for 0.8% of all gram-negative infections and 3–6% of all healthcare-associated Enterobacteriaceae isolates. While the mortality rate due to *Citrobacter* infections was 6.8% in hospitalized patients, this rate reached 17.8–56% in patients who developed bacteremia [20].

33.4 Pathogenesis

The virulence factors of *Citrobacter* species are largely unknown. Although *Citrobacter* infections are rare in childhood, neonatal infections are the most common.

Factors facilitating the development of meningitis and brain abscess, particularly the susceptibility of newborns to *Citrobacter* infections, have been extensively studied. The 32-kilodalton (kD) outer membrane protein of *C. koseri* is considered to be a virulence factor involved in brain abscess formation [21]. The entry of *C. koseri* into macrophages is facilitated through serum opsonization and the FcγI receptor. The bacteria can live in the phagolysosome and escape the immune system by living and multiplying within macrophages, thus causing chronic infection [22].

During *C. koseri* infection, nitric oxide, tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-1 beta (β), among other factors, are released via myeloid differentiation primary response gene 88 (MyD88). These molecules activate microglia. Moreover, *C. koseri* can live and multiply in brain microglial cells, and it can cause meningitis and brain abscesses in neonates and immunocompromised individuals [23]. Myo-inositol is an abundant carbohydrate in certain human body organs, particularly the brain. Presumably, *C. koseri* can actively colonize and cause infection using myo-inositol as the carbon source for growth [24].

Citrobacter freundii can invade and replicate in microvascular endothelial cells in the blood–brain barrier. In this process, support from microfilaments, microtubules, endosome acidification, and de novo protein synthesis is essential [25]. *Citrobacter* species produce biofilms using type 3 fimbriae. Biofilm formation also plays an important role in the development of catheter-related urinary tract infections [26]. In *C. freundii*, which has been detected as an etiological agent in diarrhea, *Shiga*-like toxins, heat-resistant toxins, and toxins homologous to the cholera toxin B subunit have been identified as the major virulence factors [27]. In addition, a cytotoxic and aggregative *C. freundii* strain that causes diarrhea in humans has been described [28].

33.5 Clinical Manifestations

Although *Citrobacter* species rarely infect humans, they can cause severe clinical conditions, such as bacteremia, meningitis, brain abscess, endophthalmitis, osteomyelitis, septic arthritis, endocarditis, pyopericardium, arterial aneurysm, pneumonia, hemolytic uremic syndrome, peritonitis, and other intra-abdominal infections, particularly in newborns and immunocompromised hosts [2, 18, 19, 29–39]. Bacteremia caused by *Citrobacter* isolates other than *C. freundii* and *C. koseri* is mainly related to healthcare-associated and intra-abdominal infections [40]. In a case report, an adult patient with malignancy died due to *C. farmeri*-related meningitis [41].

In a study evaluating 298 *Citrobacter* isolates between 1972 and 1978, most patients were elderly and presented with underlying diseases [2]. Half of the isolates

were identified as *C. koseri* and the rest as the *C. freundii* complex. Moreover, half of the isolates were obtained from urine, and the rest from sputum, wound, body fluids, and tissues. In another study, bacteremia agents were investigated in all age groups in a single center in India from 1998 to 2001; 3% of the causative agents were *Citrobacter* species, of which 79% were *C. koseri,* and 21% were *C. freundii* [29]. In addition, over half of the patients were children younger than 10 years of age. While 58% of the growths were from pus, 42% were from other gram-negative pathogens or *Staphylococcus aureus*.

In a single-center study evaluating the susceptibility of 563 *Citrobacter* isolates in India, 70% were *C. koseri,* and 30% were *C. freundii* [17]. Moreover, 48% of samples were obtained from pus, 24% from urine, 20% from sputum, and the rest from body fluids and blood. While 87.4% of the isolates were of healthcare-associated origin, only 7.6% were obtained from children.

In a study of *Citrobacter* species isolated from 205 Indian patients, 90% of the isolates were *C. koseri,* and 10% were *C. freundii*. The majority (94.6%) of the samples were of healthcare-associated origin, and an underlying disease was detected in 88% of the patients; 46% of the isolates were obtained from urine, 16% from the respiratory tract, 16% from blood, 12% from pus, and 9% from sterile body fluids. Approximately half of the patients received antibiotics at the time of diagnosis of *Citrobacter* infection [42].

In Greece, 78 *Citrobacter* isolates were obtained from adult patients over 12 years; 71.8% of the isolates were *C. freundii*, 23.1% were *C. koseri*, and 3.1% were *C. braakii*. *Citrobacter*-related urinary tract infections were the most prevalent (52.6%), followed by intra-abdominal (14.1%), surgical site (7.7%), skin and soft tissue (6.4%), and respiratory tract (6.4%) infections. *Citrobacter* was a component of polymicrobial infection in approximately one-third of all patients, excluding those with urinary tract infections. Underlying diseases were reported in approximately 80% of the patients [16].

Of 1008 consecutive *C. freundii* isolates collected in the United States of America (USA) between 2017 and 2019, 45.9% were obtained from patients with complicated urinary tract infections, 19.3% from the skin and soft tissue infections, 11% from bloodstream infections, and 10.5% from pneumonia [43].

33.6 Diagnosis

Citrobacter infections can only be identified using culture. *Citrobacter* species can grow in different culture media, and 37 °C is the most suitable temperature [11]. *Citrobacter freundii* forms small, circular, convex, dark pink colonies on MacConkey agar. Coarse or mucoid forms have also been reported [11].

Citrobacter isolates can be distinguished using standard species-specific biochemical and carbon source utilization tests [2, 5, 8]. The results of antimicrobial susceptibility tests are interpreted according to the criteria used for Enterobacteriaceae.

33.7 Treatment

Citrobacter species are often resistant to cephalosporins due to the overexpression of chromosomal β-lactamases. *Citrobacter* species without acquired antibiotic resistance are susceptible to sulfonamides, trimethoprim, aminoglycosides, chloramphenicol, tetracycline, nalidixic acid, fluoroquinolones, nitrofurantoin, polymyxins, and fosfomycin [44]. Similar to other Enterobacteriaceae members, *Citrobacter* species are resistant to erythromycin and other macrolides, lincosamides, fusidic acid, and vancomycin. Like other bacteria, antibiotic resistance in *Citrobacter* species is an emerging problem worldwide. Acquired resistance to carbapenems, quinolones, and aminoglycosides has been reported. *Citrobacter* species producing extended-spectrum β-lactamases (ESBLs) have been reported at different rates in various countries [43, 45–47].

Samonis et al. [16] analyzed the antibiograms of 38 consecutive *Citrobacter* species which 29 were *C. freundii,* and found that the most effective agents were colistin (100%), fosfomycin (100%), imipenem (97.4%), gentamicin (89.5%), nitrofurantoin (89.5%), ciprofloxacin (80.6%), and cefepime (73.7%). Metri et al. [17] investigated the susceptibility of 563 *Citrobacter* isolates that 70% were *C. freundii,* and found that the most effective agents were imipenem (92%), piperacillin/tazobactam (58%), and amikacin (53%). In contrast, the isolates were highly resistant to ampicillin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, cephalexin, ceftazidime, and ciprofloxacin.

Sader et al. [43] analyzed 1008 *C. freundii* isolates and found that approximately 25% of the isolates were resistant to third-generation cephalosporins, 1% were resistant to carbapenems, and 9% were resistant to quinolone. Mohanty et al. [42] studied 205 *Citrobacter* isolates, 95% obtained from healthcare-associated infections, and 90% were *C. koseri*. The authors reported that over 80% of isolates were resistant to cefotaxime, ceftazidime, piperacillin, and ciprofloxacin. In contrast, imipenem (92.7%), meropenem (92.7%), and piperacillin/tazobactam (88.3%) were the most effective agents [42].

In a study evaluating culture results from five different pediatric clinics in the USA from 2010 to 2011, the susceptibility of *C. freundii* was examined. Ampicillin-sulbactam showed the least efficacy (38.7%), while imipenem/meropenem (99.6%), amikacin (97.9%), cefepime (96.4%), ciprofloxacin (92.2%), gentamicin (88.1%), aztreonam (85.1%), ceftriaxone (81.2%), and piperacillin/tazobactam (80.9%) were the most effective [48]. Chen et al. [49] investigated 9 *C. freundii* isolates from newborns with sepsis and meningitis during 2014–2017; all isolates were sensitive to tigecycline but resistant to cephalosporins, carbapenems, quinolones, and aminoglycosides.

Clinical *Citrobacter* isolates are usually resistant to more than one antibiotic class. Leski et al. [50] examined 70 Enterobacteriaceae isolates from urine samples and reported that *C. freundii* was the species with the highest multidrug resistance. All 22 *C. freundii* isolates were resistant to ciprofloxacin, gentamicin, and sulfisoxazole, and ESBLs were detected in 81.8% of them. Similarly, a recent study in China

investigated the antibiotic resistance of extraintestinal clinical isolates [47]. Of the 46 *Citrobacter* isolates, 26 were isolated from urine, 15 from sputum, 2 from bile, 2 from secretions, and 1 from blood. Of the 26 urine samples, 16 contained *C. freundii*, 9 had *C. koseri*, and 1 contained *C. braakii*. Moreover, of the 15 sputum samples, 8 contained *C. freundii*, 4 contained *C. koseri*, and 3 contained *C. braakii*. The two bile and secretion samples each contained *C. freundii* and *C. braakii*, and the one blood sample contained *C. koseri*. In addition, over half of the isolates were multidrug resistant; 17 of the 26 *C. freundii*, 3 of the 14 *C. koseri,* and 5 of the 6 *C. braakii* isolates. Resistance to penicillin (84.8%), cephalosporins (67.4%), and azithromycin (65.2%) was high, while resistance to carbapenems was low (13%).

Notably, the minimum duration of antibiotic therapy for *Citrobacter* infections should be 21 days or 14 days after negative cultures for meningitis and 4–6 weeks for brain abscess [1].

33.8 *Citrobacter* Infections in Children and Hearing Loss

In 2019, approximately 1.57 billion people worldwide had hearing loss (HL), corresponding to one in five people [51]. Considering the 0–15 year age group, 70 million children were affected. Moreover, 2.45 billion people are predicted to develop HL by 2050 [51]. In approximately 40% of cases, preventable HL is caused by infections [52]. While the leading causes of HL in childhood include infections and congenital factors, age-related factors are prominent in adults. In children under 5 years of age, HL is primarily caused by otitis media [51]. Hearing loss in children may be reduced by 60% with effective treatment of ear infections and control of vaccine-preventable diseases [51]. In addition to intrauterine infections, pathogens causing meningitis and chronic suppurative or nonsuppurative otitis media are important infectious causes of HL in children [53].

33.8.1 *Citrobacter* Infection of the Central Nervous System

Citrobacter infections are rare in the neonatal period. However, Stoll et al. [54] reported that *Citrobacter* infections accounted for approximately 0.4% of early-onset neonatal sepsis and 16.7% of early-onset neonatal meningitis cases. *Citrobacter* infections emerge sporadically and as epidemics in the neonatal period, as early- or late-onset infections [15, 31, 55]. *Citrobacter* bacilli can be transmitted vertically to newborns through colonies in the mother's genitourinary and gastrointestinal systems or horizontally from the contaminated environment [1, 13, 30, 56]. No clinical feature can distinguish meningitis caused by *Citrobacter* and other gram-negative bacilli.

Citrobacter-related meningitis in newborns is extremely rare. In 1960, cases of two patients with meningitis caused by *C. freundii* were reported for the first time [56]. The first report of *C. koseri*-related meningitis included three cases during an epidemic in 1971 [56]. Central nervous system (CNS) involvement is rare in older

children and immunocompetent adults. However, the case of a healthy adolescent patient with *C. koseri*-related meningitis recovering without sequelae was reported [57]. In addition, the case of an adult patient with malignancy, who died from *C. farmeri*-related meningitis, was reported [41]. Of the 14 adult patients with acute bacterial meningitis, most of whom had undergone neurosurgery, 8 presented with *C. koseri* infection, 3 with *C. freundii* infection, and 1 with *C. farmeri* infection; unfortunately, 3 of the patients died [58].

Reportedly, 1.3% of neonatal meningitis cases are attributed to *Citrobacter* species [30]. During a healthcare-associated epidemic in the neonatal ward in the USA in 1983, 21 newborns were infected with *C. koseri,* and 4 of them developed meningitis [15]. However, between 1974 and 2005, no *Citrobacter* species was detected as the causative agent in 1331 children between the ages of 1 month and 14 years definitively diagnosed with bacterial meningitis in Greece [59]. In the USA, only 3 of the 442 strains underlying bacteremia and/or meningitis episodes reported over 5 years in infants under 60 days of age were *Citrobacter* species [60]. In a study in France, including 444 neonatal meningitis cases reported over 7 years, only 2 isolates were *Citrobacter* species, although no subspecies information was provided [61]. In the United Kingdom (UK) and Ireland, during 2010–2011, an unspecified *Citrobacter* species was detected in only 1 of the 302 isolates from infants under 90 days of age who presented with bacterial meningitis [62]. Meanwhile, in Hong Kong, no *Citrobacter* species was detected in 139 infants between 0 and 3 months of age who presented with bacterial meningitis during 2004–2019 [63]. In a single-center study in 2010–2017 in the USA, *C. freundii* was detected in 1, and *C. braakii* in 1 of the 160 infants under 90 days presented with bacterial meningitis [64].

Brain abscesses are very rare in newborns and children. Except during the neonatal period, the most common cause of brain abscess is *Streptococcus milleri* in children. Brain abscess is also very rare in the neonatal period and is more often caused by gram-negative bacteria [55]. Citrobacter species was the causative agent of brain abscesses during the neonatal period in approximately 60% of cases [65].

In Türkiye, no *Citrobacter* species was detected in 75 children with brain abscesses between 1982 and 2010 [66]. Similarly, *Citrobacter* was not a causative agent of brain abscesses in cases reported in China during 2007–2016 [67]. In Tunisia, *C. koseri* was the causative agent of brain abscess in only 1 of the 41 children between 1995 and 2014 [68]. Similarly, in Italy, *C. koseri* was the causative agent of brain abscess in only 1 of the 79 children between 0 and 18 years of age, although that patient's age was not specified [69]. In France, *C. koseri* was the causative agent of brain abscess in 1 of the 116 children and 3 of the 28 infants, a total of 4 patients, among cases reported over 25 years [70]. In a case series on neonatal brain abscesses from India, *C. koseri* was the causative agent in only 1 of the 15 patients [71].

Citrobacter koseri was the causative agent in 86–92% of children who developed meningitis and brain abscesses due to *Citrobacter* species [1]. *Citrobacter freundii* is the second most frequently (4–7%) reported species, while the incidence of other species is approximately 4%. In particular, *C. koseri*-related meningitis and brain abscesses are more frequent during the first 2 months of life [1].

Although some mechanisms underlying the pathogenesis of *Citrobacter*-associated meningitis are known, it is unclear why newborns are predisposed to this type of meningitis. The risk of brain abscess development in patients with meningitis is approximately 10%, while the rate of brain abscess development in *Citrobacter*-associated meningitis is as high as 75% [56]. *Citrobacter koseri* was detected in 68 and *C. freundii* in 5 of the 74 newborns with *Citrobacter*-related meningitis, and the species could not be typed in 1 case. While 34% of the patients whose follow-up information was available died, 74% of survivors developed sequelae. Moreover, while the mortality rate was 37.5% in patients who developed brain abscesses, no deaths were reported in those who did not [56]. Unhanand et al. [72] evaluated 98 patients under 3 years of age who presented with gram-negative enteric bacillus meningitis between 1969 and 1989. Brain abscesses developed in 4 of the 9 patients with *C. koseri*-related meningitis; all patients were under 3 months of age [72]. In Portugal, 1 of the 4 newborns with *C. koseri*-related meningitis died, 1 developed a brain abscess, and all 3 surviving patients developed severe neurological deficits [73].

The complication rate, specifically the risk of brain abscess development, is relatively high in patients with *C. koseri*-related meningitis [1, 56]. In a study evaluating 68 newborns with *C. koseri*-related meningitis, brain abscesses developed in 77% of the 53 patients whose information was available [56]. Multiple brain abscesses, diffuse necrotizing meningoencephalitis, and pneumocephalus may develop in *C. koseri*-related meningitis [74–77]. Early surgical intervention to manage brain abscesses may positively affect prognosis [74]. Serial imaging should be performed in children to monitor complications, antibiotic effectiveness, and surgical outcomes, as applicable [30, 78, 79].

Brain abscesses due to *C. freundii*-related meningitis are rarer than those due to *C. koseri*-related meningitis. In a recently published series of 9 cases of neonatal sepsis caused by *C. freundii*, meningitis developed in 3 infants, but brain abscess developed in none. All patients were premature, and the cases were detected sporadically over a 4-year period [49]. Meanwhile, in Thailand, *C. freundii* was the causative agent of brain abscess in only 2 of the 107 children diagnosed between 1985 and 2005 [80]. In another study, a term infant presenting with *C. freundii*-related meningitis died due to the development of hydrocephalus and brain abscess [81].

Many studies and meta-analyses of the sequelae of bacterial meningitis in children have been published [82–87]. A meta-analysis evaluating the sequelae of 18,183 children with bacterial meningitis between 1980 and 2008 reported that 7.7% of the children developed HL, which accounted for 33.9% of all sequelae following meningitis [88]. In another meta-analysis conducted by Baraff et al. [82], 4920 children with bacterial meningitis and 1602 children who were followed up for at least 1 year were evaluated. Sensorineural HL (SNHL) was detected in approximately 10% of the patients, while bilateral HL was reported in 5% [82].

However, these meta-analyses did not include detailed data on other than the major meningitis agents, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus agalactiae*. Ouchenir et al.

[89] reported that 4.4% of the 113 infants under 3 months of age presenting with bacterial meningitis developed HL. Kostenniemi et al. [90] reported that at least 30% of the 80 children under 5 years of age presenting with bacterial meningitis developed HL, and 4% developed bilateral HL. In another study, 124 children between 1 month and 16 years of age who presented with acute bacterial meningitis were investigated. Of these, 3 children (2.4%) developed SNHL and 13 (10.5%) developed reversible HL. The cochlea has been identified as the site of lesions in both persistent sensorineural and reversible disorders. Hearing loss was 2.72 times more common in sick children for over 24 h [91]. Moreover, 185 children under 1 month of age who presented with acute bacterial meningitis were followed up for 5 years. Permanent bilateral or unilateral SNHL was detected in 10.3% of the patients. Among these patients, 31% presented with *S. pneumoniae*, 10.5% with *N. meningitidis*, and 6% with *H. influenzae* type b infections [92]. In a prospective study, 51 children with bacterial meningitis were evaluated using serial recordings of brainstem auditory evoked potentials (BAEPs) from the earliest stage of the disease. While transient BAEP abnormalities were observed in 11 (21.6%) children, permanent deafness was noted in 5 (9.8%) children [93]. In conclusion, bacterial meningitis is the most common cause of acquired SNHL in children. In survivors, the frequency of temporary HL due to bacterial meningitis was 10%, and that of permanent HL was 2.4–10.3% [91, 92].

Hearing loss is the most common neurological sequelae of bacterial meningitis in children. Damage to cochlear structures, including hair cells, supporting cells, stria vascularis, spiral ligament, and spiral ganglion neuronal cells during infection, appears to be important for the development of HL due to meningitis [94]. In addition, suppurative labyrinthitis and labyrinth ossification develop due to disruption of the blood–labyrinth barrier by bacteria reaching the cochlea via the cochlear aqueduct, leading to HL [94]. In other words, bacteria reach the labyrinth through a hematogenous or direct route. Labyrinth ossification occurs in up to one-third of suppurative labyrinthitis cases [95].

In addition to the direct effects of bacteria on tissues, cytokines, such as TNF-α, are released during the inflammatory process, and oxidants, such as nitric oxide, are involved [94]. The known major risk factors for HL in bacterial meningitis include suppurative labyrinthitis, advanced age, comorbidity, meningitis severity, low CSF glucose, elevated CSF protein level, and elevated C-reactive protein (CRP) level [96]. Sensorineural HL develops in the first few days of the disease and may be temporary or permanent.

A premature baby who developed meningitis, ventriculitis, and brain abscess due to *C. freundii* infection was treated with antibiotics and surgery [97]. The findings of neurological examination and hearing tests were reported to be normal, although sequelae remained in the brain. In a report from Spain, multiple brain abscesses developed in three newborns with *C. koseri*-related meningitis; all were treated with antibiotics and surgery [79]. While one patient was lost to follow-up, severe sequelae developed in the remaining two, with SNHL detected in one case. However, information on HL was not provided in many case series and reports of children with *Citrobacter*-related meningitis and brain abscesses [49, 73]. In some case series,

follow-up data of all patients could not be collected, or some patients died [56]. Even in studies reporting data on HL, it is impossible to determine the direct effect of *Citrobacter* infection due to other factors that may affect hearing, such as severe prematurity and aminoglycoside use [49, 75, 79, 97]. Moreover, in addition to the type of microorganism, many factors, such as patient age, time of diagnosis, disease severity at diagnosis, and administration of appropriate treatment, play pivotal roles in the development of sequelae [84].

Since acquired SNHL due to early-onset meningitis in newborns, which is caused by *Citrobacter* infections in 16.7% of the cases [54], directly contributes to language development among children, HL should be diagnosed at the latest at 3 months of age, and rehabilitation should be initiated at the latest at 6 months [98]. The role of cochlear implants is important in the hearing rehabilitation of children with acquired prelingual HL following meningitis [99]. Labyrinthitis ossificans, which can involve up to one-third of the ear after meningitis [95], eliminates the possibility of cochlear implantation in children with acquired prelingual HL. Therefore, it is necessary to confirm the diagnosis and plan hearing habilitation before developing labyrinthitis ossificans.

33.8.2 *Citrobacter* Ear Infection

Nasopharyngeal colonization of biofilm-forming microorganisms has been identified as a risk factor for recurrent acute otitis media [100]. In addition, *C. koseri* and *C. freundii* express type 3 fimbriae, adhesive organelles implicated in biofilm formation [26]. Further studies are warranted on the role of type 3 fimbriae in developing otitis caused by *Citrobacter* species.

Chronic otitis media is a common infectious disease in childhood and may lead to HL. In chronic otitis media, ongoing infection in the middle ear and a discharge from the perforated tympanic membrane are observed for at least 2 weeks. Hearing loss may also develop in patients with chronic otitis media without purulent discharge but with effusion. Such patients often present a previous history of acute otitis media [101]. Chronic suppurative otitis media is categorized into two groups: tubotympanic and/or atticoantral disease. *Citrobacter* infections are primarily noted in atticoantral disease [102]. The frequency of *Citrobacter* infections in chronic otitis media may vary between 3.6% and 20% in some African countries [103, 104].

Otitis media with effusion was detected in 44.6% of Senegalese children with meningitis and 40.9% without it [102]. In the same study, HL was noted in 67.9% of children with meningitis and 50% without it, although no conductive or sensorineural distinction was reached. The high rate of HL may be attributed to untreated bacterial otitis media.

A prospective study evaluated 2334 patients admitted to ear–nose–throat outpatient clinics between September 1994 and August 1996 [103]. Otitis was detected in 1630 (69.8%) of the patients. Of these, 1232 (52.8%) patients presented with chronic otitis media with purulent discharge and HL, and 245 (10.5%) patients presented with chronic otitis media without purulent discharge but HL. Interestingly,

the rate of HL was lower in children with acute and chronic seromucinous otitis media, 4.1%, and 2.4%, respectively. Among the identified microorganisms, the frequency of *Citrobacter* species was 3.6%. When the bacteria grown in ear discharge cultures were investigated, the frequency of *Citrobacter* species was 1.4% in 115 patients between 6 and 35 years of age presenting with otitis media [105].

In Ethiopia, culture growth from 283 ear discharges of 369 patients suspected of having ear infections was examined over 5 years. While the most commonly detected agents were *Staphylococcus aureus* (27.9%), *Proteus* species (20.8%), *Streptococcus* species (10%), and *Pseudomonas* species (8.9%), *Citrobacter* growth was detected in only 15 (5.58%) samples. Over half of the known *Citrobacter* species exhibited multidrug resistance [52]. Likewise, in Ethiopia, *Citrobacter* species were detected in the ear discharge of 10% of patients with chronic otitis media but not those with acute otitis media [106]. In Angola, 534 ear discharge cultures of patients with chronic suppurative otitis media were evaluated; *Proteus* species (14.7%) and *Pseudomonas aeruginosa* (13.2%) were the most commonly detected bacteria, while *Citrobacter* species were detected in only 3.4% of samples [107]. In a study evaluating middle ear drainage cultures of 78 children with chronic suppurative otitis media, Citrobacter species' growth frequency was 20%. *Citrobacter* was the third most common causative agent of otitis media, following *Proteus mirabilis* and *P. aeruginosa*. Ofloxacin and neomycin were the most effective agents and were recommended as the first-line topical therapy [104]. Unfortunately, subspecies information was not provided in these publications. *Citrobacter freundii* was detected in the ear discharge cultures of 569 patients with otitis media at a rate of 1.7% [108]. In a case report, a 49-year-old patient with chronic otitis media underwent surgical treatment for subdural empyema and cerebellar abscess, and *C. koseri* was detected in cultures obtained from the outer ear before surgery [109].

The low incidence of *Citrobacter* species ear infections is the most significant hindrance to specific studies of these bacteria. Most of the previous studies were conducted in very low-income countries. More importantly, no standard protocols have been established, even for sample collection. Therefore, it may be impossible to determine the effect of *Citrobacter* ear infections on HL. Further studies are imperative to assess the impacts of *Citrobacter* species on ear infections and their contribution to HL development.

In summary, processes that lead to the development of conductive HL, such as chronic suppurative or nonsuppurative otitis media, can cause mild-to-moderate HL. Hearing loss can be intermittent or permanent, and warrants close monitoring. Even mild HL can be significant in the early years of life. Hearing loss leads to severe consequences in children. Whatever the degree, HL can affect cognitive and academic functions, communication, and language skills and produce social and behavioral effects [110]. Acquired HL during the prelingual or postlingual period, similar to congenital HL, affects language development [110]. In addition, even if language development is not affected, early diagnosis and treatment of HL in children of all age groups are critical, considering that it can lead to severe problems, such as introversion, social isolation, and school failure, some of which are irreversible [111].

33.9 Conclusion

In humans, *Citrobacter* species can cause infections at any age and in any system. However, they cause invasive infections, particularly during the neonatal period. Hearing loss due to *Citrobacter* infections is mainly associated with CNS involvement and otitis media. The former causes SNHL, while the latter causes conductive HL. Prelingual SNHL and conductive HL caused by *Citrobacter* infections in newborns directly contribute to language development in childhood. Hearing loss should be diagnosed at the latest at 3 months of age, and habilitation should be initiated at the latest at 6 months [98]. Even mild-to-moderate HL due to chronic suppurative or nonsuppurative otitis media can be harmful in early life. Thus, mild-to-moderate conductive HL should not be ignored, as advanced SNHL may negatively affect children's speech and language development and academic success. As in the case of other infectious agents, the positive effects of early diagnosis and treatment on mortality and morbidity, including HL due to *Citrobacter* infections, are indisputable.

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Fusobacterium Infections in Children and Hearing Loss

34

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34.1 Introduction

Fusobacterium species are part of the normal human microbiome [1]. Fusobacteria were first discovered in the female genital tract in the late nineteenth century, and the genus *Fusobacterium* was described in the early twentieth century [1, 2]. These bacteria have been well-documented in studies over time. *Fusobacterium* species are associated with various human diseases, ranging from mild pharyngitis to sepsis [3–5]. In addition, these microorganisms are most well known as the cause of septic thrombophlebitis of the internal jugular vein (IJV), also known as Lemierre's syndrome [3].

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34.2 Etiology

Fusobacterium species, members of the phylum Fusobacteria, are pleomorphic, filamentous, nonspore-forming, thin, long, nonmotile, facultatively anaerobic gram-negative bacilli [1, 3, 6]. Clinical infections are most commonly due to *Fusobacterium nucleatum*, *Fusobacterium necrophorum*, *Fusobacterium mortiferum, Fusobacterium varium, Fusobacterium ulcerans, Fusobacterium gonidiaformans, Fusobacterium naviforme, Fusobacterium necrogenes, Fusobacterium russii,* and *Fusobacterium varium* [2, 7, 8]. Up to one-third of *Fusobacterium* infections are polymicrobial [3, 6]. The main virulence factors of *Fusobacterium* spp. are leucocidins, hemolysins, lipases, deoxyribonucleases (DNases), and hemagglutinins [2, 3]. In addition to these virulence factors, *F. necrophorum* can aggregate platelets and produce lipopolysaccharides, and *F. nucleatum* has beta-lactamases [2, 3].

Fusobacterium species are also part of the normal flora of the oropharynx, gastrointestinal, and female genital tracts [1]. In children, *Fusobacterium* spp. have been isolated from middle ear aspirates [9]. In addition, *F. nucleatum* has been detected in saliva, nasopharyngeal, and middle ear effusion samples [10]. *Fusobacterium* species are commonly found in soil and the respiratory samples of animals, such as cattle, dogs, sheep, and horses [2].

34.3 Epidemiology

With improved diagnostic techniques for anaerobic infections, non-culture-based molecular tools, superior blood culture methods, and the decreased usage of empiric antibiotics, the reported incidence of *Fusobacterium* infections has increased [3, 4, 11–14]. The incidence of *Fusobacterium* infections ranges from 0.8 to 3.6 cases per million people [15–17]. Also, there has been an increase in middle ear infections and complications due to *Fusobacterium necrophorum* in the last two decades [12, 16–18]. Although *Fusobacterium* infections are primarily seen in adolescents and young adults, severe and fatal cases have also been reported in infants and children [3]. In children, the bacilli usually will come from the middle ear and, less often, the cervical lymph node to develop localized *Fusobacterium* head and neck infections [19]. *Fusobacterium* infections developing from throat and tonsil colonization are usually seen in older children [19]. Lemierre's syndrome is mostly seen in 15–24 years old adolescents and young adults, with approximately 14 cases per million [3]. *Fusobacterium* infections are also most often seen in boys and peak in late winter [3].

Fusobacterium species have been isolated from head, neck, and upper respiratory tract infections [1–3]. Using appropriate culture and molecular tests, it has been reported that *F. necrophorum* can be detected in 20.5% of patients presenting with a sore throat and 9.5% of asymptomatic young adults [20]. *Fusobacterium necrophorum* has also been found in 10–21% of sore throat and tonsillitis, 21–23% of peritonsillar abscesses, and 13% of acute mastoiditis cases [12, 19, 21–23]. *Fusobacterium* infections, especially those due to *F. necrophorum*, are seen as acute

otitis media, mastoiditis, and the otogenic variant of Lemierre's syndrome [13]. *Fusobacterium* species have also been found in 5–21% of chronic suppurative otitis media, chronic mastoiditis, and chronically infected cholesteatoma cases [24].

34.4 Clinical Manifestations

Fusobacterium species are frequent components of human dental plaques; therefore, these bacteria are potential agents for periodontal and oropharyngeal diseases and primary sources of invasive infections such as otitis media, tonsilitis, and gingivitis [1, 3, 25, 26]. Acute or chronic otitis media, mastoiditis, peritonsillar and retropharyngeal abscesses, recurrent tonsillitis, acute or chronic sinusitis, parotitis, deep neck abscesses, and Vincent's angina are the most common clinical presentations of *Fusobacterium* spp. infections [1–3, 6, 8, 19–26].

Vincent's angina is an acute necrotizing ulcerative gingivitis, also known as trench mouth, and *Fusobacterium* spp. are among the causative organisms [9]. In addition, Ludwig's angina, a rapidly progressing, life-threatening deep tissue infection of the mouth floor, is typically a polymicrobial infection of the oral cavity flora that includes *Fusobacterium* spp. [27, 28]. The spread of microorganisms caused by this condition can result in infections of the maxillary sinus, cavernous sinus, or brain parenchyma [27, 28].

Lemierre's syndrome was first described in the early twentieth century and is the most fatal and clinically important infection caused by *Fusobacterium* spp. It is a life-threatening deep neck infection characterized by suppurative thrombophlebitis of the IJV [1, 3, 6, 8]. Lemierre's syndrome typically begins with a sore throat and fever, followed by severe neck pain, unilateral neck swelling, trismus, dysphagia, and rigors. Generally, rigors present on the fourth or fifth day following the onset of a sore throat [1, 3, 6, 8]. Tenderness in the anterior cervical triangle is often present. Suppurative thrombophlebitis of the IJV can cause sepsis or metastatic septic emboli in the lungs and other sites [1, 3, 6, 8].

With the onset of sepsis or septic emboli, pleural empyema, pyogenic arthritis, osteomyelitis, endocarditis, disseminated intravascular coagulation (DIC), and multiorgan failure can occur [1, 3, 6, 8]. Persistent headaches and neurological signs may indicate neurological complications, such as cerebral sinus venous thrombosis, meningitis, or brain abscesses [1, 3, 6, 8]. Lung or liver abscesses, pyogenic arthritis, osteomyelitis, and spondylodiscitis are generally recognized as illness complications [3]. *Fusobacterium* species, of which *F. necrophorum* is the most prevalent spp., cause 80% of Lemierre's syndrome cases [29, 30]. Otogenic-associated Lemierre's syndrome has been observed in younger children more often than pharyngitis-associated Lemierre's syndrome in older children [3, 11].

Anaerobic pathogens have been found in cultures from chronic otitis media cases and patients with acute exacerbation of Lemierre's syndrome [1, 9, 24]. A single-center study found *F. necrophorum* in 25 pediatric acute otitis media cases over 10 years, and uncomplicated acute otitis media, mastoiditis, and the otogenic variant of Lemierre's syndrome were observed in 44%, 40%, and 4% of cases in this

study population, respectively [13]. More often, *F. necrophorum* has been reported as the causative agent for otogenic infections [16–18].

Multiple studies have suggested that the incidence of ear infections due to *Fusobacterium* spp., especially *F. necrophorum*, is rapidly increasing. Gelbart et al. [12] reported the number of *Fusobacterium* ear infections increased sevenfold over a three-year period. The reasons for the increasing incidence of *F. necrophorum* infections are still unknown. However, they may be related to widespread *Streptococcus pneumoniae* vaccinations, which can increase the presence of gram-negative anaerobic microorganisms in the oropharyngeal and nasopharyngeal flora [31].

Early reports revealed that the otogenic variant of Lemierre's syndrome was approximately 30% of all Lemierre's syndrome cases [15]. Otogenic-disseminated fusobacterium infections can result in intracranial complications, including meningitis, suppurative thrombophlebitis of the lateral and/or cavernous sinuses, epidural abscesses, or septic emboli [3, 13, 14, 18]. Ulanovski et al. [18] found that mastoiditis due to *F. necrophorum*, diagnosed by culture or polymerase chain reaction (PCR), was more likely to present with higher fevers, higher C-reactive protein levels, acute/chronic otitis media, ear discharge, and subperiosteal abscess compared to that caused by other pathogens.

Thrombolytic events are commonly associated with *Fusobacterium infections* due to platelet aggregation caused by hemagglutinin secretions from these microorganisms [1–3]. Sinus venous thrombosis, commonly seen in mastoiditis due to *F. necrophorum,* can occur through the hematogenous spread, direct invasion, or via the thrombogenic effects of the microorganism [12, 14, 18].

Polymicrobial pleuropulmonary infections can occur after the aspiration of oropharyngeal secretions or severe gingival or periodontal disease [1, 8]. *Fusobacterium* species are among the anaerobic causes of pleuropulmonary, skin, and soft tissue infections [1, 8]. In addition, *Fusobacterium* species have also been isolated from blood, wounds, abscesses, and specimens of obstetric or gynecologic infectious diseases [1, 3, 6, 8]. Bacteremia due to anaerobic bacteria is increasing every year, and *Fusobacterium* bacteremia represents less than 10% of anaerobic bacteremias and less than 1% of all bacteremias [3, 4].

Although *Fusobacterial* bloodstream infections have been documented in healthy and immunosuppressed children, underlying diseases and immunosuppression increase the incidence of these infections [3, 4].

34.5 Laboratory Findings and Diagnostic Tests

Laboratory findings are nonspecific in *Fusobacterium* infections; however, elevated inflammatory markers, leukocytosis, and neutrophilia are commonly observed [1, 3, 6, 8]. In addition, hepatic biochemical tests are abnormal in 11–49% of cases of Lemierre's syndrome [3, 15, 17]. However, thrombocytopenia and evidence of DIC are seen less often in Lemierre's syndrome [3, 15, 17].

If Lemierre's syndrome is suspected, aerobic and anaerobic blood cultures should be obtained immediately to identify pathogens [6]. The culture confirmation

is related to adequate and protected specimens, optimized transportation, the culture medium, and identification [1–3, 6, 8]. Semisolid medium for fastidious anaerobic organisms or blood agar supplemented with vitamin K, hemin, menadione, and a reducing agent are suitable environments for *Fusobacterium* species growth [1–4]. On blood agar, *Fusobacterium* spp. form pinpoint colonies and can be irregular or circular, cream to yellow colored, smooth, or round [1–4]. The colonies may also demonstrate a thin zone of alpha (α) and beta (β) hemolysis on blood agar, and *F. nucleatum* may appear as breadcrumb-like colonies [1–3]. *Fusobacterium* species are sensitive to kanamycin and colistin and resistant to vancomycin [1–3, 6, 8]. Most *Fusobacterium* spp. are indole positive and produce butyric acid during the metabolization of peptones and carbohydrates [1–4, 6, 8].

Polymerase chain reaction-based molecular methods improve detection, confirmation, and identification [1–3, 6, 8, 32]. For identification, mass spectrometry for bacterial cell components, sequencing of the 16S ribosomal ribonucleic acid (rRNA) gene, and phylogenetic analysis can also be used. There are no commercial tests to diagnose *F. necrophorum* pharyngitis, and routine throat cultures do not generally screen for *F. necrophorum* [1–3, 6, 8, 32].

Imaging studies are also performed to diagnose mastoiditis, Lemierre's syndrome, and intracranial complications [12, 14, 18]. Imaging studies of the IJV and the lateral and cavernous sinuses should be obtained to confirm clinical suspicions. Contrast-enhanced computed tomography (CT) of the neck and chest helps to evaluate the IJV for thrombosis or thrombophlebitis and pulmonary emboli or abscesses [3, 13, 14, 18]. Magnetic resonance (MR) imaging of the neck has also been used to document IJV thrombosis or thrombophlebitis. Ultrasonography is an alternative diagnostic tool; however, it is less sensitive for detecting IJV thrombosis in the early stages of the illness than CT or MRI [32].

34.6 Differential Diagnoses

Fusobacterium species typically cause thrombophlebitis, odontogenic, upper respiratory tract, and otogenic infections. Fusobacterium infections should be kept in mind in the differential diagnosis of these infectious processes. Septic thrombophlebitis presents as a complication of catheter-associated bloodstream infection [33]. The presence of venous thrombosis may be revealed by ultrasonography, and microbiologic diagnosis may be based on blood culture [33]. *Candida* suppurative thrombophlebitis is an uncommon complication of invasive candidiasis [34]. In addition, bilateral IJV thrombosis has been associated with underlying malignancy, and screening for malignancy should be considered in these cases [35].

Lemierre's syndrome, deep neck infections, peritonsillar abscess, chronic rhinosinusitis, and Ludwig's angina may also be caused by *Arcanobacterium hemolyticum*, *Bacteroides* species, anaerobic streptococci, other anaerobic bacteria, and *Staphylococcus aureus* [1, 3, 36]. Bacterial pharyngitis (*Streptococcus pyogenes* [group A streptococcus], *Neisseria gonorrhoeae*), viral pharyngitis (respiratory viruses, herpangina, severe acute respiratory syndrome coronavirus-2

[SARS-CoV-2], herpes simplex virus [HSV]), and noninfectious pharyngitis (Stevens–Johnson syndrome, Kawasaki disease, Behcet syndrome, foreign body, chemical exposure, and periodic fever, aphthous stomatitis, pharyngitis, adenitis [PFAPA] syndrome) causes should be considered in the differential diagnosis for upper respiratory infections that presented as sore throat [37]. Benign or malignant tumors of the mastoid bone, perichondritis of the auricle, mumps, and periauricular cellulitis should be considered as the differential diagnosis of acute mastoiditis [38].

34.7 Treatment

Aggressive and prompt antimicrobial therapy is critical for *Fusobacterium* spp. infections. *Fusobacterium* species are susceptible to clindamycin, penicillin with a beta-lactamase inhibitory combination, metronidazole, carbapenem, cefoxitin, and ceftriaxone [3, 32, 39–41]. However, antibiotic resistance to these drugs in *Fusobacterium* spp. has been reported [1–4, 42–44]. *Fusobacterium nucleatum, F. mortiferum,* and *F. varium* produce beta-lactamases [1–4, 6, 8, 42–44]; therefore, antibiotic susceptibility testing is necessary for all *Fusobacterium* spp.

In general, antibiotic regimens that combine metronidazole or clindamycin with cephalosporins are recommended for invasive infections [3, 5, 11, 42, 43, 45]. Alternatively, monotherapy with penicillin and beta-lactamase inhibitors or carbapenem is also recommended [3, 5, 11]. Empirically, the treatment regimen for Lemierre's syndrome is recommended as meropenem 60 mg/kg/day divided q8h (120 mg/kg/day divided q8h for central nervous system [CNS] metastatic foci), or ceftriaxone 100 mg/kg/day q24h and metronidazole 40 mg/kg/day divided q8h, or clindamycin 40 mg/kg/day divided q6h [39]. If methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, vancomycin 40 mg/kg/day divided q6h (60 mg/kg/day divided q6h for CNS metastatic foci) is recommended as well [39]. Metronidazole or clindamycin are recommended for other Fusobacterium infections, such as soft tissue infections [40]. *Fusobacterium* species are generally resistant to gentamicin, fluoroquinolones, and macrolides, and tetracyclines have limited activity [1–4, 6, 8, 32]. However, the treatment duration varies according to the anatomical region and the severity of the infection and usually is suggested to be 4–6 weeks [3, 5, 8, 11, 32].

Cases with IJV thrombosis associated with Lemierre's syndrome have evidence of thrombophilia. In these cases, anticoagulant therapy to reduce septic embolic events is problematic due to insufficient data in limited case reports [3, 35, 46, 47]. However, it has been suggested that anticoagulant therapy may be used in cases with thrombosis, fever, or bacteremia after appropriate antibiotic treatment for retrograde progression into the cavernous or lateral sinuses [35]. While the ideal duration of anticoagulant therapy is uncertain, treatment may continue until the patient has clinically improved or the thrombosis is no longer progressing. Anticoagulant treatment may also be given for a longer duration in patients with an embolic disease or those with underlying prothrombotic risk factors. These findings often resolve over several months. Anticoagulant therapy remains controversial since the evidence of thrombophilia typically indicates an inflammatory, prothrombotic progression due to infection rather than a primary hypercoagulable status [32].

According to clinical findings, interventional procedures should be performed, such as drainage for purulent fluid collections or abscesses, chest tube drainage for pulmonary empyema, or the debridement of necrotic tissue [1, 3, 48]. Ligation of a thrombosed IJV has not been widely used due to the effectiveness of antibiotic therapy except in uncontrolled sepsis or septic emboli, despite appropriate antibiotic and anticoagulation treatment in rare instances [3, 49].

Surgical interventions for cortical mastoidectomy and inserting a ventilation tube have been performed in a high percentage (93–100%) of mastoiditis cases due to *F. necrophorum* [12, 14, 18].

34.8 Prognosis

Mortality and high morbidity are commonly seen with *Fusobacterium* infections [3, 41]. Meningitis, total obliteration of the mastoid, sigmoid sinus thrombosis, intracranial abscesses, and epidural or subdural empyema often occur in *Fusobacterium* infections. These complications can occur with either a pharyngeal or otogenic source of *Fusobacterium* spp.

34.9 Prevention

It is unlikely to prevent most *Fusobacterium* infections; however, prevention measures in general, such as identifying and treating predisposing conditions (e.g., exposure to tobacco smoke, use of pacifiers) and encouraging breastfeeding for protective impact of upper respiratory infection, odontogenic and otogenic infections are recommended [50, 51]. Early, adequate treatment of otogenic infections reduces the risk of mastoiditis or invasive infections [50]. Promoting good dental and oral hygiene is key to the prevention measures for odontogenic infections [1, 3, 51]. Oral antimicrobial rinses with 0.12% chlorhexidine help control dental plaque bacteria; however, prolonged application can promote the emergence of resistant microorganisms [52]. Oral probiotics may effectively prevent and treat periodontal disease in high-risk populations [53]. It is also recommended to properly clean and debride wounds, prompt removal of foreign bodies, and avoid disruption of the intestinal wall during surgery to limit the entry of these bacteria into tissues by other routes [6]. In addition, aspiration of oral flora can be prevented by improving the neurological status and oral hygiene and lowering stomach pH; thus, the risk of aspiration pneumonia can reduce [8]. Finally, the wise and judicious use of antibiotics may prevent infections [1, 3].

34.10 *Fusobacterium* Infection and Hearing Loss

Hearing loss (HL) has been reported as a rare complication of *Fusobacterium* infections in children [3, 54–56]. The current medical textbooks do not contain information on HL complications of *Fusobacterium* infections [1, 6, 8, 57]. However, the

literature search has revealed limited data on children's HL caused by *Fusobacterium* infections based on case reports [54–56].

In the first case report, a previously healthy eight-year-old girl had Lemierre's syndrome secondary to bilateral mastoiditis [54]. Antimicrobial, anticoagulant, and surgical treatments were given. *Fusobacterium necrophorum* was isolated in cultures from the left mastoid. During the follow-up, cervical fasciitis, right sixth cranial (abducens) nerve palsy, and septic arthritis of the right ankle developed. An audiogram 2 weeks after discharge revealed a unilateral sensorineural HL (SNHL) in the right ear. Irregular erosion of the posterior wall of the petrous temporal bone extending into the vestibule and posterior semicircular canal was seen. Serial audiometry at third- and sixth-month follow-ups revealed almost complete recovery of the HL with hearing aids and the other rehabilitation recommendations, along with improved all effects of the disease. It has been suggested that the possible mechanisms for HL, in this case, included the existence of labyrinthitis in which the sensory elements of the cochlea were not wholly damaged or a transient embolic event that was partly resolved with anticoagulant therapy. In addition, the fluid balance in the labyrinth may have been affected by thrombophlebitis of either the cochlear vein or the vein of the aqueduct.

The second case report was a 16-year-old previously healthy girl presenting with Lemierre's syndrome and metastatic infection resulting in bilateral petrous apicitis and meningitis caused by *F. necrophorum* [55]. During the illness, the patient complained of unilateral HL with left sixth and 12th cranial nerve palsies. Along with antibiotic treatment, left petrosectomy, and mastoidectomy surgery, the patient recovered entirely 3 months after the initial presentation with no HL.

The third case report was a 10-year-old otherwise healthy boy with complicated otitis media and petrous apicitis caused by *F. necrophorum* [56]. Sensorineural and conductive HL was observed. Along with cavernous sinus thrombosis and left internal carotid artery vasculitis developed. Antimicrobial and anticoagulant treatment was given. After a 3-month follow-up, audiological testing revealed both ears resolved neurological and ontological symptoms.

The HL in those cases was on a conductive or sensorineural basis and caused by otogenic *F. necrophorum* infections. In follow-up, the conductive and sensorineural aspects of the HL were resolved in these patients [54–56]. As mentioned above, the virulent factors of *Fusobacterium* spp., especially platelet aggregation of *F. necrophorum*, can result in thrombolytic complications [1–3].

34.11 Conclusion

Although *Fusobacterium* species are part of the normal human microbiome, *Fusobacterium* spp. have been isolated from head, neck, and upper respiratory tract infections and are known to cause Lemierre's syndrome with high mortality and morbidity rate. There has been an increase in middle ear infections and complications due to *F. necrophorum* in the last two decades [58]. Lemierre's syndrome should be kept in mind in a febrile, ill-appearing child with a sore throat, neck pain,

and swelling over the angle of the jaw with rigors. To prevent complications, early diagnosis and prompt treatment are essential. Patients with *Fusobacterium* infections should be monitored for morbidities such as neurological deficits or HL.

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Streptococcus suis Infection and Hearing Loss

35

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35.1 Introduction

Streptococcus suis is a zoonotic pathogen that can cause severe systemic infections in pigs and humans. Meningitis and septicemia are the critical clinical manifestations of the cases. Hearing loss (HL) reported by up to one-half of the patients is one of the striking features of the *S. suis* infection at presentation or a few days later [1, 2]. In addition to HL, vestibular dysfunction is another common complication among patients.

In recent years, the number of cases of *S. suis* infection has notably increased, with the highest prevalence in Southeast Asia, in which the swine consumption rate is high. Moreover, most patients are seen in Vietnam and Thailand [3]. The mortality among *S. suis* meningitis cases is lower than the cases caused by other causative agents; however, some authors reported a higher neurological sequelae ratio than other bacterial meningitis [4]. Although pig or occupational exposure is not documented in all cases of *S. suis* infection, pigs and pig-related occupations, including farming and works involving meat processing, seem to be the significant risk factor for human *S. suis* infection. The risk of infection among the general population or other risk factors such as eating habits should not be underestimated for *S. suis* diseases [3, 5].

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35.2 Epidemiology

The first report among piglets with meningitis, septicemia, and arthritis caused by *S. suis* was published in 1954 by veterinarians [6]. Human infection rarely occurs, particularly in people with a prolonged contact history with pig and pig products [7]. Pig infections due to *S. suis* are reported worldwide, from North and South America to Asia, Australia, and New Zealand, in addition to European countries [1, 8].

Asymptomatic carriage is common in pigs; furthermore, it is believed that *S. suis* might be a commensal agent in the intestinal flora of a couple of other animals, such as cats, dogs, deer, and horses [8]. First human cases with *S. suis* were reported from Denmark, followed by new patients diagnosed in other countries, including the Netherlands, England, and Hong Kong [9–11]. Since the first human case report, more *S. suis* cases have been reported over the past years. In an article published in 2009, more than 700 cases commonly originating in Southeast Asia were reported [1].

Although the exact prevalence of human carriage of *S. suis* is unknown, the carriage rate was reported as 5.3% in a study from Germany, particularly in individuals with prolonged and recurrent pig or pork exposures [1].

The increased number of cases of *S. suis* infection was commonly seen during the summer or rainy seasons. It is believed that there is a possibility that some predisposing factors have the potential to trigger more stress in pigs in hot and humid weather. As a result, this condition also enables the organism to increase infectivity via proliferation in pig carcasses during contaminated meat exposure [3].

35.3 Etiology and Transmission

Streptococcus suis infection is common among pigs. The prominent locations of *S. suis* in piglets are the upper respiratory (e.g., nasal cavities, tonsils), genital, and alimentary tracts, with an up to 80% asymptomatic carriage rate. *Streptococcus suis*, carried in the upper respiratory tract of pigs, spreads among pigs by nose-to-nose contact or by aerosol over short distances. *Streptococcus suis* infection is transmitted from pigs to humans basically through direct contact. But it may also be transmitted through mucous membranes or ingesting infected pigs' meat. Some human infections are found to be associated with wound infection.

Indirect exposure might be another infection source because of the widely available wet markets in Asian countries. The idea of whether the oral route is another transmission possibility for the *S. suis* infection has been raised because of the cases presented with diarrhea [1, 3]. Furthermore, it might be hypothesized that asymptomatic carriage might be an important transmission way for a couple of microorganisms like *Streptococcus pneumoniae* [12].

Of the 35 known serotypes, serotypes 1–9 and 14 are responsible for pig infections, and serotype 2 is considered the most pathogenic for both pigs and humans [13, 14]. Serotypes 1, 4, 14, and 16 are responsible for human infections with severe

disease courses [1]. Sialic acid-containing polysaccharide capsule lets *S. suis* enter the bloodstream and penetrate to blood–brain barrier [3].

The incubation period of *S. suis* infection ranges from 3 h to 2 weeks.

35.4 Risk Factors

The mean patient age ranged from 47 to 55 years, and the absence of pediatric cases supports that the infection is an occupational disease. A relatively high male case predominance can also be explained by the fact that the disease is mainly associated with occupation. Additionally, the male predominance was also attributed to the likelihood of exposure to pigs, and the activities like slaughtering and alcohol use have made men more prone to infection.

The annual risk of developing *S. suis* infection has been estimated at 1.2–3 cases per 100,000 population [1, 3, 10]. Slaughtering and cutting carcasses, processing sick or dead pigs, accommodation with pigs, contact with contaminated pork, and consuming uncooked or partially cooked pork products are major risk factors for infection. However, contact history with pigs or pork, or related products could not be found in a couple of cases with *S. suis* infection. Unknown skin lesions are considered an entry for organisms in those cases.

Splenectomy, diabetes mellitus, alcoholism, malignancy, and heart diseases are predisposing factors for *S. suis* infection [15, 16].

35.5 Clinical Manifestations

Meningitis and septicemia are the most common presentations of human cases with *S. suis*; meningitis is often accompanied by septicemia. Erythematous blanching rash on the extremities might indicate toxic shock syndrome. Classic meningitis signs and symptoms, such as fever, headache, mental status changes, and meningeal irritation, are found in *S. suis* meningitis cases.

Skin findings such as petechiae, purpura, ecchymoses, purpura fulminans, and gangrene of the fingers and toes may be seen in a small group of patients. Petechiae or mentioned skin signs were presented in a few reports and ranged from 3% to 7% among *S. suis* meningitis cases. Patients with such clinical features might be misdiagnosed as *S. pneumoniae* or *Neisseria meningitidis* meningitis.

The prevalence of toxic shock syndrome is changing between 2 and 28% in many studies, and it was found to be associated with high mortality, particularly in younger with a short incubation period [1–3, 7, 11].

Ocular involvement, such as nystagmus, brain stem ophthalmoplegia, endophthalmitis, and uveitis, was also reported in humans. Infective endocarditis and spondylodiscitis are fewer common manifestations of *S. suis* infection. Joint involvement (arthritis) was also shown in cases rarely [1, 17]. Visual loss was reported in a limited number of case series [1, 3, 5, 18].

The mortality rate is low compared to meningitis due to other bacterial agents in the same age group. Deaths commonly result from complications, such as sepsis, multiple organ failure, and disseminated intravascular coagulation [3]. The case-fatality rate of the cases with *S. suis* meningitis has ranged between 2.6 and 7% in some countries, including Vietnam and Netherlands, and reached up to 63% among patients with septicemia in an outbreak in China [5, 10, 19].

35.6 *Streptococcus suis* Infection and Hearing Loss

Hearing loss and vestibular disturbance seem to be the most frequent permanent sequelae of *S. suis* infection. Hearing loss caused by *S. suis* meningitis is sensorineural. It ranges from mild to severe, which might be permanent in some cases once it has already started despite the successful meningitis treatment. According to animal studies, the probable pathogenesis of HL in *S. suis* infection might be explained by the invasion of microorganisms to the perilymph via the cochlear aqueduct that results in suppurative labyrinthitis [15]. Vestibular dysfunction might be associated with HL. Vestibular dysfunction or ataxia are also other common manifestations and are seen in half of the cases with meningitis.

35.7 Diagnosis

Streptococcus suis is a gram-positive coccus and can be isolated from blood samples and cerebrospinal fluid; however, the misidentification of species or culture negativity may have been commonly seen. The awareness of clinicians and microbiologists is of great importance in making the correct diagnosis. Additionally, some clues from epidemiologic history should be carefully determined by clinicians. Polymerase chain reaction (PCR) tests are an alternative diagnostic modality [13, 20].

35.8 Treatment

Considering the *S. suis* infections such as meningitis or sepsis, antimicrobial treatment should be started as soon as possible. Although *S. suis* is susceptible to penicillin, ceftriaxone, and vancomycin, penicillin resistance has been reported in some human cases and diseased pigs. The mean minimum inhibitory concentration (MIC) for penicillin ranged between 0.015 and 0.060 μg/mL. Additionally, gentamicin, trimethoprim-sulfamethoxazole, macrolide, and tetracycline resistance were observed; fortunately, a few cases with multiple antimicrobial resistance were reported.

Like the other cases of bacterial meningitis, ceftriaxone with or without vancomycin might be the best therapeutic option for the empirical treatment of *S. suis* infection. The doses and treatment duration used in cases with meningitis due to *S. pneumoniae* are recommended in *S. suis* meningitis. High-dose intravenous

penicillin G is another therapeutic option successfully used for 2 weeks. Treatment duration may be prolonged up to 4–6 weeks in patients who experienced relapse after 2 weeks of treatment course and when complications such as meningitis, endocarditis, or spondylodiscitis are present.

Treatment recommendations may be modified in cases with overlapping conditions, including endocarditis and arthritis, or with complications such as an intracranial abscess. A combination regimen, for instance, including penicillin or cephalosporin plus an aminoglycoside, may be a better therapeutic option in cases with infective endocarditis. Recommendations in guidelines should be used in patients with such kinds of mentioned situations in terms of the need for other medications, treatment durations, and surgery [3, 5, 21, 22].

Although the data is scarce on the use of dexamethasone, the decrease in mortality and HL were reported in a limited number of studies. On the other hand, HL was associated with older age rather than corticosteroid treatment [5, 21]. However, despite these controversial data, dexamethasone treatment is recommended in adult meningitis cases in Vietnam [1].

35.9 Prevention

Since no current human vaccine is available, basic preventive measures are essential. Hand washing after exposure to raw pork meat or products and wearing gloves during handling the pig meat or slaughtering have great protective potential to decrease the *S. suis*-associated disease burden. Because *S. suis* is one of the most common causes of adult meningitis in Asian and Southeast Asian countries, such as China, Vietnam, and Thailand, travelers should be warned about eating habits in mentioned areas [1].

35.10 Conclusion

Clinicians often undiagnose *S. sui*s infection, particularly in countries with a low prevalence, resulting in delay or inadequate treatment. Understanding the epidemiologic and clinical features and predisposing factors of *S. sui*s infection is crucial to developing a proper screening and management procedure, particularly for long-term sequelae such as HL.

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Lyme Disease and Hearing Loss in Children

36

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36.1 Introduction

Lyme disease is the disease most frequently transmitted by a vector in the USA. It affects multiple body systems, and the pathogenesis involves infection by the *Borrelia burgdorferi* spirochaete combined with how the immune system responds to the infection [1]. The spirochaete is introduced into the human body when a tick of the genus *Ixodes* punctures the skin of the patient.

36.2 Background

The combination of infection with the *B. burgdorferi* organism and the immune reaction to that infection are the causes of Lyme disease, a disorder that affects multiple physiological systems [1]. The infection occurs after a tick belonging to the genus *Ixodes*, which is itself infected with *B. burgdorferi*, bites a human [2].

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The vector-borne illness occurring with the highest frequency in the USA is Lyme disease. The American CDC (Centres for Disease Control and Prevention) record at least 30,000 incidences of Lyme disease annually. In 2015, Lyme disease was in sixth place amongst disorders that are notifiable on a national basis [3]. The disorder is endemic in several regions of North America, Europe and Asia [2].

Being bitten by a tick is only spontaneously reported in between 25 and 30% of cases occurring in the USA, early on in infection. The history must therefore be directed towards asking about the possibility of such an occurrence. Epidemiological factors strongly influence the likelihood of the diagnosis. There is a raised risk of Lyme disease in individuals who have contact with ticks. Such individuals have usually spent some time outside in woods or areas of brush or extensive grass in locales where Lyme disease is endemic. The peak frequency for bites is May to November [2].

Lyme disease causes a characteristic dermatological exanthem, the so-called erythema migrans, early on in infection. It also provokes a non-specific pyrexia. The early stage encompasses the period from 1–30 days following introduction of the spirochaete into the body from a tick bite [2].

The effects of the disease generally begin to disseminate around 3–10 weeks after the initial entry of the pathogen into the body. The symptoms occurring with highest frequency affect the musculoskeletal and nervous systems, whilst symptoms affecting the heart and eyes are less frequently noted. Where the eyes are affected, conjunctivitis is the usual presentation [2].

In certain cases, the infection passes through a latent phase, which may last between months and years after inoculation of the spirochaete. These cases are termed late or chronic presentations of Lyme disease. In chronic cases, the main presenting features affect the joints or the nervous system [2].

36.3 The Infectious Transmission Cycle of B. Burgdorferi

The *B. burgdorferi* bacterium passes through several stages in its transmission cycle. It colonises or infects ticks of the genus *Ixodes*. This arthropod then bites various mammals, such as humans, transmitting the bacterium to a new host. The membrane proteins of *B. burgdorferi* alter according to the surrounding environment and the response of the host. The changing patterns of membrane proteins on the spirochaete are a vital element in the determination of pathogenic virulence [2].

The life cycle of the tick encompasses four developmental stages, namely egg stage, larval stage, nymph stage and full adult maturity. The tick feeds on blood as a larva, nymph or female adult. Transmission of Lyme disease only occurs by bites from nymphs or adults [2].

The entire life cycle takes 2 years. The egg laying occurs in spring, with emergence of the larvae during the summer months. The larvae eat a single blood meal towards the end of the summer, parasitising a variety of small mammalian species, such as mice. The next year, in the spring, the nymph stage begins. These organisms again feed on a single occasion, either in spring or summer. Whilst the preferred host is a white-footed mouse, other species may sometimes be parasitised in this

way. During the autumn, transformation into the adult form is complete, and again a single feed occurs, this time on a larger host, such as a white-tailed deer. If this species is unavailable, another is targetted [2].

The tick may itself become infected from the blood of an infected mammalian host at any point during larval, nymphal or adult life. It is not possible for *B. burgdorferi* to be transferred from a tick to a human unless the tick has previously fed on another infected host. Even in cases where an infected tick bites a host, that animal may not develop signs of infection. Mice, for example, although they have the spirochaete in their blood, seemingly do not suffer from a murine form of Lyme disease. Thus, their carriage of the bacterium may be considered more like an infestation than an infection. Deer inoculated with *B. burgdorferi* demonstrate, likewise, host incompetence [2].

The spirochaete is resident in the midgut of an infected tick. The way humans become infected is via puncture of the skin by an infected tick. The bacterium passes from the midgut to the salivary glands of the tick, before entering the human host through the skin puncture [2].

The risk of contracting Lyme disease is maximal when the *Ixodes* tick nymphs are at the point where they need to feed on a host. Even though adult ticks are twice as likely as nymphs to be carrying the spirochaete, some 90% of cases of human Lyme disease occur through being bitten by a tick nymph. This apparently paradoxical situation is due to several factors, including the higher numbers of nymphs than adult ticks, their smaller size, which means the patient may not notice them in time to remove the tick before transmission can occur, and the fact that patients spent the most time outdoors during the summer months, which coincides with the feeding time for nymphs.

The length of time the tick that remains attached to the human host has a major influence on the rate of transmission of the spirochaete. The tick can only attach itself properly to the host after several hours. It has been shown experimentally that transmission of the spirochaete requires the tick to be attached for between 36 and 48 h, if a nymph, and between 48 and 72 h, if an adult. This is due to the need for the spirochaete to divide sufficiently to be present in an infective dose. The reproduction of the spirochaete is triggered by the nutrients from the host blood [2].

36.4 Pathogenesis

There are three possible outcomes from the presence of *B. burgdorferi* organisms in the skin, namely[2]:

- The immune system of the host may be able to attack and destroy the bacterium.
- The bacterium may survive immune attack and remain confined to the skin, in which case, the erythema migrans clinical presentation is seen, providing the diagnosis of Lyme disease.
- After some days or weeks, the bacterium may break out of the skin and spread to the rest of the body via the lymphatic system or blood vessels.

Once the spirochaete has entered the circulatory system, it preferentially resides in the skin, cardiac tissues, brain and spinal cord, joints or ocular tissues. Even though this tropism occurs, the pathogen has also been found elsewhere in the body, such as the bone marrow, spleen, lymph glands, hepatic tissues, testes or placenta, during the early stages of dissemination via the bloodstream. Histopathological confirmation of the spirochaete in all these tissues has been reported [2].

Clinically, three distinct stages in the progression of Lyme disease are recognised, i.e. early localised, early disseminated and chronic disseminated. Each of these stages may be susceptible to cure with antibiotic administration. Around a half of patients untreated for the early stages of Lyme disease go on to develop disseminated infection. It seems that most of the cases where the spirochaete becomes widely disseminated within the body are due to a restricted number of specific bacterial genotypes [4].

36.4.1 Stage 1 Disease

The initial stage (Stage 1) may be termed primary or early localised infection. This stage typically takes place no more than 30 days after bacterial inoculation. In the majority of cases, erythema migrans is observed at the location where the tick attached itself, around one to 2 weeks after the event. Erythema migrans is a specific type of exanthem that expands outwards. There may also be some less specific indications of *B. burgdorferi* infection, such as [2]:

- Feeling fatigued.
- Muscular aches.
- Joint pain.
- Headache.
- Pyrexia.
- Shivering and feeling cold.
- Nuchal rigidity.

36.4.2 Stage 2 Disease

The second stage of infection may also be termed ‘early disseminated disease’. This stage generally starts from some weeks or months after initial inoculation. Symptoms typically affect the musculoskeletal or nervous system. Although cardiac symptoms and skin problems do occur, they are less frequent [2].

The *B. burgdorferi* bacterium disseminates systemically and symptoms occur due to direct invasion of the tissue, especially in the initial phases. This is how erythema migrans occurs. The spirochaete is a difficult organism to grow in culture; hence, confirmation of its presence in particular tissues is challenging. The multiple lesions seen with erythema migrans are almost certainly the result of the immune

system reaction to the infection. Virtually every case in which there are multiple lesions exhibits seropositivity [5].

There is demonstrable cross-reactivity between immunoglobulin-targeting proteins on the surface of *B. burgdorferi* and nervous or connective tissue. This epitopic similarity may cause an autoimmune response to occur. The pattern of early and late phases of infection resembles that seen with a different spirochaete, i.e. *Treponema pallidum*.

It is reported in the literature that in approximately 10% of cases of erythema migrans without any evidence of disseminated Lyme disease, DNA from *B. burgdorferi* can be isolated from blood samples. Furthermore, at the stage where erythema migrans is still the main symptom (i.e. the initial phase), DNA from the pathogen can be found in the cerebrospinal fluid, which implies that the central nervous system has already been invaded at that point in the disease progression. Spirochaetal DNA can be identified even in cases where there are no symptoms indicative of nervous system involvement [2].

One study established the striking fact that 43.7% ($n = 93$) of some 213 patients tested for circulating spirochaetes were positive on bacterial culture, provided a sufficiently large volume of plasma was sampled (i.e. 9 mL). In a number of the cases where the test was positive, the only symptom was erythema migrans, with no indication of systemic involvement [2, 6].

36.4.3 Third-Stage Disease

The third (chronic) phase in Lyme disease takes place between months and years after the initial inoculation. There may be an intervening latent period in the presentation. In the chronic stage, musculoskeletal complaints are frequent, as are nervous system manifestations. Joint pain is especially common [2].

The immune reaction to the presence of *B. burgdorferi* may itself cause some symptomatic presentation, even where the spirochaete does not appear to have invaded the organ involved. The arthritis seen in patients with Lyme disease is linked to specific characteristics of the immune response, such as synthesis of proinflammatory cytokines and immune complex formation. There are also genetic influences, with arthritis more common in individuals who carry the human leucocyte antigen (HLA) complexes DR4 and DR2 [2].

The probability that arthritis will be long-lasting increases in individuals who carry HLA-DR4 or HLA-DR2, as well as being positive for OspA and B (Osp = outer surface protein) on aspirated synovial fluid. The most likely mechanism is that certain genes predispose the patient to an autoimmune arthritis which may not resolve, even when *B. burgdorferi* appears to have been completely eradicated [2].

The pathogenetic mechanism for nervous system involvement by *B. burgdorferi* (neuroborreliosis) appears to involve the astrocytes and microglia, at least according to animal models. One hypothesis is that astrocytic expression of interleukin-6 causes oligodendrocytes to undergo programmed cell death, which is the mechanism by which tissue injury then occurs [7].

B. burgdorferi is also capable of remaining within the skin for prolonged periods. It has been shown experimentally that this pathogen can invade and persist within human fibroblasts, despite surrounding extracellular fluid containing ceftriaxone at a level considerable higher than that normally required to cause bacterial death. Despite the lack of evidence for this process occurring in vivo, there remains the possibility that this is how the spirochaete manages to escape from the host's immune response [2].

36.5 Aetiology

The usual cause of Lyme disease is the spirochaetic bacterium, *B. burgdorferi*. The entire bacterial genome for this species was published in 1998 [2].

The designation *B. burgdorferi* can be applied in a wide sense to any of the following three more narrowly defined organisms [2]:

- *B. burgdorferi* in the strict sense.
- *B garinii.*
- *B afzelii.*

The strict application of the name *B. burgdorferi* applies to a group of bacterial strains that are highly similar to each other, yet still contain some important genetic differences. This is the group that is mostly isolated in North American patients and is present in some European cases, too. The *B. afzelii* species is mostly isolated in European cases, and *B. garinii* does not occur outside Europe [2].

The different subspecies cause differences in how the patient presents clinically, probably reflecting the genetic diversity. The species *B. burgdorferi* in its strict sense tends to be associated with arthritis. In cases of erythema migrans diagnosed in European countries, around 80% of the lesions contain *B. afzelii*, with a further 15% being due to *B. garinii* [8]. The *B. afzelii* subspecies generally localises to the skin, where it may become chronic, resulting in dermatological complaints, including acrodermatitis chronica atrophicans [2].

The *B. garinii* subspecies has a tropism for the nervous system. The majority of cases of lymphocytic meningoradiculitis (also termed Bannwarth Syndrome) are due to this organism, as are cases of white matter encephalitis. Most such cases occur outside North America. Despite this neurotropism, patients infected with *B. garinii* may still have any of the dermatological signs associated with Lyme disease [2].

There may also exist other variants of *B. burgdorferi* which, by virtue of their genomic difference, may qualify as separate bacterial strains. This possibility is still the subject of ongoing research [2]. If such species do exist, however, they are unlikely to be responsible for many cases of infection.

It was reported in 2016 that researchers based at the Mayo Clinic had identified a previously unknown subspecies of *Borrelia*, for which the name *B. mayonii* was proposed. This spirochaete had caused Lyme disease in 6 patients from the

Midwestern USA. The clinical features differed somewhat from the usual presentation in cases of *B. burgdorferi* infection, insofar as these cases involved vomiting, diffuse skin exanthemata and the presence of exceptionally high numbers of spirochaetes in the circulation. The cases were diagnosed by polymerase chain reaction amplification of the oppA1 gene carried by all major subspecies of *B. burgdorferi* [9].

The mode of transmission involves the patient being bitten by a tick belonging to the *Ixodes* genus. *Ixodes scapularis* (alternatively called *Ixodes dammini*) is the usual vector in cases occurring in the north east and midwest of the USA. The usual vector in the northwest USA is, however, *Ixodes pacificus*. There are other Ixodid species which transmit Lyme disease elsewhere in the world. Although there are other genera of tick and indeed insects that may potentially transmit *B. burgdorferi* infections, these other species are seldom responsible. One tick that is occasionally responsible is *Amblyomma americanum* [2]. This tick was implicated in some cases resembling Lyme disease reported from the southern and mid-central USA. In the cases from the Southern states, *B. burgdorferi* was not isolated, but the features suggested a spirochaetic infection by a bacterium closely related to *B. burgdorferi*, namely *B. lonestarii*. However, in very few cases could this pathogen be definitely identified in cases of erythema migrans occurring in the Southern states [10, 11].

36.6 Prognosis

Provided antibiotic treatment of an appropriate kind is initiated at an early stage, the prognosis for patients affected by Lyme disease is excellent. It is worth considering, however, that if the patient is again bitten by a tick, Lyme disease may recur. In such cases, the pathogen responsible is generally a closely related, though different, member of the *Borrelia* genus [12].

In cases, particularly amongst adults, where prompt treatment does not occur or where neither doxycycline nor amoxicillin are selected for initial therapy, there may be persistent complications, such as prolonged musculoskeletal complaints, memory problems, inability to concentrate or feeling fatigued. These complications can cause debilitation and are difficult to treat adequately [2].

In some cases, chronic joint inflammation may occur, due to an immune reaction, rather than as a response to persistent infection. This immune-mediated arthritis occurs more frequently in patients who possess particular haplotypes, namely HLA-DR2, 3 or 4. The use of antibiotics does not benefit the condition. However, palliative treatments are generally beneficial and the arthritis does usually resolve completely in the end [13].

It is unusual for Lyme disease to affect the heart on a chronic basis. Nonetheless, in some cases where third-degree heart block develops, a temporary pacemaker may be required. Somewhat rarely, patients require a permanent pacemaker to be implanted [2].

The data show that Lyme disease seldom causes a fatal outcome. In cases where a fatality has been reported, it is common for an additional pathogen to have been

transmitted at the same time by tick bite. Examples of co-transmission have been reported with bacteria of the *Ehrlichia* genus or with *Babesia microti*. European fatal cases have occurred with co-occurrence of Lyme disease and tick-borne encephalitis. A study by the US CDC which reviewed causes of death between 1999 and 2003 noted that, whilst 114 records named Lyme disease as the actual or contributing cause of death, there was only a single record in which the clinical features were consistent with a diagnosis of Lyme disease [14].

There are very infrequent reports showing that deaths have occurred in utero or neonatally in the offspring of mothers with symptomatic Lyme disease who either received inadequate or no treatment for the disease. The CDC has studied these adverse outcomes for the foetus and concluded that it is improbable that *B. burgdorferi* infection can be vertically transmitted and therefore likely did not cause these deaths [2].

36.7 Post-Treatment Lyme Disease Syndrome

In approximately 10–20% of cases where Lyme disease is treated according to the guidelines, some symptoms persist, even 6 months after eradication of the infection [3]. Symptoms which are frequently noted included thinking problems, excessive tiredness, arthralgia or myalgia, headaches, auditory impairment, dizziness, mood dysregulation, pins and needles and insomnia. Some clinicians use the diagnostic label chronic Lyme disease, but a more appropriate term may be post-treatment Lyme disease syndrome (PTLDS) [2].

There are no data indicating benefit from the use of antibiotics in PTLDS. Resolution of PTLDS virtually always occurs, albeit the time scale involved may exceed 6 months in particular patients [3].

One study noted that patients with a previous diagnosis of Lyme disease from between 1 and 11 years before still complained of symptoms or reported difficulty in activities of living. However, comparison of this group of individuals with controls of the same age revealed that symptoms occurred at a similar rate in both groups [15].

A different study assessed musculoskeletal problems, nervous system symptoms and neurocognitive performance in patients whose diagnosis of Lyme disease had occurred on average 6 years previously, comparing these with healthy controls. No differences were noted. When the study examined arthralgia, memory issues and lower functional status resulting from pain, it was noted that the patients with previous Lyme disease had worse results [2, 16].

36.8 Signs and Symptoms

The symptomatic presentation and physical findings in patients with Lyme disease vary according to the progress of the disease. In the initial stages, the following physical findings may be noted [2]:

- Influenza-like syndrome, featuring pyrexia, chills, feeling generally unwell, muscle and joint pain and headaches.
- Tender lymph nodes in the region where the bite occurred.
- Typical exanthem of erythema migrans type.

The physical findings at the stage where the bacterium has begun to disseminate include the following:

- Erythema migrans. There may be a single or several lesions.
- Headache.
- Pyrexia.
- Tender lymph nodes in a particular region or all over the body.
- Rarely, conjunctivitis, although not as a principal complaint.
- Cardiac inflammation, evident as cardiac block.
- Meningismus, indicating aseptic meningitis.
- Cranial nerve neuropathy. This is typically in the facial nerve and may cause Bell's palsy, in which there is unilateral paresis of the facial nerve, without frontal sparing.

At the later stages of the condition, arthritis is the usual presenting feature. This usually affects the large joints, particularly the knee. The features which help in diagnosing arthritis rather than simply joint pain are the presence of a swollen effusion and limitation on movement of the joint.

36.9 Diagnosis

Cases which occur in areas where Borreliosis is endemic and present with an exanthem resembling erythema migrans should be treated immediately, without waiting for laboratory confirmation by testing blood. The CDCs advise that serology should involve the two steps described below, namely [2, 17]:

- First step. Quantification of the total Lyme titre or the levels of immunoglobulins G and M. This should be performed using enzyme immunoassay or immunofluorescence techniques.
- Second step. Western blotting.

The second step is only needed if the first procedure gives a positive or potentially positive result. For cases where the stigmata of Lyme disease have been evident for no more than 30 days, both immunoglobulin G and M should be tested by Western blotting. Where these stigmata have been evident for longer than a 30-day period, Western blotting for IgG only is appropriate [2].

The decision to proceed with Western blotting depends only on the need to exclude potential false-positive results returned by enzyme immunoassay or immunofluorescence. Thus, Western blotting should be performed as a reflex

confirmatory procedure. The majority of commercial laboratory services routinely undertake the procedure for both classes of immunoglobulin [2].

Since July 2019, however, the US FDA has licensed the use of enzyme immunoassays concurrently or sequentially to confirm Lyme disease, without the need for Western blotting. This decision was reached following submission of evidence from clinical trials where this approach was shown to be equally efficacious to immunochemical testing followed by Western blotting. The new approach is termed the modified two-tier test [18].

For patients with a history of travel or residence in Europe, there is a specialised C6 peptide ELISA (enzyme-linked immunosorbent assay) test available. This has superior accuracy to Western blotting, since the European strains of *B. burgdorferi* differ from those endemic to the USA. Although the C6 peptide test is less costly than Western blotting and has comparable sensitivity and specificity for detection of *B. burgdorferi*, it has not been widely adopted to confirm Lyme disease in American patients [2].

36.10 Management

Provided suitable antibiotic therapy is used, the majority of cases of Lyme disease feature complete recovery in a short period of time. The choice of agent, route of administration and length of course depend on several factors, in particular the clinical presentation, stage of the disorder, the existence of co-morbidities and any allergic hypersensitivity [2].

The following are the recommended therapeutic regimens [2]:

- For cases where there is erythema migrans occurring in the initial, localised stage or shortly after disseminated infection begins, suitable agents to use are doxycycline, amoxicillin or cefuroxime axetil.
- For patients below the age of 8 years or women in pregnancy or during lactation, and where the disease is at the initial localised stage or has just begun to disseminate, amoxicillin or cefuroxime axetil are suitable choices.
- For cases where the nervous system is involved, penicillin, ceftriaxone or cefotaxime should be administered intravenously. Where Lyme disease is associated with meningitis, a seventh nerve palsy or radiculitis, oral doxycycline is suitable, provided there are no contraindications.

The following are suggested therapeutic strategies in arthritis occurring in Lyme disease [2]:

- Antibiotics may be given by mouth for a course lasting 28 days.
- If the joints remain swollen to a mild degree, a second oral course is suitable.
- Where the lesion exhibits treatment resistance, intravenously administered antibiotics are required.
- If PCR amplification of bacterial DNA in synovial fluid is positive, administration of antibiotics by mouth should continue for a further 28 days.

- If PCR is negative, NSAIDs may be prescribed. If needed, hydroxychloroquine may be added.
- For cases where palliative treatment is ineffective, an arthroscopic synovectomy may be necessary.

The treatment for cardiac involvement in Lyme disease is a 14-day course of antibiotics, which can be by mouth or parenterally administered. In some cases, 21 days may be required. If any of the following indications apply, it is recommended that the patient be admitted to hospital for continuous observation. A temporary pacemaker may need to be used [2].

- Cardiac-related symptoms (fainting, shortness of breath, pain in the chest).
- Atrioventricular conduction problems, i.e. block of second or third degree.
- Heart block of first degree with lengthening of the PR interval, so that it exceeds 300 ms. Heart block may be variable and can rapidly deteriorate in this group of patients.

36.11 Lyme Disease and Auditory Impairment

Lyme disease is also associated with a variety of ENT-related symptoms, namely pharyngitis, earache, swollen tender cervical lymph nodes, seventh cranial nerve palsy, ringing in the ears, dizziness and auditory impairment. Loss of hearing has been described by multiple authorities [19–22]; however, the abrupt onset of deafness is less frequently reported [20, 23–26].

Lyme disease may cause lesions of inflammatory or angiopathic type, and these potentially result in sudden sensorineural hearing loss. Greater duration of the infection is associated with higher risk of permanent and non-treatable injury to the nerves of the cochlea and the auditory nerve. Treating cases where serology indicates infection with *B. burgdorferi* in a rapid and appropriate fashion also protects against other potentially grave consequences of chronic Lyme disease [22, 23, 27].

Deafness arising in Lyme disease has unusual characteristics, namely its association with Bell palsy and positivity of serology. However, serology on cerebrospinal fluid (CSF) may be negative, and antibiotic therapy may fail to improve deafness. A study examining acute onset one-sided auditory impairment found that CSF serology was negative [28], whilst antibiotic therapy was of equivocal benefit in improving auditory function. Other studies have also shown the limited utility of antimicrobial pharmacotherapy [29, 30]. Whilst the ability to diagnose Lyme disease accurately as a cause of hearing loss does depend on laboratory confirmation, there are concerns about how sensitive and specific the available methods currently are. When different series of cases of abrupt onset auditory impairment are compared, the rate of positivity of serology ranges from 21% amongst 47 cases [29] to 0% in a meta-analysis combing the data on 1973 individuals [30]. This variability in positive serology is not explicable solely as due to differences in the extent to which Lyme disease is endemic in particular locales [31].

A case series of 47 individuals presenting consecutively with abrupt onset auditory impairment and reported by Lorenzi et al. [20] noted that 21.3% (n = 10) had immunoglobulins specific to *B. burgdorferi* when enzyme immunoassay was used for serology, the confirmation then being made by Western blotting. The frequency of IgG to *B. burgdorferi* was 12.1% (n = 20 of 165) in cases of sudden sensorineural hearing loss, according to a study undertaken by Peltomaa. In the same study, PCR positivity was obtained in 2 cases, whilst a further 2 patients were noted to have erythema migrans [21, 23].

A study from Switzerland [32], which retrospectively reviewed cases of sensorineural hearing loss, only found 1 case in which serology for anti-spirochaetic immunoglobulins was positive. When this patient was more closely investigated, however, the putative diagnosis of Lyme disease was withdrawn. These findings match those by Hyden et al., who found immunoglobulin-targeting *B. burgdorferi* in 4 out of 21 cases. A study where CSF serology was carried out on patients suspected to have Lyme disease did not report any positive serology, which put the original diagnosis in doubt [24]. There are individual case reports of individuals with auditory impairment of sensorineural type associated with Lyme disease. One report described a presentation in which sensorineural hearing loss occurred in both ears and spastic paraparesis was present in an individual suffering from Lyme disease. There was no information available for this case about the circumstances of inoculation, but infection with *B. burgdorferi* was established through positivity of plasma serology, involving enzyme immunoassay, dot-blot and enzyme-linked immunosorbent assay [23, 33].

Auditory impairment is a potential complication of Lyme disease. The type of deafness appears to be partly linked to the progress of the disease generally. Auditory impairment affecting one ear only and of sensorineural type typically occurs in the second (dissemination) phase of the disease, and this timing means it may be hard to establish an aetiology for the deafness. It has been shown that sensorineural auditory impairment affects both ears and progressively worsens in third-stage Lyme disease. It occurs together with other nervous system complications connected to chronic lymphocytic meningitis. There are many unknown elements concerning how deafness occurs in Lyme disease, with a need for further research to elucidate the differences between cases where deafness is of abrupt onset and affects only one ear and where chronic, progressive deafness occurs, affecting both ears. The pathogenetic mechanism, when known, may help clinicians understand why audiological outcomes following therapy vary so widely [31].

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Tuberculosis in Children and Hearing Loss

37

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37.1 Introduction

Tuberculosis is, by far, the most deadly of all vaccine-preventable diseases worldwide [1]. It has been revealed that tuberculosis disease was present in Africa's first human societies at least 70,000 years ago and migrated with them in the global spread of humans [2]. The disease was also shown in Stone Age skeletons and mummies from ancient Egypt, 2400 BC [3]. It is thought that tuberculosis has not evolved from a zoonotic infection as previously supposed; instead, the disease and its human host co-evolved together, changing over time [2].

Tuberculosis is one of the most important infectious diseases globally regarding morbidity and mortality. Prior to the coronavirus pandemic, it was the leading cause of death from a single organism. Although many successes have been achieved in controlling the disease, tuberculosis continues to be an important public health problem worldwide.

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This chapter focuses on tuberculosis in children and related hearing loss and reviews pediatric patients with tuberculous otitis or mastoiditis reported in the literature.

37.2 Etiology

Mycobacteria are nonmotile, pleomorphic, non-spore-forming, weakly stained Gram-positive, and acid-fast microorganisms 1–5 mm in length. Acid resistance is due to a large amount of lipids in the cell wall of the bacillus, which gives the bacterium the ability to resist decolorization by acids during staining with the Ziehl–Neelsen method [4].

A group of mycobacteria called the *Mycobacterium tuberculosis* complex causes tuberculosis infection; this group includes *M. tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti,* and *Mycobacterium canettii*. *Mycobacterium tuberculosis* is the most common cause of tuberculosis disease in humans. The slow growth rate is the hallmark of *M. tuberculosis* bacteria; it may take 2–6 weeks to isolate in solid media and 7–14 days in liquid media.

37.3 Epidemiology and Transmission

According to the World Health Organization (WHO) data, a quarter of the world's population is infected with *M. tuberculosis* [5]. Tuberculosis kills more than 4000 people every day. An estimated 9.9 million (range 8.9–11.0 million) people globally developed tuberculosis in 2020, of which 11% were children under the age of 15 years [5].

Although tuberculosis can be seen in every geographical region, it is the most common in societies with poor living conditions. Some conditions, such as measles infection and treatment with tumor necrosis factor-alpha (TNF-α) antagonists, adversely affect the immune system and cause a tendency to tuberculosis disease. Severe malnutrition is a risk factor for life-threatening childhood tuberculosis [6].

Tuberculosis in children may be underdiagnosed as it is difficult to confirm the diagnosis microbiologically. Mathematical modeling studies have calculated that approximately 35% of pediatric tuberculosis cases in 22 countries with 80% of the world's tuberculosis burden are diagnosed, and the rest of the patients remain undiagnosed [7].

Tuberculosis bacilli are most commonly transmitted from person to person in droplet infection by the aerosol route. Droplets carrying bacilli are released into the air when a patient with active tuberculosis coughs, sneezes, or even speaks. Except for droplet infection, transmission is rare. Gastrointestinal transmission occurs when raw milk is consumed, in which the causative agent generally is *M. bovis*. Intrauterine transmission is infrequent but can occur if the mother has extensive tuberculosis disease in which the placenta is also affected or has disseminated disease.

Various factors affecting transmission have been identified. People with close and long-term contact with a patient suffering from the active contagious disease (the index case), especially those who share the same house, are more likely to be infected with *M. tuberculosis*. Being in a poorly ventilated indoor environment devoid of ultraviolet rays adds additional risk to the transmission of the bacilli. On the other hand, past tuberculosis disease and getting the Bacille Calmette-Guérin (BCG) vaccine have some protective effects on the progression of the disease.

37.4 Pathogenesis, Immunity, and Pathology

The tuberculosis incubation period starts with introducing the bacilli into the body and lasts until the tuberculin skin test (TST) is positive. This interval is usually 4–6 weeks and can be as short as 2 weeks and as long as 12 weeks.

When bacilli enter the body due to contact with an index case, the episode may result in a confined infection called latent tuberculosis infection (LTBI). In this case, the TST or interferon-ɣ release assay (IGRA) becomes positive, and no accompanying clinical finding develops. However, if the host's defense mechanisms cannot limit the infection, the process progresses to the disease. Reactivation develops in 5–10% of people with LTBI who do not have an underlying medical problem and ends with active disease. After ingesting the tuberculosis bacilli, the emergence of clinical disease is most likely within the first 2 years after infection. Being under 5 years of age, under immunosuppressive therapy, living with human immunodeficiency virus (HIV) infection, or suffering from chronic renal failure, leukemia, lymphoma, or other malignancies are the main risk factors increasing the conversion rate from tuberculosis infection to disease.

In a meta-analysis examining the probability of progression to tuberculosis disease in persons who did not receive LTBI treatment within 2 years after exposure, the highest rate was found in children under 2 years of age [8]. Also, the risk of progression to tuberculosis disease in children aged 2–5 years was 19%, not 5%, as is common in adults.

The pathogenesis of tuberculosis is a process in which complex immunological events occur. Bacilli enter the respiratory system like a foreign body in tiny droplets (5–10 μm in diameter) to reach and settle in the pulmonary alveoli. A non-specific exudate appears first in the alveoli. Serum, fibrin, polymorphonuclear leukocytes, and macrophages accumulate in this exudate. Neutrophils and alveolar macrophages phagocytose bacilli but cannot kill all. With the formation of the initial exudate, the lymphatic system also is involved in the inflammation. Epithelioid histiocytes and Langhans-type histiocytic giant cells appear in this pneumonic infiltration within a few weeks. With the appearance of histiocytes, the infiltration loses its exudative character and takes on a proliferative appearance. Necrosis occurs in the middle of the residual infiltration area, where the bacilli continue to multiply. A fibrous region appears around the focus. Epithelioid histiocytes can destroy the bacilli in small foci. However, caseification occurs, and some bacilli remain alive if the focus is large. Calcium precipitates into this inflammation area over time.

The lesion that occurs at the first installation of the bacilli is defined as the primary focus or Ghon focus; when involving an adjacent lymph node, it is called the primary complex (Ghon complex). Lymph nodes associated with the pulmonary area containing the primary focus are also infected with bacilli. Even in the calcified lymph node, caseification may continue, and bacilli may survive for years. Since lymph nodes tend to enlarge and caseify, they play a primary role in spreading the infection to the bronchi, blood vessels, pericardium, esophagus, and primary disease progression.

The characteristic morphology seen in tuberculosis disease is a necrotizing granulomatous reaction. The presence of necrosis is not essential, and in the case of a weak immune response, typical and organized granulomas may not readily form. Although pulmonary tuberculosis in infants and young children can affect any part of the respiratory system, the periphery and lower parts of the lungs are mostly involved. The cavitation lesion is usually at the apex of the lung.

Mycobacteria are drained from the lymphatic channels in the lung parenchyma to the hilar and mediastinal lymph nodes. If the bacillary load is high, dissemination also can occur in the venous system via the thoracic duct to reach the bloodstream. There can also be a direct passage from the lung parenchyma to the pulmonary venous system. Early lymphohematogenous spread precedes the development of cellular immunity and is particularly common in infants and young children.

37.5 Clinical Manifestations

No part of the body is immune to tuberculosis. Tuberculosis affects the lungs in 75% of patients, and extrapulmonary involvement is around 25% [9]. On clinical basis, tuberculosis is classified into five categories in the spectrum from infection to disease as follows [10]:

- Eliminated tuberculosis infection: The stage is that the innate or acquired immune response clears the tuberculosis bacilli after exposure, or the condition is terminated with antituberculosis drugs. The individual no longer has alive tuberculosis bacilli.
- Latent tuberculosis infection (LTBI): An individual infected with viable tuberculosis bacilli but lacks clinical, radiological, or microbiological evidence and will probably not progress to an advanced disease stage soon.
- Incipient tuberculosis infection: The stage can progress to active disease, but there is no clinical, radiological, or microbiological evidence of active tuberculosis.
- Subclinical tuberculosis disease: Symptoms and signs of active disease do not exist yet, but radiological findings are present, or alive tuberculosis bacilli are detected with microbiological tests.
- Active tuberculosis disease: Clinical symptoms, abnormal radiological findings, or microbiological evidence are present.

37.6 Complications

Tuberculosis disease mainly affects the lungs; however, many organs and systems can be involved, including other parts of the respiratory system, skin, liver, spleen, lymphoid, central nervous, digestive, musculoskeletal, reproductive systems, and middle ear. Regardless of which organ system is affected, tuberculosis causes dysfunction of the relevant organ and can cause growth retardation and developmental delay in children. Anemia of chronic disease, amyloidosis, impaired immunity, and systemic spread are tuberculosis's late and inevitable complications.

37.7 Differential Diagnosis

The differential diagnosis of tuberculosis disease is broad and should be considered according to the affected organ. Acute or chronic bacterial, viral, fungal, or protozoal infections, malignancies, and autoimmune or infiltrative disorders are clinical conditions bearing similar signs and symptoms to tuberculosis.

37.8 Laboratory Findings and Diagnosis

Two main groups of tests are used in the diagnosis of tuberculosis.

37.8.1 Microbiology-Based Tests

A definitive diagnosis of tuberculosis disease requires the isolation of the pathogen in culture from the affected part of the body. Various specimens can be collected for the detection of *M. tuberculosis* and performing antituberculous drug susceptibility tests [11]. There is a linear relationship between the bacterial load in the host and the course of tuberculosis disease. The more advanced the clinical tuberculosis stage, the more likely the pathogen can be detected [12]. The mycobacterial culture is the gold standard reference test for tuberculosis disease, while no reference test for tuberculosis infection exists.

Microbiology-based tests reveal the infectious agent or its parts. For diagnosing pulmonary tuberculosis, taking sputum cultures three times in the morning from pediatric patients is traditionally recommended. If the culture is positive, 95% of the time, it will be so in the first two samples [13].

Proper sampling will make it easier to prove the presence of tuberculosis bacilli. Since it is difficult for children to produce sputum spontaneously, methods of morning gastric fluid, stimulated sputum, and nasopharyngeal swab sampling techniques are described in detail elsewhere [14].

The string test is more easily tolerated than the morning sampling of gastric fluid in children as young as 4 years old [15]. The buccal mucosal swab method may be

helpful in children [16]. Comparable to reference standard specimens, two nasopharyngeal aspirates (NFAs) or 1 NFA plus 1 stool or 1 NFA plus 1 urine material has been reported to have the same diagnostic yield as less invasive microbiological specimens for tuberculosis in children younger than 5 years of age [17]. In a meta-analysis of 16 studies performed on nearly 2500 children investigating the detection of *M. tuberculosis* deoxyribonucleic acid (DNA) in stool as a fast, easy, and non-invasive sample collection method, the specificity was 98%, the sensitivity 57% compared to culture [18].

Diagnosis of tuberculosis, mainly pulmonary, in childhood is difficult. The primary reason is the inability of children to produce adequate sputum to be used as an examination sample. In addition, pulmonary tuberculosis foci in children contain few bacilli, and the positive results are 10–15% in smear examination and 30–40% in culture. Waiting for the culture result in cases where positivity cannot be obtained in the direct microscopic examination is essential.

In the research phase and routine use, diagnostic tests and biomarkers with a shorter test time and higher sensitivity are not primarily aimed at children. Although new tests based on microbiological and host immune responses shorten the time to reach results, they have not yet been validated in children, and none offer greater sensitivity than culture [19]. Related to the difficulties in microbiological evidence, the histopathological examination obtained by biopsy contributes to diagnosing mass lesions such as lymph node tuberculosis [11, 13].

There are many biomarkers under development for use in the diagnosis of tuberculosis. The ideal biomarker is measurable even in small samples (e.g., blood, urine, feces, saliva). It is expected to reveal the causative agent without being affected by conditions such as age, nutritional status, or HIV infection. In addition, it should be able to distinguish active tuberculosis disease from latent infection and should be easily accessible and applicable wherever the patient is followed [20].

The WHO-approved polymerase chain reaction (PCR)-based Cepheid GeneXpert® MTB/RIF and Xpert Ultra molecular tests can efficiently detect *M. tuberculosis* and rifampin (RIF) resistance. Because it does not distinguish between live and dead organisms, it should be used as an initial diagnostic test and not investigate the response to treatment and eradication of tuberculosis bacilli [21]. The new molecular, fast, portable, bedside, WHO-approved Truenat® MTB/MTB Plus/MTB-RIF tests, and chip-based PCR tests can be used for smear-negative tuberculosis in children; RIF resistance also can be detected [21]. The WHO-approved, loop-mediated isothermal amplification TB-LAMP® test is a manual diagnostic method that can be used in place of microscopy in small hospitals for children [21].

Adenosine deaminase (ADA) measurement is used in tuberculous serositis. In the meta-analysis of 174 studies, including 27,009 pediatric and adult patients, in the diagnosis of tuberculous pleurisy, when the ADA threshold was >65 IU/L, the sensitivity was 86%, and the specificity was 94% [22]. In studies conducted in meta-analyses, ADA has been shown to have clinical value with a sensitivity of 89% and a specificity of 91% in tuberculous meningitis [23], a sensitivity of 88%, a specificity of 83% in tuberculous pericarditis [24].

37.8.2 Immune-Based Tests

The tuberculin skin test shows the host's response to the mycobacteria in vivo, revealing whether the body has encountered the bacilli before. The tuberculin protein used in the TST is a purified protein derivative (PPD) extracted from cultures of *M. tuberculosis*, improved by Seibert [25]. Robert Koch first developed it to treat tuberculosis [26], but the approach was unsuccessful, and von Pirquet defined it as an immune response test against antigens derived from *M. tuberculosis* [27].

The current application of TST is an intradermal technique described by Mantoux. Various PPD solutions have equivalent efficacy, although their contents are not identical [28]. The PPD fluid is applied to the forearm of the individual and evaluated by measuring the induration diameter formed after 48–72 h [29]. The interpretation of TST may vary slightly in low-middle- and high-income countries [30, 31]. Induration of diameter ≥5 mm is considered positive in children with severe immunosuppression (either congenital or acquired, as in HIV infection, or related to therapy, as in immunosuppressive treatment) in all guidelines [30, 31]. Induration ≥5 mm is also considered positive in the United States of America (USA) for children suspected of tuberculosis disease (consistent clinical or radiological evidence) or who have contact with an active contagious tuberculous case [30].

The induration of diameter ≥10 mm is considered positive in all other children in low and middle-income countries [31]. The same threshold is deemed positive for children at increased risk of disseminated disease in the USA. Children without risk factors are also thought to have a positive TST when the reaction is ≥15 mm induration.

The induration size of TST is affected by various conditions, such as the individual's previous medical history and the number of BCG vaccinations [32, 33]. There are web-based applications that facilitate TST interpretation [34].

Interferon-gamma (IFN-γ) release assay (IGRA) measures the amount of IFN-γ produced ex vivo by the patient's T lymphocytes or detects the total number of lymphocytes secreting IFN-γ. Unfortunately, neither test can distinguish the active disease from latent infection [30, 31].

Two different IGRA tests are in use; QuantiFERON-TB Gold Plus® (QFT-Plus®), which is the new generation of QTF-Gold in Tube® assay (QFT-GIT®), and T-SPOT. TB® test. The IGRA tests use the antigens of the tuberculosis bacillus known as ESAT-6 and CFP-10 in whole blood, primarily eliciting a CD4+ T-cell response. QFT-Plus® includes an additional antigen tube that targets to measure specific CD8+ response, improving the test performance of the predecessor QFT-GIT®. The T-SPOT.TB® test is an enzyme-linked immune absorbent spot (ELISPOT) assay in which ESAT-6 and CFP-10 are incubated with peripheral blood mononuclear cells. Although the specificity and sensitivity of IGRA tests are very high, they give indeterminate results in some cases due to the failure of either the negative or positive control test. The QFT-Plus® test is approved in adults, with low rates of indeterminate results, and has been found helpful in children with suspected tuberculosis infection or disease [35].

Which of the QFT-GIT® and T-SPOT.TB® tests yield more "indeterminate" results was evaluated in a meta-analysis of 133 studies involving more than 100,000 pediatric participants [36]. Indeterminate results were obtained in one out of every 25 IGRAs, and there was no significant difference between the two tests. Non-HIV immunocompromised children had less indeterminate results with T-SPOT.TB® test. Administration of prednisone or its equivalent less than 1 mg/kg/day for shorter than 2 weeks as adjuvant therapy for pneumonia, asthma exacerbation, or acute respiratory distress syndrome in children with normal immunity resulted in a higher rate of indeterminate IGRA results [37]. Therefore, patients should be questioned about steroid therapy before the IGRA test.

The incidence of developing tuberculosis disease was scrutinized in a meta-analysis of more than 130,000 children exposed to tuberculosis in 46 cohort studies from 34 countries [8]. The meta-analysis detected that 96% of tuberculosis-exposed children younger than 5 years old with a TST/IGRA positivity, within 90 days, tuberculosis disease was diagnosed. Accordingly, the risk of development of tuberculosis disease is high in small children who had contact with an index case scattering the bacilli.

The C-Tb® test, a highly specific skin test for the diagnosis of LTBI designed to address some of the drawbacks of TST and IGRAs, is based on ESAT-6 and CFP-10 antigens and provides the diagnostic accuracy of IGRA tests at low cost as well as bearing the simplicity of an intradermal test [38]. Also, BCG vaccination status does not affect the outcome [38]. The C-Tb® test has a similar safety profile to the conventional PPD tuberculin skin test [39].

The Diaskintest® is an innovative intradermal test using CFP-10 and ESAT-6 for the mass screening of tuberculosis, which won the international Prix Galien award in biopharmaceuticals in 2014 [40]. In children, the results are highly specific and suitable for mass screening. The Diaskintest® provided performance comparable to an IGRA in BCG-vaccinated children [41].

37.9 Treatment

More than 160,000 publications on tuberculosis, including abundant literature on disease pathogenesis, biomarkers, and treatment, have been available [42].

Before modern antituberculous therapy, the average annual death rate from tuberculosis per million population in England and Wales between 1891 and 1900 was most commonly reported in children aged 0–5 years [11, 43]. At present, tuberculosis is an infectious disease that can be cured almost entirely with appropriate treatment. The success of the treatment increases with the combination of multiple drugs to which the bacterium is susceptible, the treatment for a sufficient time, and good adherence. Monitoring should be done regarding drug side effects; however, they are less common in children than adults. Directly observed therapy (DOT) may be preferred to increase patient adherence. All patients should be tested for HIV infection before treatment.

Table 37.1 Doses and side effects of major drugs used in treating tuberculosis[a]

Drug name	Dosage (mg/kg/day)	Maximum daily dose	Common side effects
Isoniazid	10–15	300 mg	Hepatotoxicity, peripheral neuritis, hypersensitivity
Rifampin	15–20	600 mg	Orange discoloration of urine and body secretions, hepatotoxicity, gastrointestinal upset, flu-like reaction, thrombocytopenia
Pyrazinamide	30–40	2 g	Hepatotoxicity, hyperuricemia, arthralgia, gastrointestinal upset, rash
Ethambutol	15–25	1 g	Optic neuritis, gastrointestinal upset, hypersensitivity

[a]Adopted from Ref. [30]

In presumptive or definite drug-susceptible pediatric tuberculosis, treatment with isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (ETM), also named the first-line antituberculosis drugs, for the first 2 months (initial phase) and with INH and RIF for the next 4 months (consolidation phase) is appropriate (Table 37.1) [30, 44]. In a recently published study on shortened treatment period in pediatric tuberculosis, 4 months of treatment with INH + RIF + PZA+/−ETM was non-inferior to 6 months of treatment in children under 16 years of age with smear-negative tuberculous lymphadenitis and non-severe respiratory tuberculosis [45]. Trials of shortening the treatment of drug-susceptible tuberculosis using fluoroquinolone or higher doses of RIF are ongoing and promising [46].

Continuing the second phase of therapy longer (3–6 months longer) may be considered in patients with cavitary tuberculosis, a positive sputum culture after 2 months of therapy, extrapulmonary or miliary disease, except for central nervous system (CNS) tuberculosis [30, 47]. The continuation phase should be 7–10 months in tuberculous meningitis. Some experts recommend ethionamide or streptomycin instead of ETM [30]. In patients with complex conditions such as cerebral tuberculoma or brain abscess, a further extension of the consolidation phase may be considered for 3–12 months [47]. Ethionamide has good blood-brain barrier penetration. In line with current WHO recommendations [48], short-term therapy consisting of 6 months (6-month intensive regimen) of INH + RIF + PZA + ethionamide if HIV-negative or 9 months if HIV positive is preferred in children with tuberculous meningitis as it has lower mortality [49].

In all patients with tuberculous meningitis, adding corticosteroids during the first 2–4 weeks of treatment is recommended to reduce intracranial inflammation [44]. The steroid dose should be tapered and discontinued within 2 weeks. In the presence of widespread inflammation, corticosteroids can also be used during the treatment of tuberculosis disease of serous membranes such as pleurisy, pericarditis, or peritonitis, for endobronchial tuberculosis to relieve airway obstruction, and also for miliary disease with impaired gas exchange.

Multidrug-resistant/RIF-resistant tuberculosis (MDR/RR-TB), the resistance of *M. tuberculosis* at least to INH and RIF, requires second-line drugs, which are less effective, more toxic, and more expensive than first-line drugs [50]. The term extensively resistant tuberculosis (XDR-TB) was first defined in 2006 for cases of tuberculosis disease caused by bacilli having a broader resistance. The XDR-TB definition has evolved as the drugs used to treat MDR-TB. The most recent definition of XDR-TB is a disease caused by *M. tuberculosis* strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (e.g., levofloxacin, moxifloxacin) and at least one additional Group A drug (bedaquiline or linezolid) [50]. Successful results are obtained with MDR/RR-TB and XDR-TB treatment in children; however, it should be done under the supervision of an expert [51]. The use of amikacin and streptomycin for treating MDR/RR-TB was the leading cause of antituberculous therapy-related hearing loss (HL). The recently published WHO 2021 guideline recommends injectable aminoglycosides to treat MDR-TB only if drug susceptibility testing (DST) results confirm susceptibility and high-quality audiometry monitoring for HL can be ensured [52].

The main recommendations for treating contact and tuberculosis infection are to use 6–9 months INH (9 months in immunocompromised patients), 4 months RIF, 3 months INH + RIF, 3 months weekly rifapentine + INH, or 1-month daily rifapentine + INH [30]. In a multicenter, open-label study in the treatment of latent tuberculosis, the use of RIF for 4 months and INH for 9 months was compared; the RIF group had better adherence, although both groups had similar side effects [53]. Studies to shorten the treatment period of latent tuberculosis by up to 1 month are also being carried out [46].

For treatment of close contacts and infection with MDR-TB, 6 months of levofloxacin/moxifloxacin ± PZA/ETM is recommended [54]. For both drug-susceptible and resistant tuberculosis, a 1-time intramuscular injection of bedaquiline was found promising as a single-dose trial in treating latent tuberculosis in a mouse study [55]. Preventive therapy for household contacts of active disease and latent infection did not increase the risk of developing drug resistance of a yet undiagnosed active tuberculosis [56, 57].

37.10 Prognosis

The prognosis of tuberculosis may be affected by the virulence of *M. tuberculosis* and host characteristics [58]. The outcome mainly depends on the age at the time of diagnosis of the primary infection. Genetic factors of the host increase susceptibility to infection and progression to disease. Without intervention, the prognosis is poor and often ends with hematogenous spread and tuberculous meningitis. Outcomes in children with drug-susceptible tuberculosis are generally good. Both MDR- and XDR-TB have a better prognosis in children than adults, as long as good adherence to treatment and minimizing drug side effects are possible [59, 60].

37.11 Prevention and Control

Life-threatening childhood primary tuberculosis may be based on congenital or acquired immunodeficiencies, and appropriate immunological tests are recommended at the time of diagnosis.

The live and attenuated BCG vaccine has been used worldwide, obtained from an *M. bovis* strain (lait de Nocard, in 1908) from a cow with tuberculosis mastitis, developed by Calmette and Guérin. Licensed BCG formulations differ significantly in bacterial viability, ribonucleic acid (RNA) content, and immune activation [61].

Other than the vaccines against the new coronavirus disease (COVID-19) caused by SARS-CoV-2, the BCG vaccine has been the most widely used vaccine globally for vaccine-preventable diseases [1].

Although the effectiveness of the BCG vaccine varies widely (between 0 and 80%) with age, it primarily protects against tuberculosis disease [62]. In a systematic review including 18 studies, the protection of BCG was reported to reach 69% against pulmonary tuberculosis and 90% against meningitis and miliary tuberculosis in infants [62]. Based on the IGRA tests performed on vaccinated children, BCG provides 27% protection against LTBI and 58% protection against latent infection-to-disease transformation [63, 64]. The protection of the BCG vaccine lasts for at least 5–6 decades [65]. The BCG vaccine is suitable for safety and immunity when administered to stable babies over 30 weeks of gestation and a birth weight of 1500 g within the postnatal first 7 days [66].

The WHO experts on tuberculosis stated an urgent need for more immunogenic and reliable new tuberculosis vaccines that do not contain the handicaps of the century-old BCG vaccine [67].

Finding the infectious index cases and testing the people in contact is crucial to properly controlling tuberculosis in the community. The risk of transmission is quite high in active and untreated tuberculosis. The incidence of tuberculosis infection and disease among family contacts of newly diagnosed adult tuberculosis patients was 41% and 6%, respectively [68]. For household exposure, chemoprophylaxis with proven efficacy should be prescribed to all infected close contacts, regardless of age.

It is estimated that a quarter of the world population has LTBI, with a 24.8% mean prevalence [69]. The effectiveness of preventive treatment reaches 91% in TST/IGRA-positive children [8].

37.12 Tuberculosis Disease and Hearing Loss

Approximately 466 million people, 6.1% of the world population, were affected by hearing impairment, according to 2018 data [70]. The prevalence of mild unilateral HL was reported to be1.4 billion persons in 2017; 90% of people with HL live in low- and middle-income countries [70]. Fifty percent of HL is thought to be

preventable. Severe HL will negatively affect speech and language development and preclude children from establishing verbal and auditory communication. Tuberculosis is a leading problem in low- and middle-income countries, and the necessary funding for tuberculosis-related HL has not been allocated [70].

Tuberculosis disease is associated with HL in several ways. Hearing loss can develop because of middle/inner ear tuberculosis, CNS tuberculosis in which the auditory center is affected, or as a side effect of several antituberculosis drugs. Tuberculosis disease can cause HL by infecting the middle and inner ear and the nasopharyngeal structures. Intracranial tuberculosis extending toward the ear can cause tuberculosis-related HL. Hearing loss can also be caused by aminoglycosides such as streptomycin, a first-line drug in treating tuberculosis disease, and amikacin, kanamycin, and capreomycin used to treat drug-resistant tuberculosis cases.

37.12.1 Tuberculosis Otomastoiditis and Hearing Loss

While Robert Koch had not yet discovered the tuberculosis bacillus, Jean Louis Petit, a French surgeon, first described tuberculous mastoiditis in the eighteenth century [71]. The causative agent of this disease, whose clinical features have been known for decades, was isolated from middle ear fluid for the first time in 1883 from a patient who had pulmonary tuberculosis for 7 weeks and complained of ear discharge and hearing impairment for 3 weeks [72].

The medical literature on middle ear tuberculosis (tuberculous otitis media; TOM), defined as a primary lesion, was published in detail at the beginning of the last century [73].

The advances in microbiological diagnostic methods, cross-sectional imaging techniques, and therapies with effective antituberculosis drugs have provided a detailed view of the pathogenesis, pathology, clinical features, diagnosis, treatment, prognosis, and complications of aural tuberculosis [71].

37.12.1.1 Etiology

Mycobacterium tuberculosis is the leading causative agent of ear tuberculosis. Rarely non-tuberculous mycobacteria also play a role in the etiology. There are reports of middle ear infections due to BCG when the vaccine is administered orally [71, 74].

37.12.1.2 Epidemiology

In the early twentieth-century publications, the frequency of TOM differed due to the variability of the diagnostic criteria from center to center, the inadequacy of radiological examination, the lack of autopsies, and because temporal bone involvement was not investigated in every postmortem case. However, TOM is rare among all tuberculosis cases, more common in women, and the incidence increases with age [71].

The incidence of clinically diagnosed TOM was 1.3–15.4%, on average 2.7%, in an evaluation of 8555 otitis media cases, including patients followed in various centers between 1915 and 1934 [75]. At that time, there was no effective

antituberculosis treatment yet. While it was reported that the cause was tuberculosis in 4.7% of adults with chronic purulent otitis media, this rate rises to 14% in children [76, 77]. More than a century ago, the incidence of TOM was around 50% under the age of one diagnosed with otitis media [71]. Severe HL was reported in many TOM cases [73, 75–79].

The incidence of TOM decreased considerably in the second half of the twentieth century compared to the first half, which parallels the advent of antituberculous therapy in this period. For this reason, the disease may be diagnosed delayed by the physicians and may progress to HL, facial paralysis, and even tuberculous meningitis [80].

The medical records of more than 15,000 patients with chronic otitis at various ages were evaluated [81]. Tuberculous mastoiditis was the most common between the ages of 1 and 2 years, and 0.8% of the mastoiditis cases were caused by tuberculosis. Tuberculous otitis was diagnosed in 1.3% of 4285 suppurative middle ear infections in a center for 10 years [82].

Many hearing problems can also be related to tuberculosis in countries with a high incidence of tuberculosis. In Angola, 36% of children with chronic suppurative otitis media had tuberculosis in history, and 30% had bilateral HL [83].

The incidence of tuberculosis otitis in adults with pulmonary tuberculosis was reported as 1.7% [84]. Only 1 of 1391 patients with extrapulmonary tuberculosis had TOM from 1984 to 2000 in Italy [85]. Of the 3750 tuberculosis patients in a series, 230 had extrapulmonary involvement, and only 6 had TOM resulting in HL [86].

In necropsy examinations of 269 children with tuberculosis, TOM was found in 15 cases with tuberculosis in other organs [87]. Tuberculosis of the primary external auditory canal is very rare [76]. In cases of TOM, the infection can be transmitted congenitally and lead to HL [71, 88, 89].

37.12.1.3 Pathogenesis and Immunity

The anatomical features of the Eustachian tube in children and adults show differences. While the tube is 34–36 mm in adults, it is much shorter in children and less than 20 mm in newborns. It is broader in infants than that in adults. Additionally, the place where the Eustachian tube opens into the middle ear cavity is lower than that of the adult, and its pharyngeal orifice is nearby to the choanae. This means that the airflow more easily displaces an object in the Eustachian tube in children [73]. The Eustachian tube facilitates the air containing bacilli to move back and forth during the infant's suckling and paves the way for the spread of the infection. While the child with pulmonary tuberculosis is supine, infected pulmonary secretions easily spread to the pharynx and nasopharynx and then to the ears [71, 90].

During the development of tuberculosis disease in the middle ear structures, the bacilli reach the cavum tympani in several ways [73]: (1) The air passing through the Eustachian tube reaches the middle ear cavity, (2) spread in the middle ear mucosa with involvement of the Eustachian mucosa, (3) lymphatic spread from a tuberculosis focus elsewhere in the body, (4) spread by blood from a tuberculosis focus elsewhere in the body, and (5) progression of the outer ear infection to the middle ear. Of

all these routes, especially if there is abundant respiratory secretion production, frequent coughing is a leading factor in the spread of tuberculosis to the Eustachian tube.

Otitis and mastoiditis may develop during miliary tuberculosis by the lymphohematogenous spread. Secondary tuberculosis is almost invariably seen in adults; TOM accompanies or follows chronic or advanced pulmonary tuberculosis. Ear tuberculosis in adults tends to be a complication of cavitary tuberculosis of the lung. This is presumed since copious sputum from the cavitary pulmonary lesion quickly drains into the middle ear during frequent episodes of cavity-induced coughing [73]. In adults, the pathological changes are limited to the middle ear and are not accompanied by an unfavorable prognosis [76].

However, tuberculosis is most frequently seen in infants as the primary type, and aural involvement is liable to be acute and extensive, with appreciable destruction of the temporal bone [76]. Otitis media and mastoiditis may develop during miliary tuberculosis, most likely with lymphohematogenous spread, as presented by Saltzman and Feigin in an infant [79]. Ear tuberculosis may rarely occur when the infection in the head progresses backward to the middle ear and reaches through the inner auditory canal and labyrinth [91]. In any way, TOM can produce a significant hearing defect at any age.

37.12.1.4 Pathology

In TOM, the cavum tympani, the mastoid antrum, and the Eustachian tube are involved. The temporal bone, mid-cranial cavity, meningeal membranes, and brain parenchyma may be affected [73].

Pathological changes in TOM were described in detail by examining the membrane lining the middle ear cavity, the TM, and parts of the affected temporal bone [73]. Involvement can range from infiltration of the lining mucosa to diffuse severe destruction of the temporal bone. In acute TOM, ulceration of tuberculomas leads to perforation in the TM due to tissue loss, followed by the formation of granulation tissue. Small perforations may merge to form a single large opening in the TM. This wide connection between the outer and the middle ear leads to the passage of many pyogenic bacteria to the middle ear cavity and contributes to the alteration of the pathological process.

Tubercles in the middle ear cavity first appear on the promontory mucosa, on the inner surface of the TM, or the mastoid antrum mucosa. The tuberculoma enlarges to form caseation and necrosis in the bone. The ossicles in the middle ear gradually dissolve and disappear; then, the infection progresses to the labyrinth [71, 92].

In pulmonary and otic tuberculosis, the ear lesion was similar to that in the thorax [76]. In other words, if the lesion in the thorax is exudative, the lesion in the ear is also exudative; if the pulmonary lesion progresses to fibrosis, the lesion in the ear becomes fibrotic.

37.12.1.5 Clinical Manifestations

It is not precisely known how often TOM does occur in the absence of pulmonary tuberculosis. Depending on the rarity of sole TOM, the patients will mainly have the symptoms and signs of pulmonary tuberculosis. Systemic signs, such as fever,

weight loss, and weakness, are common in tuberculosis. Fever is typically not high; however, extensive caseated tubercles or secondary ear infections with bacteria can cause irregularities in body temperature. Cough and sputum are present among the symptoms when pulmonary tuberculosis accompanies the event [73]. The sputum can be bloody in adults [71].

Tuberculous otitis media can have a rapid or chronic clinical course, the latter being more common [73, 93]. The duration of symptoms of chronic TOM can vary widely, from several weeks to a decade [94–96].

Usually, the first complaints are a feeling of fullness in the ear and decreased hearing after maneuvers such as blowing or coughing, without severe signs of inflammation of the TM. These symptoms can be put into words by adolescents and adults. Unlike acute pyogenic middle ear infections, otoscopy does not show pulsation of the TM [76]. The TM is perforated in a few days or weeks, and painless ear discharge accompanies [76]. On examination, a pearl-gray tuberculoma the size of a millet seed can be seen on the TM [71]. Perforation is usually the result of several tuberculomas on the TM progressing to caseify and necrosis at more than one location. The TM is generally perforated from the posterosuperior quadrant, and this location for perforation is considered almost pathognomonic for TOM [73, 97]. Multiple small perforations in the TM coalesce into marginal or complete perforation [95]. Some patients experience tinnitus before the TM ruptures [71, 91].

One of the most common and earliest symptoms in infants and young children is ear discharge. The discharge is usually painless, straw-yellow, and thin [71]. Depending on the destruction and fragmentation of the middle ear bones, the discharge may be bloody and have sandy particles [86]. Sometimes parents may comment that chronic ear discharge is related to ear-cleaning cotton that may have been forgotten [98]. Typically, there is no or very mild pain in the ear because the inflammation of the middle ear mucosa is not severe. One of the reasons for the absence of pain is that the pressure decreases due to the premature perforation of the TM and the emptying of the middle ear contents; the inflammation around the nerves does not create pressure on the nerves since it is not severe. Even the products that emerge during the destruction of the waxy envelope of the tuberculosis bacilli have an anesthetic effect. The thin, sometimes slightly blood-smeared discharge then changes to a mucoid and thick-consistent character. It turns into a foul-smelling discharge by adding putrefactive bacteria to the infection by advancing through the perforated membrane into the middle ear cavity [71, 73].

Hearing loss is the second most frequently reported symptom [90] and aids in diagnosis in the early stages of TOM. The audiogram measures an average of 40–50 db of loss [71]. Deafness can be temporary, permanent, or progressive. Hearing loss can be conductive, sensory, or both [99]. Conductive HL (CHL) develops due to perforation of the TM in the early stages of the disease, but sensorineural HL (SNHL) occurs when labyrinthitis occurs [100]. Hearing loss may occur in only one ear, with consecutive involvement, or in both ears simultaneously [101]. Weber test is impaired in the affected ear with a negative Rinne test [102].

The middle ear cavity is lined with a pale membrane and filled with loose granulation tissue [73]. Granulation in the middle ear tends to bleed even with minor

trauma. This should draw the attending physician's attention to the possibility of tuberculosis [103]. Sometimes, this granulation tissue may extend from the perforated TM to the external auditory canal [71]. A Bezold abscess may occur at the end of the mastoid bone [84].

The middle ear ossicles are more frequently affected in TOM than in any other middle ear inflammation. Necrosis of the foot of the stapes bone is considered pathognomonic for tuberculosis. When this damage occurs, the oval window opens, and the infection progresses to the labyrinth. In intrauterine life, the stapes bone is formed by a blood supply from the stapedial artery, which atrophies and disappears at the end of pregnancy. However, it may remain patent in the first postnatal years and may play a role in spreading tuberculosis into the middle ear by blood flow in young children [73].

When tuberculosis infection occurs through the bloodstream of the middle ear, it is called primary TOM. The effect of disease on the middle ear with the blood flow is age-related and occurs mainly in young children. Mastoiditis is not uncommon and may develop without middle ear cavity involvement. If tissue destruction progresses from the middle ear structures to the periosteum of the mastoid cells and reaches the outer surface of the head, it may turn into a chronic draining wound. The infection may progress up to the dura mater in the intracranial structures. Subperiosteal abscess of the outer wall of the mastoid antrum can open out and turn into a fistula tract [71, 73].

Facial nerve involvement can lead to facial neuritis and paralysis [71, 86, 96]. Facial paralysis usually occurs suddenly and may escape from parents' attention in young children and infants. With the damage to the chorda tympani, a branch of the seventh cranial nerve, the complaint of taste loss may develop. Injury to the eighth cranial nerve leads to a progression of the infection to the meninges. Similarly, vertigo may occur if semicircular canals are affected [73].

The presence of tuberculosis bacilli in the middle ear causes the neighboring lymph nodes to become infected [73, 103]. Enlargement of the lymph nodes due to TOM is most common in the mastoid, parotid, and retropharyngeal lymph nodes and may develop long before the middle ear findings appear. When TOM occurs due to tuberculosis elsewhere in the body, enlargement of the neck lymph nodes is usually not observed; however, in primary TOM, early-stage enlargement of the lymphoid glands is a typical finding [73].

37.12.1.6 Complications

Complications of TOM have been less common with better nutritional conditions and the introduction of more effective treatments. Hearing can be severely affected, disproportionate to the duration of the ear discharge [102]. The patient may have a "dead ear" [94]. Impairment in hearing function in young children negatively affects language and cognitive development. The components that contribute to HL in TOM are listed below [73]:

- Perforation of the TM
- Filling of the middle ear cavity with fluid and granulation tissue

- Adhesions in middle ear structures with dense fibrous tissue during healing
- Melting in the ear ossicles
- Labyrinthitis
- Inflammation of the eighth cranial nerve

Middle ear tuberculosis in children is a more severe condition than in adults. While the disease is rarely life-threatening in adults, serious complications such as meningitis, facial palsy, brain parenchymal abscess, epidural abscess [104], carotid artery ulceration [76], and severe ataxia [105] may develop in children. Facial paralysis is seen at a much higher rate in TOM than in suppurative middle ear infections [73].

Among chronic middle ear infections, those due to tuberculosis cause intracranial complications less frequently than other infections. The progression of tuberculosis to the meninges is fatal if left untreated. Intracranial spread is usually via the inner ear meatus. Since the petrous and mastoid temporal bone parts have not yet united in infancy, spread to the meninges is more common at this age [73].

Bacterial infection may also accompany TOM, and a pyogenic inflammatory fistula may occur behind the ear [106]. Very rarely, chronic tuberculous otitis externa may develop. A case with tuberculoma in the external ear canal was reported years after the perforated TM was repaired [107].

37.12.1.7 Differential Diagnosis

Acute and chronic bacterial, viral, fungal infections in the middle ear, otitis externa, foreign body in the external ear canal, perforation in the TM, acute labyrinthitis, and nasopharynx neoplasia can cause ear discharge, pain, and inflammatory appearance and can be confused with TOM. Occult TOM can be diagnosed during labyrinthectomy to treat vertigo, purulent labyrinthitis, diffuse cholesteatoma, and malignant lesion [108].

37.12.1.8 Laboratory Findings

A meta-analysis studying the literature on TOM publications before 1953 [102] reported biopsies and cultures were performed less often [84]. However, after 1953, although the disease frequency decreased, biopsies and cultures were performed more often [84].

The primary causative agent of TOM is *M. tuberculosis*. At the beginning of the ear discharge, the tuberculosis bacilli in the liquid are dense and easy to isolate [103]. In consuming contaminated milk without pasteurization, *M. bovis* may be the causative agent and associated with a recurrent middle ear infection and HL [109].

Four out of every five cases are accompanied by bacterial infection, mostly due to *Proteus* spp. [110]. The presence of other bacteria in tuberculosis ear infections reduces the possibility of isolating tuberculosis bacilli in culture [103, 110]. In some case series, TOM developed secondary to chronic bacterial middle ear infection. Therefore, the isolation of other bacteria does not exclude the diagnosis of TOM [94].

The TST or IGRA is positive in most, but not all, patients with TOM [110]. For a definitive diagnosis, Ziehl–Neelsen (EZN) staining, PCR test, and histopathological examination should be performed [93, 111]. The biopsy taken with the first

surgical intervention may not always be diagnostic, and a repeat surgical procedure may be required [81]. Granuloma formation, epithelioid histiocytes, and Langhans-type giant cells are often seen histopathologically. Erosion is seen in the ossicular ear chain. Histopathological findings such as abrasion on the malleus handle with no soft tissue cover were evaluated as a pathognomonic sign, a feature not encountered in other chronic otitis media pathologies [110].

37.12.1.9 Imaging Studies

Before cross-sectional imaging methods such as computed tomography (CT) and magnetic resonance (MR) imaging were developed, radiography of the temporal bone was used. It was thought that a well-ventilated mastoid bone in a patient with chronic middle ear infection suggested the presence of tuberculosis [71]. Computed tomography findings are also not specific to tuberculosis and may vary widely, ranging from increased density in the mastoid space to bone sequestration of the temporal bone. While the destruction of the ear bones is common, especially in patients with miliary pulmonary tuberculosis [95], bone destruction is rare in CT findings in patients with cholesteatoma [93].

Anatomical studies were performed on the osseous cranial base of patients diagnosed with active tuberculosis at the time of death, and its potential effect on hearing was evaluated [112]. The petro-occipital fissure and cochlear aqueduct ossification were similar to the changes in age-related HL. Posterior occipital fossa and cochlear canal ossification occurred significantly faster in people with active tuberculosis than in other infections. It has been suggested that this change does not disrupt the fluid connection between the cerebrospinal fluid (CSF) and the perilymph of the inner ear, but it increases the turbulent blood flow and can be the reason for the patient's HL and tinnitus [112].

37.12.1.10 Diagnosis

More than 100 years ago, Paul Mathews [73] published a case series of TOM in children and described the clinical features, symptoms, pathogenesis, postmortem pathological findings, surgical treatment approaches, and prognosis of the disease in great detail. Early diagnosis was emphasized to have a good prognosis of the disease at that time as it is today [73, 84].

A high level of suspicion is required to diagnose TOM [100]. The disease is most common in children under 2–3 years of age and rarely resolves spontaneously [73]. The presence of multiple perforations, especially in the posterosuperior quadrant, with the absence of inflammation in the TM, is noteworthy for diagnosis. In some cases, tubercles can be seen on the TM.

Despite widespread destructive changes in the middle ear, the absence of pain is the characteristic finding of TOM [73]. Hearing loss disproportionate to examination findings, recurrence of granuloma tissue after mastoidectomy, slow wound healing, persistent ear discharge, and bone sequestration should suggest the diagnosis of TOM [81, 103, 113]. Demonstration of the tubercle bacillus in ear discharge provides the definitive diagnosis.

Ear discharge and HL are the most common symptoms and signs of all patients. While the frequency of HL was defined as 62% in publications before 1953, its incidence reached 90% afterward [84].

The diagnostic criteria for TOM were recently established using the data of 502 patients with chronic otitis media who underwent tympanoplasty–mastoidectomy and 25 patients with TOM [113]. Accordingly, one major and two minor criteria are required to diagnose TOM. If the major criterion is not met, there is a high probability that TOM is present if at least three minor criteria are present.

Major criteria:

- The acid-resistant bacilli (ARB) identified in tissue biopsy
- The ARB identified on smear or in the culture of ear discharge
- Positive PCR test in ear fluid or biopsy

Minor criteria:

- Multiple punctures in the TM
- Abundant pale-colored granulations
- Severe HL
- Bone sequestration
- General infection symptoms
- Facial paralysis

Although its frequency has decreased in the twenty-first century, TOM should be investigated in patients with chronic perforated otitis media and HL that do not improve despite antibiotics [114, 115]. The current literature review reported macroscopic ear lesion appearances of TOM, cross-sectional radiological images, and histopathological details [116].

In summary, the foremost step in diagnosing tuberculosis is considering the possibility of its presence. As a second step, temporal bone CT should be performed primarily in patients with facial paralysis and sudden HL without pain or ear discharge. Although microbiological and histopathological confirmation is valuable, negative results should not exclude the diagnosis of tuberculosis [93].

37.12.1.11 Treatment

Before the era of antituberculosis treatment, no effective treatment for TOM could be made. When the disease was first described, it was recommended to make an incision in the TM at an early stage. In this way, it was aimed to discharge the fluid in the middle ear and ventilate it. The applications of iodine, boric acid, glycerin phenol, or mercurochrome were suggested for antisepsis. It has been reported that reflecting sunlight directly onto the TM, called heliotherapy, using a concave mirror for 5–10 min each day, could work in some chronic cases [117]. Injection of tuberculin solution has also been tried in some adult patients [91]. The importance of clean air and good nutrition in treating tuberculosis was emphasized.

As the first discovered antituberculosis agents, streptomycin and para-aminosalicylic acid (PAS) were used to treat TOM and the more common forms of tuberculosis [102]. With this treatment, the perforation of the TM was sometimes prevented. Later, with the development and use of more effective antituberculosis drugs, tuberculous otitis gradually decreased. Currently, medical treatment of aural tuberculosis is the same as for pulmonary tuberculosis and is very effective: The overall cure rate is reported as 96.8% [118].

Cortical, modified, and radical mastoidectomy techniques have been used in the surgical treatment of tuberculosis otitis. In particular, surgical intervention is required to relieve facial nerve paralysis and clean necrotic tissues in which antibiotics do not penetrate well. Notably, the degree of HL is often greater than expected from the apparent damage in the ear [119]. In tuberculous mastoiditis, surgery should be performed to incise and drain the postauricular abscess and remove the bone sequestrum [81]. Reconstructive procedures can improve hearing after drug therapy [90]. Cochlear implantation can be performed in patients with HL. However, ossification of the labyrinth due to chronic infection may complicate implant placement. The primary surgical challenge of cochlear implant placement is the inability to mark the round window area correctly. In cases with tuberculosis, the difficulty of marking is mentioned as these areas are severely eroded [120].

37.12.1.12 Prognosis

Before antituberculosis drug treatment was available, TOM usually healed in the form of cholesteatoma and chronic adhesive middle ear disease [75].

Tuberculosis should be investigated in every child with a chronic discharging middle ear infection, especially with multiple perforations in the TM. Facial paralysis and HL may be less common with early diagnosis and treatment. Hearing loss often develops early in the disease process [121]. Unfortunately, even today, treatment of TOM may not make a significant difference for HL. Delayed diagnosis is one of the main reasons for not improving HL [122].

Mortality was found at 2% and hearing sequelae at 75.5% in a meta-analysis of 336 patients aged between 1 month and 87 years from 42 countries reported since January 1, 2000 [118]. Facial paralysis is most prominent at the age of <5 years, and the shorter the duration of this finding (1–5 days versus 2–3 months), the sooner it resolves after antituberculosis treatment is started [81].

Sensorineural HL can develop after starting antituberculosis treatment in rare instances of miliary tuberculosis. It has been suggested that this is caused by a paradoxical reaction called immune reconstitution inflammatory syndrome (IRIS), caused by the recovery of the host's immune response as tuberculosis is treated [123].

Despite modern diagnostic methods, increasing awareness, and effective antituberculous treatment, the reported mortality rate due to tuberculous ear infection was 2% in all ages in a recent meta-analysis mentioned above, and it often accompanied meningeal involvement [118].

37.12.1.13 Prevention and Control

All individuals suffering from tuberculosis disease should be carefully evaluated for tuberculous otitis, especially when ear complaints occur, with particular attention to the development of tinnitus, ear fullness, and HL [102]. According to the analysis presenting the twenty-first-century aural tuberculosis cases in the medical literature, BCG vaccination was 54.5% and was not protective against aural tuberculosis [118].

37.12.2 Tuberculosis Nasopharyngitis and Hearing Loss

Nasopharyngeal lesions were seen in 36% of adults with active pulmonary tuberculosis [124]; however, primary nasopharyngeal tuberculosis is rarely seen. The most common presenting finding is lymphadenitis in the neck, and HL is the second [125]. Diagnosis is made by detecting tuberculosis disease in the nasopharyngeal adenoids [126]. Serous otitis secondary to nasopharyngitis is the cause of HL [127].

Nasopharyngeal tuberculosis has been reported very rarely in the literature. It causes chronic effusion in the middle ear and HL with a mass effect on the Eustachian tube, which opens the nasopharyngeal cavity. A decrease in hearing may be accompanied by tinnitus [128]. Nasopharyngeal tuberculosis can also be seen in children and is more common in girls. Ear discharge and HL were accompanied by double vision in a pediatric patient [129]. It usually occurs without systemic and pulmonary involvement [130]. Tuberculous osteomyelitis was accompanied by tuberculous otitis in another case in the literature [129].

Pharyngeal tuberculosis may cause Eustachian tube dysfunction and deafness due to thin gray diffuse inflammation in the posterior wall of the pharynx [131]. The retropharyngeal tuberculous abscess is a rare condition that causes a mass in the posterior pharynx, resulting in otitis media with effusion and CHL [132].

Primary Eustachian tube tuberculosis creates mechanical obstruction in the Eustachian tube, resulting in a pressure mismatch between the middle ear and the outer atmosphere, resulting in ear fullness and reduced hearing [133].

37.12.3 Tuberculous Meningitis and Hearing Loss

If untreated, tuberculous meningitis results in coma and death within 3 weeks. One of its non-fatal complications is SNHL, usually severe. Regarding its incidence 50 years ago in the United Kingdom, 106 (7%) of 1509 children with HL were recorded to have tuberculous meningitis [134]. The frequency of HL in children with tuberculous meningitis was 16–39.3% [135, 136]. Of 93 patients with intracranial tuberculosis, including meningitis, tuberculoma, abscess, and encephalopathy, death in 26.9%, neurological sequelae in 40.9%, and HL in 2.2% were detected

[137]. All patients with tuberculous meningitis should undergo a hearing assessment. Evaluation of children with tuberculous meningitis with brainstem auditory evoked response (BAER) helps to investigate hearing impairment in a non-invasive fashion. Abnormal BAER test was found in 24% and total HL in 16% of children with tuberculous meningitis at admission [138].

The use of streptomycin in high doses in the first years after its discovery as a tuberculosis drug without realizing its toxicity suggested that deafness in tuberculous meningitis was an adverse effect rather than the disease itself. However, HL frequently occurs after tuberculous meningitis, even when streptomycin and aminoglycoside medications are not used [134].

The following histopathological findings were obtained in the postmortem temporal bone examination of a patient with tuberculous meningitis who developed SNHL [139]: (1) Inflammation is especially evident in the internal auditory canal, the modiolus, and the Rozental canal and extends to the osseous spiral ligament, (2) Organ of Corti cochlear nerve fibers and spiral ganglion cells degenerate heavily.

Infection proceeds from the meninges to the inner ear through the modiolus and the cochlear canal [140]. Involvement of the labyrinth, which causes SNHL, occurs when the infection progresses from the meninges to the inner ear in a retrocochlear pattern, as in bacterial meningitis [139].

In tuberculous meningitis, adjunctive steroid therapy combined with antituberculous drugs is given to prevent severe neurological sequelae such as meningeal adhesions and hydrocephalus. Recommendations on steroid dosage vary. Sixty-three children with tuberculous meningitis received different doses of steroids, and the complications were evaluated in a randomized study [141]. Compared to those in the groups of prednisolone administered 2 or 4 mg/kg/day for full 4 weeks, patients in the protocol of 4 mg/kg/day for 1 week and 2 mg/kg/day for the next 3 weeks had less tuberculoma and infarction while having higher rates of HL.

37.13 Pediatric Case Reports and Series of Tuberculous Otitis and Mastoiditis

Case reports and series of tuberculous otitis and/or mastoiditis in children (≤18 years) published in English as full text in the PubMed database until October 29, 2022, were searched. The clinical features of 216 eligible cases reported in these articles are presented in Table 37.2 [9, 73, 75, 79, 81, 89, 97, 98, 103, 109, 110, 115, 117, 121, 122, 129, 142–216]. Varying degrees of HL were reported in 117 children. Although a systematic review on middle ear tuberculosis in adults has been published very recently [217], there is no comprehensive publication in this area in the pediatric age, as far as we know.

Table 37.2 Characteristics of pediatric patients with tuberculous otitis and/or mastoiditis reported in case reports and series published in English as full text in the PubMed database (in chronological order)[a]

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Crockett (1906) [142]	5.5 y/M	Ear discharge	Perforation anterior and posterior to the malleus with a slight serous discharge				+				+	Iodoform and boric acid powder, open-air treatment	Improved
Crockett (1906) [142]	4 y/M	Ear discharge	Ear discharge, a postaural abscess, painless to pressure and not red				+		Abscess drainage, mastoid operation removing a large sequestrum	Tuberculous sequestrum		Iodoform powder, open-air treatment	Improved
Crockett (1906) [142]	1,5 y/F	Ear discharge	A cold abscess over the mastoid				+		Mastoid operation, sequestrum removal from the external auditory canal	Tuberculous sequestrum		Iodoform powder, open-air treatment	Improved
Crockett (1906) [142]	7 m/M	Ear discharge	Numerous granulations, swollen parotids, postaural abscess, gland masses in the neck, pus discharging from some glands		+		+		Mastoid operation, lymph nodes removal	Granulations in the middle ear and mastoid		Iodoform powder, open-air treatment	Improved
Crockett (1906) [142]	10 m/M	Ear discharge	Parotid swelling, facial nerve paralysis, postauricular swelling				–		Mastoid operation, lymph nodes removal	Tubercular sequestra		Iodoform powder, open-air treatment	Improved
Mathews (1907) [73]	9 m/NR	Swelling behind and below the ear, ear discharge/2 months	Marked swelling over mastoid, ear discharge, enlarged glands, perforation into the antrum	Miliary pattern			+		Mastoid abscess opened, carious temporal bone scraped away	Postmortem: The apex of the petrous temporal bone was carious	+		Died
Mathews (1907) [73]	3 m/M	A lump below the ear, facial paralysis, ear discharge/3 weeks	Large masses of glands below the ear, membrane destroyed	Miliary pattern			–		Caseous enlarged glands removed, carious material scraped away	Postmortem: The dura was thickened over the aperture in the middle cranial fossa	+	Iodoform gauze, peroxide of hydrogen	Died
Mathews (1907) [73]	2 y/NR	No symptom	Cervical gland tuberculosis	Lung, larynx, pericardium, mesenteric lymph nodes			–			Postmortem: Carious temporal bone, the apex of the pars petrosa, and the cavum tympani contained caseous debris	+		Died

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Mathews (1907) [73]	13 m/NR	Otorrhea/1 month	Swelling over the mastoid, foul-smelling discharge from the ear				–		Carious temporal bone scraped away	The antrum was filled with caseous debris and granulation tissue	+		Improved
Mathews (1907) [73]	6 y/NR	Facial paralysis, ear discharge, enlarged glands in the neck/18 months	Facial paralysis, enlarged cervical glands, fetid ear discharge, meningitis	Tabes mesenterica, meninges							+		Died
Mathews (1907) [73]	21 m/NR	Diarrhea, vomiting, cough/2 weeks	Coma	Lungs, meninges			–			Postmortem: Caries in both temporal bones, thick pus in both middle ears	+		Died
Mathews (1907) [73]	2,5 y/NR	Otorrhea, enlargement of cervical glands/4 months	Facial paralysis, ear discharge, enlarged cervical glands	Cervical, intrathoracic, and abdominal lymph nodes			+				+		Died
Mathews (1907) [73]	18 m/NR	Otorrhea/3 months	Ear discharge from both ears, perforated ear membranes	Lungs, liver peritoneum, mesenteric lymph nodes						Postmortem: Caries of the temporal bone in the region of the inner ear and mastoid, the tympanic cavity being filled with debris	+		Died
Mathews (1907) [73]	1 y/NR	Otorrhea, enlargement of the mastoid gland, purpuric rash/3 months	A discharging sinus over the mastoid, palpable abdominal glands and spleen,	Lungs, spleen, mesenteric lymph nodes			–		The sinus over the mastoid was opened up, and the carious bone scraped		+		Died
Mathews (1907) [73]	4 m/NR	Otorrhea, swelling of glands behind and below the ears, facial paralysis/2 months	Facial paralysis, fetid discharge from destroyed ear membrane, enlarged glands below, behind, and in front of the ear, carious bone	Miliary pattern, lungs, mesenteric and mediastinal lymph nodes, dura, temporal bone			+			Postmortem: Carious remains of the temporal bone, the mastoid antrum, and cavum completely destroyed, thickening of the dura covering the tegmen tympani	+		Died
Mathews (1907) [73]	5,5 y/NR	Otorrhea, enlarged glands/4,5 years	Ear discharge from both ears, destroyed ear membrane, carious bone, enlarged parotid glands, nerve deafness				+		Glands excised or scraped, antrum opened up, and carious bone was removed	Caseating glands	+		Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Mathews (1907) [73]	2,5 y/NR	Swelling over mastoid, otorrhea, night sweating/2 months	Otorrhea, a fluctuating mass behind the ear, enlarged cervical glands				+		The antrum was opened up, and caseous debris was cleared out. A caseating gland below the ear was scraped out		+		Improved
Briggs (1914) [117]	12 y/F	Swelling, pain, discharge of the mastoid/9 years	Mastoid swelling, discharge				+		Mastoid swelling incised, leaving a sinus through the cortex, filled with pale granulations and discharge. Surgery repeated many times	Granulation tissue and sequestra, containing typical cheesy masses, giant and epithelioid cells; cholesteatoma			Improved
Briggs (1914) [117]	4 y/F	Fever, ear discharge, tenderness, and swelling over the mastoid/1 month	Ear discharge, mastoid process filled with granulations				+		Mastoid operation, tonsils, and adenoid removed	Granulations, typical tuberculous changes			Improved
Turner et al. (1915) [143, 144]	15 m/NR	Ear discharge from both ears/some months Facial asymmetry/1 month	Paralysis of one side of the face, foul pus in the meatus, and swelling of the posterior wall	Lung, bronchial, and mesenteric lymph nodes			–		Mastoid operation	Postmortem: Granulation tissue, tubercular nodules	+		Died
Turner et al. (1915) [143, 144]	9 m/M	Ear discharge/6 months	Profuse nasal discharge, enlarged glands around the ear, fistula discharging pus, facial paralysis	Meninges			–		Mastoid operation	Postmortem: Tubercular granulation tissue, caseation and necrosis in the Eustachian tube, bony marrow and cochlea and other internal ear structures, fibro-ossifying type of tubercular otitis			Died
Turner et al. (1915) [143, 144]	9 m/M	Otorrhea, swelling behind ear/10 weeks	Marked adenoids, perforated tympanic membrane	Meninges			–		Radical mastoid and adenoid operation	Postmortem: Tubercles in the middle ear, fistula into the labyrinth, and cochlea			Died
Mollison (1919) [145]	13 m/NR	Otorrhea/7 months Swelling over the mastoid process/4 days	Bilateral profuse foul otorrhea, swelling and redness over the mastoid process, double facial paralysis	Preauricular and infra-mastoid lymph glands			–		Mastoid operation	Soft and necrotic mastoid process, sequestra, dura mater of the middle fossa covered with granulations			Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Baar et al. (1941) [146]	6 m/F	Bilateral ear discharge, swelling behind and below ear/2 months	A fluctuating swelling over the mastoid process, purulent discharge at the external auditory meatus, enlarged lymph nodes below the mastoid process	Miliary pattern, lungs, pleura, spleen, jejunum, thoracic and mesenteric lymph nodes			–	Positive	Mastoidectomy	Necrotic caseating granulation tissue in petrous bone, ossicles absent			Died
Proctor et al. (1942) [75]	4 y/F	Headache, vomiting, loss of weight, fever/1 week		Miliary pattern, meninges, lungs, liver, spleen, bone marrow, kidneys, ileum, hilar, mediastinal, and abdominal lymph nodes			+	Positive		Postmortem: Several foci of fibrocaseous miliary tuberculosis in the temporal bone, acute exudative infiltration of the leptomeninges in the internal auditory meatus, labyrinthitis, giant cells, tubercle bacilli in the bone marrow of the temporal bone			Died
Proctor et al. (1942) [75]	22 m/F	Cough, fever, irritability/3 weeks	Listlessness, neck rigidity	Miliary pattern, meninges, lungs, liver, spleen, bone marrow, kidneys, ileum, mediastinal and abdominal lymph nodes				Positive		Postmortem: Epitympanum, mastoid antrum, mastoid air cells, and ossicular chain contained considerable tuberculous granulation tissue in both ears; caseating tubercles, exudate. Petrous marrow and internal auditory meatus were also involved			Died

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Proctor et al. (1942) [75]	2,5 y/F	Bilateral otalgia, otorrhea, fever, drowsiness, vomiting/1–8 weeks	Bilateral mastoiditis, otitic hydrocephalus, coma	Miliary pattern, meninges, lungs			–	Negative	Mastoidectomy	Postmortem: Tuberculosis of the temporal bone and marrow, tubercles containing giant cells in the external canal and air cell system, ulcerated tympanic membrane, tuberculous granulation tissue around the ossicular chain, fibrinopurulent exúdate in the lumen of the eustachian tube, cholesteatoma		Sulfanilamide, sulfapyridine	Died
Proctor et al. (1942) [75]	5 m/M	Fever, cough, wheezing/5 weeks Ear discharge/2 weeks	Bilateral otitis media, polypoid granulations in the ear	Lungs, meninges		X-ray: Cellular breakdown in the mastoid	+	Positive	Myringotomy, mastoidectomy	Trabeculae of the mastoid cells destroyed, tuberculous granulation tissue	+		Died
Proctor et al. (1942) [75]	14 y/M	Otorrhea	Perforated tympanic membrane	Lung, meninges, vertebrae, hip						Chronic tuberculous adhesive otitis media, mastoiditis. Tuberculous changes, with round cell and giant cell infiltration of the tympanic membrane in both ears			Died
Proctor et al. (1942) [75]	6 y/M	Painful lump on the back/6 months Fever, headache/1 week	Chronic suppurative otitis media and mastoiditis, unconscious state	Miliary pattern, meninges, lungs, liver, spleen, bone marrow, kidneys, vertebrae						Postmortem: Destroyed tympanic membrane, miliary tubercles in petrous marrow, squama of the temporal bone flattened, cholesteatoma			Died
Proctor et al. (1942) [75]	11 y/F	Fetid otorrhea/2 years	Many draining sinuses about the ear, polyps in the auditory canal		+	X-ray: Extensive invaded perilabyrinthine areas and the apex	–	Positive	Radical mastoidectomy	Tuberculosis of temporal bone, the mastoid cavity filled with irregular tracts of granulation tissue			Improved
Proctor et al. (1942) [75]	5 y/M	Discharging ear/2 weeks	Draining abscesses in the preauricular and cervical regions, profuse otorrhea, inflamed mastoid	Lung		X-ray: Complete clouding of the mastoid and petrosa		Negative	Mastoidectomy	Tuberculous granulation tissue			Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Fisher et al. (1948) [147]	8 w/F	Otorrhea/7 days Facial palsy/2 days	Profuse mucoid foul-smelling discharge from the ear, granulation, facial palsy, enlarged submandibular gland				–	Positive	Cortical mastoidectomy	Granulation tissue and some areas of caseous necrosis	+	SM	Improved
Banham et al. (1951) [148]	7 y/M	Bilateral earache/3 weeks	Fever, both tympanic membranes opaque and injected, a tender swelling over the mastoid	Adenoids	+	X-ray: Mastoiditis with marked bone destruction	–	Positive	Cortical mastoidectomy	Tuberculous granulation tissue, giant cells, and caseation		SM (systemic and local)	Improved
Dickson et al. (1951) [149]	3 y/M	Recurrent ear pain, ear discharge, facial paralysis/1 year	Soft, fluctuant abscess under the mastoid scar, granulations, seropurulent discharge, facial asymmetry		+		+		Cortical mastoidectomy, abscess drainage	Tuberculous histologic findings	+	SM, PAS	Improved
Kollar (1952) [150]	20 m/F	Soft parts behind the auricle thickened/3 weeks Abundant pus discharging from ear fistula/10 days	Soft parts above the mastoid process thickened, injected, 2 fistulas discharging pus	Lungs, tonsils, meninges			+		Curettage from the fistula	Tuberculous granulation tissue	+	SM (systemic and local)	Improved, then died
Kollar (1952) [150]	3 m/F	An enormous mass of enlarged lymph nodes below the ear/5 weeks Ear discharge/3 weeks Facial paralysis/1 week	Sanguinopurulent otorrhea, destroyed auditory canal and covered with granulations, facial paralysis, fever	Lungs, cervical lymph nodes			+	Positive	Radical ear operation	Tuberculous granulation tissue	+	SM (systemic and local)	Improved
Jeanes et al. (1960) [151]	5 y/M	Sore throat, earache, and discharge/2 weeks	Tympanic membrane bulging, with perforation, mucopurulent discharge in meatus		+	X-ray: Acellular mastoid	–		Cortical mastoidectomy	Mastoid cells filled with pale mucous membrane, tuberculous granulation tissue			NR
Jeanes et al. (1960) [151]	10 y/M	Occasional painless serous discharge from ear/5 months	Granulations were seen in the posterosuperior margin of the tympanic membrane	Hip, elbow	+				Radical mastoidectomy	Tuberculous granulation tissue		SM	NR
Jeanes et al. (1960) [151]	6 y/M	Aural discharge following an attack of acute otitis media and acute mastoiditis/6 weeks	Purulent discharge in meatus, postaural wound filled with granulation tissue, and discharging pus		+	X-ray: Cloudy mastoids	–		Cortical mastoidectomy	Tuberculous granulation tissue			NR
Jeanes et al. (1960) [151]	2 y/F	Discharge from ear/7 days	Pulsating discharge in meatus, perforated tympanic membrane	Lung	+				Radical mastoidectomy	Fibrosis and tuberculous granulation tissue, tubercles with giant cells		INH, SM	NR

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Jeanes et al. (1960) [151]	16 y/M	Intermittent discharge from ear/12 years	Large attic polyp	Lung	+	X-ray: Partly cellular, the cells opaque			Radical mastoidectomy, removal of polyp and granulations	Mastoid filled with granulations, aural polyp contains tuberculous granulation tissue	+	SM	NR
Jeanes et al. (1960) [151]	12 y/F	Earache, ear discharge/3 weeks	Tympanic membrane reddened and slightly swollen			X-ray: Mastoids to be cellular, with some cloudiness	–		Mastoid exploration	Extensive granulations in the tympanic cavity, infiltration of bone by tuberculous granulation tissue containing large numbers of giant cells of the Langhans-type surrounding necrotic foci		INH, SM	NR
Jeanes et al. (1960) [151]	5 y/M	Discharge from both ears/18 months	Granulations over both tympanic membranes, postaural sinus behind the ear		+	X-ray: Mastoid cells cloudy	–	Positive	Removal of aural granulations	Tuberculous granulation tissue	+	INH, SM	NR
Craig (1962) [152]	2 m/F	Ear discharge/3 weeks Swelling behind ear/1 week	Profuse seropurulent discharge from the ear, tympanic membrane perforation, fluctuating swelling over mastoid, enlarged cervical glands		+		–	Positive	Mastoid operation	Pus in the mastoid, necrotic debris, and tuberculous granulation tissue		Ultraviolet light	Improved
Craig (1962) [152]	3 m/F	Swelling in front of and behind ear/2 weeks	Purulent discharge, granulation tissue in external meatus of both ears, enlarged cervical glands		+		–	Positive	Mastoid operation	Tuberculous granulation tissue, giant cells			Improved
Craig (1962) [152]	3 m/M	Ear discharge, swelling behind ear/6 weeks	Purulent discharge, granulation tissue in the external meatus of both ears, enlarged cervical glands, fluctuating red swelling over the mastoid process	Hilar lymph nodes	+		–	Positive	Mastoidectomy, lymph node evacuation	Tuberculous granulation tissue, giant cells	+	SM	Improved
Craig (1962) [152]	3,5 m/F	Ear discharge/4 weeks Swelling in front of and behind ear and neck/1–2 weeks	Mucopurulent discharge from the ear, granulation tissue protruding external meatus, enlarged cervical glands, fluctuating swelling over the mastoid process		+		–	Positive	Mastoid operation, repeated	Necrotic bone in mastoid process, granulation tissue, mononuclear and giant cells characteristic of tuberculous infiltration	+		Improved
Craig (1962) [152]	5 m/F	Swelling in front of and behind ear and neck, ill-appearing/2 months	Profuse otorrhea, granulation tissue in external meatus, preauricular and cervical glands enlarged, mastoid process edematous	Lung, hilar lymph nodes	+		–	Positive	Mastoid operation, repeated, cervical gland evacuated	Cellular and necrotic mass with giant cells characteristic of tuberculosis	+	SM	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Craig (1962) [152]	7 m/F	Ear discharge/3 weeks Swelling behind ear/1 week	Profuse otorrhea, granulation tissue in external meatus, preauricular and cervical glands enlarged, mastoid process edematous	Lungs, tibia	+		+		Mastoid operation	Necrotic bone in mastoid process, tuberculous granulation tissue	+	SM, PAS	Improved
Craig (1962) [152]	1 y/F	Profuse bilateral ear discharge/2 weeks	Profuse bilateral otorrhea, perforation in ears, preauricular and cervical glands enlarged	Lung, hilar lymph nodes	+		+	Positive	Mastoid operation, cervical gland evacuated	Necrotic mastoid bone, granulation tissue, mononuclear cells, and giant cells indicative of tuberculosis		SM	Improved
Craig (1962) [152]	5 y/F	Ear discharge, fever/8 days	Tenderness over mastoid process, enlarged cervical glands		+		+	Positive	Mastoid operation, repeated, tonsils and adenoids removed	Granulation tissue and bone necrosis, mononuclear cells, and giant cells indicative of tuberculosis		SM	Improved
Harbert et al. (1964) [103]	14 y/M	Chronic, bilateral, scanty purulent aural discharge/8 years	Bilateral double central perforations of the pars tensa, granuloma	Lung	+	X-ray: Bilateral underdevelopment and sclerosis of the mastoids	+	Positive	Radical mastoidectomy	Chronic granulomatous tissue	+	INH, PAS, SM	Improved
Williams (1965) [153]	17 y/M	Chronic suppurative otitis media, deafness/indefinite period	Granulation tissue on the tympanic membrane	Lung	+		+		Radical mastoidectomy, re-operated	Chronic inflammatory infiltration, epithelioid and giant cells, tuberculous granulation tissue	+	INH, PAS, SM	Improved
Fields (1967) [98]	3 m/M	Bilateral ear discharge/1 month	Swollen, tender bilateral external canals filled with white, cheesy material, facial paralysis, granulation tissue in the external canal		+	X-ray: Numerous small irregular densities in the mastoids	+		Radical mastoidectomy	A chronic granulomatous, inflammatory process with caseous necrosis, cold Bezold's abscess	+		Improved
Smoler et al. (1969) [154]	6 y/F	Productive cough, fever otorrhea, tender neck mass/1 month	Purulent otorrhea, palpable masses over the neck, giant polyp obstructing the external canal	Miliary pattern, lung	+	X-ray: Diminished pneumatization of the mastoid			Polyp removal	Chronic inflammatory process	+	INH, PAS, SM	Improved
Smoler et al. (1969) [154]	4 y/F	Otorrhea, facial paralysis, fever/8 months Retroauricular draining mass/4 months	Bilateral purulent ear secretion, retroauricular fistula, facial paralysis, fever, destruction of the tympanic membrane, granulations in the tympanic cavity	Miliary pattern, lung, knee	+				Radical mastoidectomy	Tuberculous granulomata	+		Improved

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Smoler et al. (1969) [154]	16 m/M	Retroauricular draining mass/2 months	Retroauricular foul-smelling draining fistula, temporal abscess, facial paresis	Meninges, lung					Radical mastoidectomy	Osteomyelitis of temporal bone, granulations	+	INH, PAS, SM	Improved
Saltzman et al. (1971) [79]	3 m/M	Ear drainage/3 weeks	Profuse, odorless, watery discharge obscured the tympanic membrane	Miliary pattern, lung	+	X-ray: Erosion of the mastoid	+	Negative		Granulomata	+	INH, PAS, SM	NR
Marlowe (1972) [155]	19 m/F	Recurrent otitis media/15 months	Ear canal containing cheesy and purulent material, central perforation of the tympanic membrane			X-ray: Poor pneumatization	+	Positive	Simple mastoidectomy	Granulation tissue	+	INH	Improved
Wolfowitz (1972) [156]	3 y/M	Proptosis, profuse bilateral otorrhea	Discharging pus from both ears and postauricular fistula			X-ray: Dense mastoids, not pneumatized		Positive	Mastoidectomy	Tuberculous granulomata with caseation		INH, SM	Improved
Wolfowitz (1972) [156]	8 y/M	Otorrhea, facial paralysis/1 month	Granulations in the external auditory meatus, postauricular fistula discharging pus, facial paralysis		+	X-ray: Sclerotic mastoid		Positive	Radical mastoidectomy	Bone and connective tissue infiltrated by lymphocytes, plasma cells, epithelioid cells, giant cells of the Langhans type		INH, PAS, SM	Improved
Wolfowitz (1972) [156]	2 y/M	Otorrhea, pain in the ear/1 week	Acute mastoiditis, a large fluctuant abscess behind the pinna	Lung	+	X-ray: Mastoid opacity and cellular breakdown		Positive	Radical mastoidectomy	Caseous tissue and granulomata containing Langhans cells and epithelioid cells		INH, SM	Improved
Palva et al. (1973) [157]	18 y/M	Facial paralysis, recurrent ear drainage/2 years	Draining ear, facial paralysis		+	X-ray: Cloudiness of mastoid air cells			Cortical mastoidectomy	Granulation tissue, epithelioid and giant cell tubercles	+	INH, PAS, SM	Improved
Palva et al. (1973) [157]	6 m/M	Ear discharge/3 months	Swelling under the mastoid process	Lung	+				Mastoidectomy	Granulation tissue contained bony sequestra and large caseous areas	+	INH, PAS, SM	Improved
Sellars et al. (1973) [158]	6 m/M	Painless otorrhea/2 weeks	Granulations over middle ear mucosa	Lung					Cortical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	2 y/M	Painless otorrhea, facial palsy/3 weeks	Granulations over middle ear mucosa, facial palsy	Lung					Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	2 y/M	Painless otorrhea/8 weeks	Granulations over middle ear mucosa	Lung, meninges					Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	2,5 y/M	Painless otorrhea/8 weeks	Granulations over middle ear mucosa						Polypectomy	Tuberculous granulomatous tissue	+	INH, PAS, SM	Improved
Sellars et al. (1973) [158]	4 y/F	Painless bilateral otorrhea/years	Granulations over the middle ear mucosa of both ear	Lung					Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	5 y/F	Facial palsy	Granulations over middle ear mucosa						Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Sellars et al. (1973) [158]	6y/F	Painless otorrhea/ years	Granulations over middle ear mucosa	Lung					Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	9 y/M	Painless otorrhea/ years	Granulations over middle ear mucosa, postaural fistula						Radical mastoidectomy	Tuberculous granulomatous tissue		INH, PAS, SM	Improved
Sellars et al. (1973) [158]	11 y/F	Painless bilateral otorrhea/years	Granulations over the middle ear mucosa of both ear						Radical mastoidectomy			INH, PAS, SM	Improved
David et al. (1973) [159]	15 y/M	Fever, headache, vomiting, stiffness of the neck, discharge of pus from ear/2 weeks	Thick foul-smelling purulent discharge in the ear, thickened and perforated tympanic membrane, tenderness over the mastoid, facial palsy	Meninges	+	X-ray: Sclerosis of the mastoid		Negative			+	INH, PAS, SM	Died
Emmett et al. (1977) [160]	18 y/F	Chronic, intermittent, purulent otorrhea/5 years	Posterior perforation of the membrane		+	X-ray: Sclerotic mastoid		Positive	Simple mastoidectomy and tympanoplasty, modified radical mastoidectomy, repeated mastoid surgeries	Granulation tissue, cholesteatoma, granulomatous inflammation, and caseation	+	INH, ETM	Improved
Emmett et al. (1977) [160]	16 y/F	Recurrent otorrhea	Necrotic bone in the external auditory canal, granulation tissue	Lung	+	CT: Bony destruction	+	Positive	Simple mastoidectomy and tympanoplasty, repeated mastoid surgeries	Polypoid granulation tissue filling the mastoid bowl and middle ear	+	INH, RIF, ETM	Improved
MacAdam et al. (1977) [121]	5 y/F	Ear pain, pharyngitis, bilateral ear drainage/1 year	Bilateral tympanic membranes perforated, cervical lymphadenopathy	Lung	+	X-ray: Decreased aeration of both mastoids	+	Positive	Tonsillectomy, adenoidectomy	Granulomatous inflammation and caseous necrosis of the tonsils	+	INH, PAS, SM	Improved
MacAdam et al. (1977) [121]	3,5 y/M	Recurrent bilateral otitis media/14 months	Purulent-whitish drainage from both ears and tympanic membrane perforations	Lung	+	X-ray: Chronic mastoiditis	+	Positive			+	INH, PAS	Improved
MacAdam et al. (1977) [121]	3 y/M	Ear drainage, cervical lymphadenopathy/8 months Facial paralysis/2 weeks	Purulent drainage from the ear, facial paralysis	Miliary pattern, lungs	+	X-ray: Sclerosis of mastod	+	Positive	Simple mastoidectomy, facial nerve decompression	Caseous debris and granulomatous material	+	INH, PAS, SM	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Esmer et al. (1979) [161]	5 y/M	Bilateral otorrhea/2 months Swelling and pain behind the ear, fever/10 days	Purulent discharge from both ears, polyp-like structures in the external auditory canal, perforated tympanic membrane	Mediastinal lymph nodes	+	X-ray: Cavity on one side, lessened pneumatization on the other side of the mastoid bone	–		Retroauricular incision and pus drainage, mastoidectomy	Necrotic foci surrounded by giant cells, histiocytes, and lymphocytes in granulation tissue typical for tuberculosis		INH, RIF	Improved
Brutoco et al. (1980) [162]	16 y/M	Intermittently draining thick, green, odorless fluid from the ear canal/11 years	Purulent, greenish, odorless drainage in the external auditory canal, perforation of the tympanic membrane, exuberant "popcorn-like" tissue	Lung	+	X-ray: Sclerosis of the mastoid CT: An absence of distinct middle ear structures	+	Positive			+	INH, RIF, ETM	Improved
Brutoco et al. (1980) [162]	6 y/F	Draining ear	Green, odorless fluid draining from the ear, perforation of the tympanic membrane	Lung, bone	+		+	Positive			+	INH, RIF	Improved
Glover et al. (1981) [163]	14 m/M	Painless discharge/2 months	Large central perforation of tympanic membrane			X-ray: Bony lesions in mastoid air cells	+	Positive			+	Anti-TB therapy	Improved
Glover et al. (1981) [163]	13 y/F	Painless discharge/2 years	Otalgia, attic perforation, facial paralysis		+		+		Modified radical mastoidectomy	Pale granulations	+	Anti-TB therapy	Improved
Mugiyo et al. (1981) [164]	2 y/M	Chronic, painless auricular drainage	Perforated otitis media, abscess cf. the mastoid, sequester	Lung, pleura, mediastinal lymph nodes			–	Positive	Mastoid surgery	Tubercle formation with Langhans giant cells and some caseation		INH, PAS, SM	Improved
Mumtaz et al. (1983) [165]	8 y/M	Intermittent otorrhea/3 months	Perforated tympanic membrane, granulation tissue in the ear canal, facial palsy Ventilation tube				+	Positive	Simple mastoidectomy	Granulation tissue containing multinucleated giant cells	+	Anti-TB therapy	Improved
Hawkins et al. (1983) [166]	18 m/NR	Otalgia, postauricular swelling, erythema, tenderness, fever/days–weeks	Mastoiditis with subperiosteal abscess			X-ray: Clouding of the mastoid air cells			Mastoidectomy	Pus and granulations overlying the mastoid cavity	+	INH, RIF, ETM	NR
Hawkins et al. (1983) [166]	4 y/NR	Otalgia, postauricular swelling, erythema, tenderness, fever/days–weeks	Mastoiditis with subperiosteal abscess			X-ray: Clouding of the mastoid air cells			Radical mastoidectomy	Pus and granulations overlying the mastoid cavity	+	INH, RIF, ETM	NR
Reddy et al. (1984) [167]	18 m/M	Postaural swelling/1 week	Fluctuant and non-tender swelling causing displacement of the pinna, dull-looking tympanic membrane			X-ray: A cavity in the mastoid			Incision and drainage of mastoid abscess	Tuberculous granulation tissue		Anti-TB therapy	Improved
Ramages et al. (1985) [168]	1 y/M	Suppurative otitis media with persistent otorrhea	Persistent granulations	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy	Suggestive of tuberculosis		Anti-TB therapy	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Ramages et al. (1985) [168]	2 y/F	Suppurative bilateral otitis media with persistent otorrhea	Postauricular fistula, granulations in both ears	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Modified radical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	7 y/M	Suppurative otitis media with persistent otorrhea	Sequestra, granulations, facial palsy, sequestra	Lung	+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy	Suggestive of tuberculosis		Anti-TB therapy	Improved
Ramages et al. (1985) [168]	11 y/F	Suppurative otitis media with persistent otorrhea	Pale granulations		+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Biopsy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	4 y/F	Suppurative otitis media with persistent otorrhea	Postauricular abscess in one ear, glue ear in the other			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy, myringotomy, and tube	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	2,5 y/F	Suppurative otitis media with persistent otorrhea, cervical adenopathy	Granulations			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cervical lymph node biopsy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	8 y/M	Suppurative otitis media with persistent otorrhea	Postauricular fistula, polyp		+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	1 y/M	Suppurative otitis media with persistent otorrhea	Polyp, granulations in both ears			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy, biopsy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	12 y/M	Suppurative otitis media with persistent otorrhea	Granulations		+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	2 y/M	Suppurative otitis media with persistent otorrhea	Facial palsy			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	6 y/M	Suppurative otitis media with persistent otorrhea	Postauricular abscess			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy		+	Anti-TB therapy	Improved

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Ramages et al. (1985) [168]	5 m/F	Suppurative otitis media with persistent otorrhea	Postauricular abscess	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	12 y/M	Suppurative otitis media with persistent otorrhea	Postauricular abscess, granulations	Lung	+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	3 y/M	Suppurative otitis media with persistent otorrhea	Facial palsy, granulations	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy	Suggestive of tuberculosis		Anti-TB therapy	Improved
Ramages et al. (1985) [168]	2 y/M	Suppurative otitis media with persistent otorrhea	Granulations in both ears			X-ray: Well-developed mastoid air cell system with a cloudy appearance			Biopsy	Suggestive of tuberculosis		Anti-TB therapy	Improved
Ramages et al. (1985) [168]	8 y/F	Suppurative otitis media with persistent otorrhea	Granulations		+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Biopsy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	2 y/F	Suppurative otitis media with persistent otorrhea	Facial palsy, granulations, aural polyp	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	3 y/M	Suppurative otitis media with persistent otorrhea	Postauricular abscess	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	8 m/F	Suppurative otitis media with persistent otorrhea	Facial palsy, granulations, perforation in both ears	Lung	+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Radical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	14 m/F	Suppurative otitis media with persistent otorrhea	Postauricular fistula	Lung		X-ray: Well-developed mastoid air cell system with a cloudy appearance			Cortical mastoidectomy		+	Anti-TB therapy	Improved
Ramages et al. (1985) [168]	8 y/F	Suppurative otitis media with persistent otorrhea	Postauricular fistula		+	X-ray: Well-developed mastoid air cell system with a cloudy appearance			Biopsy	Suggestive of tuberculosis	+	Anti-TB therapy	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Yaniv, et al. (1986) [110]	24 case series 9 m-18 y (mean age 8 y)/15 M, 9 F	Otorrhea in all cases/1 week to 13 years	The proliferation of granulation tissue in all cases Acute mastoiditis in 6 cases Central perforations of the tympanic membrane in 9 cases Total perforations in 13 cases Atelectatic tympanic membranes in 3 cases Polyp in 4 cases Eroded malleus in 7 cases Bone sequestra in 2 cases Facial paralysis in 1 case	Lung and neck in 2 cases Lung in 11 cases Lung and eye (keratitis) in 1 case	+ in all cases	X-ray: Sclerotic mastoids in 18 ears; bone destruction in 8 ears; poorly pneumatized mastoids with clouding of the cells in 6 ears	+ in 4 cases	Positive in all cases	Mastoidectomy in 12 cases Cortical mastoidectomy in 5 cases Modified or radical mastoidectomy in 7 cases Middle ear biopsy in 8 cases	Typical tubercle with central caseation, epitheloid cells, and Langhans giant cells in all cases Cholesteatoma in 4 cases	+ in 3 cases	INH, RIF, PZA, ETM in all cases	All cases improved
Massachusetts General Hospital (1987) [169]	7 y/M	Drainage from ear/7 days Postauricular swelling, fever/2 days	Swelling of external ear canal obscuring tympanic membrane; auricle bulging away from the head, pus in the ear canal	Lung	+	X-ray: Diffuse increase in density of mastoid CT: Diffuse increase in density in the middle ear cavity and mastoid bone	–	Negative	Cortical mastoidectomy, tympanotomy	Granulomatous inflammation with necrosis and ulceration, epithelioid cells, Langhans-type giant cells	+ (INH- and ETM-resistant TB)	RIF, PZA, SM	Improved
Davidson et al. (1989) [170]	8 y/M	Recurrent purulent bilateral otitis media/2 months	Ear discharge, enlarged fluctuating cervical lymph node, fever Bilateral ventilation tubes		+		–	Positive	Radical mastoidectomy	Granulomatous process typical of tuberculosis	+	INH, PAS, RIF	Improved
Marion et al. (1989) [171]	22 m/F	Cough, spontaneous serous drainage from the ear, fever/3 months	Serous otitis media, tympanic membrane perforation, a pale middle ear polypoid mass	Miliary pattern, meninges, lungs, liver, spleen, bone marrow, kidneys				Positive		Postmortem: Tuberculous granulomas demonstrating early caseation and associated multinucleated giant cells			Died
Naranbhai et al. (1989) [172]	68 d (born at 27 weeks, gestation)/M	Whitish seropurulent discharge of the ear, preauricular and cervical lymphadenopathy/12 days	Granuloma in the auditory canal	Placenta (congenital tuberculosis)			+			Placenta: Infarcted villi, hemorrhage and fibrin deposits, caseous necrosis Granuloma from ear canal: Epitheloid granuloma	+	INH, RIF, PZA, ETM	Improved
Naranbhai et al. (1989) [172]	5 w (born at 36 weeks, gestation)	Ear discharge/4 days	Friable granulation tissue and thin pus filling the auditory canal, firm, non-tender, left-sided periauricular lymphadenopathy	Miliary tuberculosis of the mother (congenital tuberculosis)			+	Negative		Granulation tissue from the ear	+	INH, RIF, PZA, ETM	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Grewal et al. (1991) [173]	8 y/M	Acute respiratory distress along with stiffness of the neck, high fever, and dysphagia	Marked swelling of the floor of the mouth, tongue, and lateral pharyngeal wall, and torticollis (Para pharyngeal abscess)						Tympanomastoidectomy, emergency tracheostomy	Granulations from the mastoid showing features of tuberculosis		Anti-TB therapy	Improved
Singh (1991) [81]	2 y/F	Otorrhea/2 weeks Facial palsy/3 months	Otorrhea, granulation tissue in the external ear canal, ipsilateral facial palsy, submandibular and cervical lymphadenopathy	Lung			+		Biopsy	Caseating granuloma in the external ear canal	+	INH, RIF, PZA, ETM	Improved
Singh (1991) [81]	7 y/M	Bilateral otorrhea, facial palsy, neck swelling, and unsteady gait	Bilateral axillary and cervical lymphadenopathy, hepatosplenomegaly with ascites, bilateral otitis media, facial palsy, hemiparesis	Lung, brain					Biopsy	Caseating granulation tissue of the external ear canal	+	INH, RIF, PZA, ETM	Improved
Singh (1991) [81]	14 y/M	Cough/3 months	Bilateral otitis media with multiple perforations	Lungs, kidneys			+		Biopsy	Tuberculoid granuloma with multinucleated giant cells	+	INH, RIF, PZA, ETM	Improved
Singh (1991) [81]	6 y/M	Postauricular subperiosteal abscess and otorrhoea/10 weeks	Profuse otorrhea, granulation tissue in the external ear canal						Mastoid surgery	Sequestrated bone and tuberculous granulation tissue	+	INH, RIF, PZA, ETM	Improved
Ozcelik et al. (1995) [109]	7 y/M	Recurrent purulent otitis media/3 years	2 central tympanic membrane perforations, painless, odorless purulent discharge, Mastoid red, inflamed, and tender on palpation		+			Positive	Radical mastoidectomy	Granulomatous process typical of tuberculosis	+ (*Mycobacterium bovis*)	INH, RIF	Improved
Grewal et al. (1995) [174]	10 y/M	Recurrent discharge from ear, pain, fever/6 years Hearing loss, facial palsy/2 years	Yellowish, profuse, unremitting, foul-smelling, occasionally blood-tinged ear discharge, facial paralysis, swelling in the temporoparietal region, sinus on the mastoid bone		+	CT: A hypodense round, soft tissue mass in the temporal bone with generalized expansion and occlusion of the external auditory canal, peripheral enhancement of this lesion with multiple septae			Aural polypectomy, tympanomastoidectomy	Tubercles made up of caseous necrosis, epitheloid cells, Langhans giant cells, lymphocytes, and fibroblasts		INH, RIF, ETM	Improved
Robertson et al. (1995) [175]	19 m/M	Discharge from the ear, painless postauricular swelling/1 month	White discharge in the external canal, tympanic membrane not visualized, nonfluctuant 2 cm mass over the mastoid process	Lung, bone		CT: A solid soft tissue mass overlying the mastoid process, destruction of the bony trabeculae		Positive	Simple mastoidectomy	Caseating granuloma	+	INH, RIF, PZA	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Ng et al. (1995) [176]	10 w (born at 28 weeks, gestation)/M	Yellow seropurulent discharge from the ear, cervical lymphadenopathy/1 week	Otitis media with tympanic membrane perforation		+		+		Fine needle aspiration biopsy		+	INH, RIF, PZA, ETM	Improved
Zahraa et al. (1996) [177]	4 y/M	Acute ear drainage Knee pain, limping and persistent fever/>1 month	Perforated tympanic membrane, otitis media, and mastoiditis	Femur, knee	+	CT: Marked bony destruction of the mastoid with complete opacification and extensive involvement of the middle ear and external auditory canal	–	Positive	Mastoidectomy	Caseating granulomas filling the mastoid cavity and middle ear	+	INH, RIF, PZA, ETM	Improved
Zahraa et al. (1996) [177]	11 m/M	Irritability, swelling of the knee, ear drainage/1 week	Fever, perforation of the anterior tympanic membrane with draining fluid	Knee, gastrocnemius muscle abscess			+	Positive	Ear drainage sampling		+	INH, RIF, PZA	Improved
Farrugia et al. (1997) [178]	17 y/F	Earache/2 days	Perforation in the tympanic membrane, facial paralysis Ventilation tube	Lung	+		+		Tympanotomy and cortical mastoidectomy	Necrotic inflammatory tissue with histiocytic cells focally palisaded	+	Anti-TB therapy	Improved
Barlas et al. (1997) [179]	4 m/M	Neck masses and fever/20 days Ear draining/3 days	Draining tympanic membrane, preauricular and postauricular masses, polypoid mass in ear				–	Positive	Biopsy, simple mastoidectomy, lymphadenopathy excision	Caseous granulomatous tissue, Langhans giant cells		INH, RIF	Improved
Bitsori et al. (1999) [180]	4 y/F	Fever, ear discharge/2 weeks Multiple episodes of otitis media with ear discharge/since infancy	Swelling of the mastoid area and associated lymphadenitis			CT: Inflammatory swelling of the middle ear and the mastoid air cells		Positive	Excision of a polyp-like structure from the middle ear	Granulomatous tissue, with necrosis and Langhans giant cells		INH, RIF	Improved
Pulec et al. (1999) [181]	5 y/F	Purulent otorrhea	Total perforation of the pars tensa, thick pus covering middle ear structures						Tympanoplasty and mastoidectomy		+	Anti-TB therapy	NR
Pavlopoulou et al. (2000) [182]	6 y/M	Painless otorrhea/18 months	Perforation and thickening of the tympanic membrane, the outer ear canal full of white caseous material and granulation tissue	Hip	+	CT: Clouding of mastoid air cells and destruction of the bone structure	+	Positive	Mastoidectomy	Granulation tissue	+ (MDR-TB)	Ofloxacin, PZA, and EMB, ethionamide, cycloserine (MDR-TB treatment)	Improved
Pavlopoulou et al. (2000) [182]	4,5 y/F	Chronic ear otorrhoea and mastoid tenderness/10 months	Ear drainage and mastoid tenderness		+	X-ray: Partial opacification of the mastoid air cells		Positive	Mastoidectomy	Exuberant granulation tissue, granulomatous inflammation with caseous necrosis	+ (INH-resistant TB)	RIF, PZA, ETM, cycloserine (INH-resistant TB)	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Saunders et al. (2002) [183]	7 y/F	Recurrent ear infections, an intermittently discharging ear, a worsening bilateral conductive hearing loss/4 years	Grossly retracted anterior segments of both tympanic membranes with adherent perforations Ventilation tube	Lung	+	CT: Petro-mastoid air cells and middle ear clefts filled with soft tissue and a defect in the external canal	+		Cortical mastoidectomy	Granulation tissue and granulomas, including epithelioid cells and Langhans-type giant cells	+	INH, RIF, PZA	Improved
Pejham et al. (2002) [184]	9 w (born at 33 weeks, gestation)/F	Ear drainage, eyelid weakness, drooling, and poor feedings/6 weeks Facial drooping and enlarged lymph nodes around the ears and neck/2 weeks	Erythematous and perforated both tympanic membranes with purulent otorrhea, bilateral cervical lymphadenopathy, dysphagia, decreased gag reflex, hepatomegaly, facial nerve palsy	Lungs, brain, cervical lymph nodes, the endometrium of the mother (congenital tuberculosis)		CT: Osteomyelitis of the petromastoid region of the temporal bone, cervical lymph node calcification, inflammatory changes of the facial nerve canal	+	Positive	Biopsy	Caseating granulomas in the ear canal, mastoid bone, and cervical lymph node, necrotizing granulomatous endometritis of the mother	+	INH, RIF, PZA	Improved
Joshi et al. (2002) [185]	14 m/F	Painless otorrhoea/2–3 months Facial palsy	Bulging of the tympanic membrane with granulation tissue			CT: Abnormal soft tissue in mastoid air cells, external and middle ear with nonvisualization of normal ossicular chain and erosion of the lateral wall of the mastoid bone, sigmoid plate erosion, and cochlear deformity			Histopathological sample scraped	Tuberculous granulation tissue		NR	NR
Mongkolrattanothai et al. (2003) [186]	3 y/F	Chronic bilateral ear drainage/2 months Asymmetric smile, unsteady when walking/2 weeks	Profuse white granulation tissue in both external auditory canals obscured the tympanic membranes Facial palsy and ataxic gait Brain tuberculous abscesses	Lungs, brain	+	CT: Bilateral soft tissue density, a sizeable destructive process within the temporal bone, destruction of the tegmen tympani, partial destruction and distortion of the ossicles, and destruction of the temporal bone	–	Positive	Radical mastoidectomy, external ventricular drainage surgery, and a ventriculoperitoneal shunt	Diffuse polypoid granulation tissue in both external auditory canals extending to the middle ears suggestive of bilateral cholesteatoma; fibrinocellular inflammatory debris	+	INH, RIF, PZA, SM, ETM	Improved
Vaamonde et al. (2004) [122]	4 y/M	Refractory otorrhea/10 months	Perforation of the tympanic membrane		+		+	Positive	Mastoid surgery	Granulomas with caseation necrosis, epithelioid cells, and Langhans giant cells	+	INH, RIF, PZA	Improved
Pitcher et al. (2004) [187]	3 y/M	Bilateral suppurative discharge from both ears/2 months Bilateral discharging neck sinuses/8 months	Bilateral suppurative otitis media and suppurative submandibular lymphadenitis, facial palsies		+	CT: Extensive destruction of the mastoid bone and ossicular chain bilaterally			Incision and drainage of cervical lymphadenitis		+	NR	NR

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Sethi et al. (2005) [129]	11 y/F	Ear discharge, hearing loss/2 months Diplopia, headache/1 month	A scant, mucopurulent, odorless discharge in the external auditory canal, lateral rectus palsy		+	X-ray: Sclerosis of bilateral mastoid air cells			Drainage of the petrous apex abscess	A caseating granulomatous lesion suggestive of tuberculosis	+	INH, RIF, PZA, ETM	Improved
Meher et al. (2006) [188]	4 y/M	Ear discharge/6 months Swelling behind the ear/1 month	Central perforation with pale granulations, sagging of external auditory canal, and postaural scar and granulations			X-ray: Mastoid sclerosis	–		Modified radical mastoidectomy	The cortex of the mastoid bone eroded, the malleus and incus necrosed, and the antrum full of granulations, suggesting tubercular otitis media		Anti-TB therapy	Improved
Meher et al. (2006) [188]	10 y/F	Ear discharge and hearing loss/4 years Swelling behind the ear/2 weeks	Postaural fistula, significant central perforation, and polypoidal mass in the middle ear		+	X-ray: Lytic lesion of mastoid	–		Modified radical mastoidectomy	Mastoid antrum full of tubercular granulation		Anti-TB therapy	Improved
Meher et al. (2006) [188]	13 y/M	Ear discharge, decreased hearing, swelling, and discharge from multiple sinuses next to the ear	Watery thin, colorless, and odorless discharge		+		–		Cortical mastoidectomy, fistula excision	Tubercular granulations		Anti-TB therapy	Improved
Meher et al. (2006) [188]	5 y/M	Ear discharge and pain	Granulation in the ear canal and foul-smelling discharge				–		Modified radical mastoidectomy	Cholesteatoma in the antrum, along with tubercular granulation		Anti-TB therapy	Improved
Meher et al. (2006) [188]	3 y/F	Ear discharge and facial nerve palsy	Pale granulations in the middle ear and antrum				–		Mastoidectomy with facial nerve exploration	Tubercular granulation		Anti-TB therapy	Improved
Nicolau et al. (2006) [189]	8 m/F	Coughing, fever, dyspnea/several days	Both ears infected Meningeal irritability signs, comatose	Miliary pattern, lungs, meninges			+			Postmortem: Tuberculous granulomas in both middle ear and mastoid, consisting of lymphocytes, epithelioid cells, and Langhans multinucleated giant cells, with areas of caseous necrosis	+	INH, RIF, SM	Died

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Halvorse et al. (2006) [190]	22 m/M	Bilateral persistent/recurrent suppurative otitis media/16 months Previous tympanostomy tube insertion/11 months	Cloudy fluid in both ear canals and perforations in both grayish-looking tympanic membranes	Mediastinal lymph nodes, spleen	+	CT: Complete opacification of the middle ear cavities and mastoid air cells	–	Negative	Suction debridement of ear drainage		+	INH, RIF, PZA	Improved
Kim et al. (2007) [191]	8 y/M	Painless otorrhea/3 months Previous tympanostomy tube insertion in both ears/6 months	Perforation in the tympanic membrane with pulsatile discharge, edematous middle ear mucosa		+	CT: Soft tissue density in the mastoid and middle ear space	+		Tympanotomy and cortical mastoidectomy	Polypoid middle ear mucosa, caseating granulomas with epitheloid cells and Langhans giant cells in the mastoid and middle ear		INH, RIF, PZA, ETM	Improved
Sens et al. (2008) [192]	10 y/M	Bilateral otorrhea/4 months	Abundant purulent secretion and granulation in both ear canals, enlarged lymph nodes of neck chain	Miliary pattern, lungs	+	CT: Soft tissue density material within the middle ear and mucosal thickening in the maxillary sinuses	+	Negative	Biopsy	Granulation tissue in the ear canal, chronic inflammation that suggested tuberculosis		INH, RIF, PZA	Improved
Vitali (2008) [193]	10 y/M	A progressively enlarging occipital swelling/3 months Painless, chronic discharge from the ear	A large, soft mass in the occipital area, the lesion covered with skin, and suppurative ulcerations present at the top and around the base	Calvarium bone		CT and MRI: Occipital encephalocele with mastoiditis, extradural granulations, bone destruction, occlusion of the sigmoid sinus			Excision of acquired encephalocele, mastoidectomy	Necrotizing granulomatous inflammation, epithelioid histiocyte aggregates with surrounding lymphocytes and Langhans-type giant cells	+	INH, RIF, PZA, ETM	Improved
Chmielik et al. (2008) [194]	4 y/M	Chronic middle ear inflammation, fever/2 months	Swollen, reddened, and thickened tympanic membrane, signs of tuberosities appearing, granulation		+	CT: Complete airlessness of the mastoid cells, bone destruction		Negative	Paracentesis, antromastoidectomy	Caseous substance from ear drainage	+	INH, RIF, PZA	Improved
Verma et al. (2009) [195]	7 y/M	Ear discharge, fever, submandibular lymph nodes/3 months	Purulent discharge, a fluctuant, tender abscess in the postauricular area, otitis media with mastoiditis with osteomyelitis, and an abscess involving the petrous apex				+	Positive	Modified radical mastoidectomy	Lymph node: Epithelioid granulomas and Langhans giant cells, lymphocytes, histiocytes, and necrosis suggestive of tuberculous etiology		INH, RIF, PZA	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Munoz et al. (2009) [196]	3 y/M	Bilateral retroauricular tumefaction/3 months Bilateral ear pain and fever/2 days	Tympanic perforation and thick purulent discharge, displacement of pinna			CT: Filling of bilateral tympanic and mastoid cavities by soft tissue material, osteitis, periauricular collections, neck adenopathies MRI: Extensive soft tissue material filling both bilateral temporal and mastoid bones sparing the inner ears		Negative	Surgical draining of the ear	Non-necrotizing granuloma	+	INH, RIF, PZA, ETM	Improved
Arya t al. (2009) [197]	14 y/F	Painless ear discharge/4 months Decreased hearing, swelling behind ear/2 months	Multiple tympanic membrane perforation, postauricular abscess		+	X-ray: Bilateral absence of mastoid cells	–	Positive	Local dressing of abscess	Caseous necrotic background and lymphocytes, multinucleated giant cells, clusters of epithelioid cells	+	Anti-TB therapy	Improved
Tang et al. (2010) [198]	5 y/M	Decreased hearing, otalgia, and multiple bilateral neck swellings/4 months	Multiple, bilateral cervical lymphadenitis, a thin, watery, clear discharge with swelling of the external ear canal, central perforation of the tympanic membrane			X-ray: Sclerotic mastoid antrum			Cortical mastoidectomy	Tuberculous lymphadenitis, granulations containing tuberculosis infection		Anti-TB therapy	Improved
Park et al. (2010) [199]	40 d/M	Neck swelling, fever, ear discharge/several days	External ear canal granulation, purulent otorrhea, neck swelling, facial palsy	Miliary pattern, lung	+	CT: A soft tissue density in the middle ear and mastoid cavity, multiple necrotic lymph nodes at the neck	+		Removal of granulation tissue from the external canal	Necrotic granulation tissue with inflammatory cells	+	INH, RIF, PZA, SM	Improved
Bal et al. (2012) [200]	11 y/M	Ear discharge and otalgia/2 months	Swelling in the mastoid area	Sigmoid sinus thrombosis		MRI: Inflammatory swelling in the middle ear and the mastoid air cells MRI venography: Thrombosis in the left sigmoid and jugular vein	+	Positive	Mastoid surgery	Granulomatous tissue with necrosis and Langhans giant cells	+	INH, RIF, PZA	Improved
Oberdorfer et al. (2012) [201]	14 y/F	Chronic otitis media/2 years High fever, headache, alteration of consciousness, and a generalized seizure/10 days	Febrile, papilledema, signs of cerebellar dysfunction, yellow discharge from the ear canal			CT: Otomastoiditis with early brain abscess of the cerebellum	–		Radical mastoidectomy and aspiration of the cerebellar abscess	Pus from brain abscess	+	INH, RIF, PZA, ETM	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Manigandan et al. (2013) [202]	5 y/M	Recurrent fever, painless and clear discharge from both ears/3 months Pus discharge from ear with pain and impaired hearing/1 week	Febrile, toxic, submandibular, cervical, and axillary lymph nodes significantly enlarged bilaterally Multiple healed perforations in both tympanic membranes with granulation tissue, furuncle, and pus discharge from one ear	Miliary pattern	+		–	Negative	A fine needle aspiration cytology of the cervical node	Caseating granulomas suggestive of tuberculosis		Anti-TB therapy	Improved
Chakravarti et al. (2014) [203]	5 m/M	Postaural swelling/15 days	Subperiosteal abscess over the mastoid			CT: Destructive process involving the mastoid region, a large soft tissue swelling over the mastoid	–	Positive	Incision and drainage of mastoid abscess, cortical mastoidectomy	Pale granulation tissue, caseating granuloma composed of neutrophils, macrophages, epithelioid cells, Langhans cells	+	Anti-TB therapy	Improved
Chakravarti et al. (2014) [203]	18 m/M	Ear discharge/2 months Facial palsy/2 days	Perforation in the ear, facial palsy			CT: A large cavity with the destruction of bone and erosion of ossicles	+	Positive	Mastoidectomy with facial nerve decompression	Pale granulation tissue suggestive of tuberculosis		Anti-TB therapy	Improved
Chakravarti et al. (2014) [203]	6 m/M	Ear discharge, facial palsy/5 weeks	Perforation in the ear, facial palsy			CT: A large osteolytic lesion involving the mastoid	+	Positive	Mastoidectomy with facial nerve decompression	Pale granulation tissue	+	Anti-TB therapy	Improved
Rajesh Gandham et al. (2014) [204]	6 y/F	Recurrent otorrhea/6 months Painless, purulent ear discharge/10 days Fever, cough/3–5 days	Thick purulent pus in the external auditory canal, perforated tympanic membrane, palpable submandibular and supraclavicular lymph nodes,			X-ray: Insignificant mastoid region	–	Negative	Sampling of ear discharge	Granulation tissue on tympanic membrane	+	Anti-TB therapy	Improved
Diplan Rubio et al. (2015) [9]	18 y/M	Otorrhea, otalgia, hearing loss/1 month	Total perforation, lymphadenopathy, involvement of cranial nerves II, III, V, VII. VIII, IX, X, meningeal signs	Meninges	+				Cortical mastoidectomy	Granulation tissue	+	Anti-TB therapy	NR
Scorpecci et al. (2015) [205]	4 y/M	Recurrent, painless, purulent otorrhea/2 years	Perforation of the tympanic membrane, granulomatous and whitish epitympanic material		+	CT: Soft tissue-like material occupying the mastoid cells and the tympanic cavity, eroding the ossicles	+	Positive	Tympanomastoidectomy, tympanic membrane reconstruction	Granulomatous, non-necrotizing tissue	+	INH, RIF, PZA, boric acid	Improved
Scorpecci et al. (2015) [205]	5 y/F	Recurrent otorrhea/2 years	Perforation of the tympanic membrane, cholesteatoma	Lung, mediastinal lymph nodes	+	CT: Complete obliteration of the mastoid cavity and middle ear by soft tissue-like material, erosion of the mastoid cortical bone			Tympanomastoidectomy	Granulation tissue	+ (MDR-TB)	INH, RIF, SM Linezolid, moxifloxacin	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Petrucci et al. (2015) [206]	11 y/F	Bilateral chronic otitis media and hearing loss/1 year	A diffuse tympanic granulomatosis		+		+	Positive	Auricular secretion collection	Granulomas in the ear canal	+	INH, RIF, PZA, ETM, levofloxacin	Improved
Maniu et al. (2016) [207]	5 y/F	Painless otorrhoea/2 months Facial palsy/1 week	Bulging of the tympanic membrane with granulation tissue			CT: Entire tympanum and mastoid air cells occupied by soft tissue, bone destruction, and sequestra			Cortical mastoidectomy	Granulation tissue with epithelioid cells and multinucleated giant cells, areas of central necrosis, lymphocytic infiltration, ulcerations, and superficial resorption of the involved bone (granulomatous type tuberculous mastoiditis)		Anti-TB therapy	NR
Aldana-Aguirre et al. (2018) [89]	8 w (born at 25 weeks' gestation)/F	Otorrhea	Necrotizing otitis media, facial nerve paralysis, osteomyelitis from the temporal bone, cervical lymphadenitis	Cervical lymph nodes, the endometrium of the mother (congenital tuberculosis)	+	CT: Occlusion of the external auditory canal and opacification of the middle ear with temporal bone erosion	+		Surgical decompression, debridement, and cortical mastoidectomy	Endometrium biopsy of mother positive for tubercle bacilli	+	INH, RIF, PZA	Improved
Eswaran et al. (2019) [208]	15 y/F	Painless, persistent discharge, hearing loss/6 months Swelling in infraauricular region/1 month	Posterosuperior canal wall sagging with discharge, granulation over tympanic membrane		+	CT: Soft tissue opacification in the middle ear cavity and mastoid antrum with the breach in the mastoid tip, erosion in the posterior bony canal wall, hypodense collection deep to the superior part of the sternocleidomastoid (Bezold's abscess)			Modified radical mastoidectomy, Bezold's abscess drainage	Extensive granulation tissue filling the mastoid and middle ear, multinucleated giant cells with chronic granulomatous inflammation	+	INH, RIF, PZA, ETM	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Jayakody et al. (2019) [209]	2 y/M	Otalgia/6 weeks Posterior auricular swelling and sudden deterioration with drowsiness and lethargy	Middle ear effusion, temporo-auricular swelling	Brain		CT: Mastoiditis, a subperiosteal abscess, and an extradural abscess with extensive bony defects	+		Mastoid exploration and drainage of the extradural and peri-sigmoid sinus collection	Parietal subperiosteal abscess with bony defects and granulation tissue connecting with an extradural abscess; granulomatous osteomyelitis due to necrotizing granulomatous inflammation	+	INH, RIF, PZA, ETM	Improved
Sebastian et al. (2020) [115]	17 y/M	Ear discharge, decreased hearing, tinnitus/>2 months	Postaural fistula leading to mastoid cavity, granulations and bone destruction, sequestra formation		+	CT: Soft tissue density in the middle ear cleft, erosion of ossicles, and mastoid cortex			Granulation tissue removal from the middle ear and mastoid	Granulations with abscess formation	+	INH, RIF, PZA, ETM	Improved
Sebastian et al. (2020) [115]	11 y/F	Recurrent discharge from both ears/>2 months	Perforation of tympanic membrane		+	CT: Soft tissue density in the middle ear cleft			Granulation tissue removal from the middle ear and mastoid	Epitheloid granuloma with focal necrosis	+	INH, RIF, PZA, ETM	Improved
Sebastian et al. (2020) [210]	4 y/F	Recurrent ear discharge/3 years Postaural swelling, discharging fistula/2 weeks	Perforation with whitish flakes			CT: Soft tissue density in the middle ear cavity, erosion of the mastoid bone			Modified radical mastoidectomy	Cholesteatoma with thick, foul-smelling pus, necrosis of the ossicles, granulomatous inflammation	+	INH, RIF, PZA, ETM	Improved
Sebastian et al. (2020) [210]	12 y/F	Recurrent episodes of foul-smelling bilateral ear discharge/early childhood Recurrent fever/1 year	Perforation with pulsatile discharge in both ears		+	CT: Erosion of mastoid bone filled with soft tissue			Mastoid exploration	Tuberculous granulomas with necrosis		Anti-TB therapy	NR
Sebastian et al. (2020) [210]	13 y/M	Ear discharge/early childhood Headache, drowsiness, fever/3 days	Neck rigidity, mucopurulent discharge in the external canal with perforation of the tympanic membrane		+	CT: Soft tissue density in the epitympanum and mastoid cells, erosion of ossicles, bone destruction			Mastoid exploration	Cholesteatoma and tuberculous granulomas	+	INH, RIF, PZA, ETM	Improved
Sebastian et al. (2020) [210]	11 y/F	Bilateral ear discharge, decreased hearing/1 year	Purulent ear discharge with retraction, congested edematous tympanic membrane		+	CT: Soft tissue filling the middle ear and mastoid cells on both sides			Mastoid exploration	Granulation tissue containing epithelioid granulomata with focal necrosis		Anti-TB therapy	Improved
Mehta et al. (2020) [97]	17 y/F	Bilateral ear discharge, hearing loss/1 year	Perforation of the tympanic membrane with granulations, mucoid and mucopurulent discharge from both ears		+	CT: Soft tissues in middle ears, mastoid air cells extend into the external auditory canal			Mastoidectomy with tympanoplasty	Necrotizing granulomatous inflammation consistent with tuberculosis	+	INH, RIF, ETM	Improved

(continued)

Table 37.2 (continued)

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Aziz et al. (2020) [211]	17 y/M	Otalgia, ear discharge, reduced hearing, nocturnal fever/2 weeks	A non-foul-smelling, yellowish discharge and postauricular swelling of the ear, the tympanic membrane not visualized		+	CT: Soft tissue density mass and bony erosions in the temporal bone	–		Incision and drainage, modified radical mastoidectomy	Tuberculous granuloma		INH, RIF, PZA, ETM	Improved
McMaster et al. (2020) [212]	2 m/NR	Ear discharge/4 days Facial asymmetry and fever/1 day	Facial nerve palsy, cervical and preauricular lymph nodes palpable	Lungs, mediastinal lymph nodes		CT: Mastoiditis with bony destruction	+		Biopsy	Necrotizing granulomatous inflammation	+	INH, RIF, PZA, ETM	Improved
Rauniyar et al. (2021) [213]	12 y/M	Chronic ear discharge and hearing loss Intermittent, foul-smelling, occasionally blood-stained ear discharge/3 years	A fleshy polyp, thick yellowish discharge		+	CT: Soft tissue opacity in the middle ear and mastoid, ossicular erosions, and destructions			Modified radical mastoidectomy	A bony mastoid cyst filled with turbid fluid; epithelioid cell granulomas, Langerhans type giant cell, chronic inflammatory cells, and granulation tissue		INH, RIF, PZA, ETM	Improved
Din et al. (2022) [214]	20 m/F	Otalgia, otorrhea/14 days	Purulent otorrhea, anterior displacement of the pinna with postauricular swelling, postauricular cellulitis		+	CT: Postauricular abscess, denuded ossicles, petromastoid opacification, bony erosion	–		Mastoid surgery	Pale granulation tissue, bony erosion, necrotizing granulomatous inflammation	+	Anti-TB therapy	Improved
Din et al. (2022) [214]	4 y/F	Otalgia, otorrhea, cough, fever, and night sweats/3 days	Purulent otorrhea, anterior displacement of the pinna with postauricular swelling	Miliary pattern, intra-abdominal organs, intracranial extension		CT: Postauricular abscess, denuded ossicles, petromastoid opacification, bony erosion, intracranial involvement	+		Mastoid surgery	Pale granulation tissue, bony erosion, necrotizing granulomatous inflammation	+	Anti-TB therapy	Improved
Din et al. (2022) [214]	1 y/F	Otalgia, otorrhea/7 days	Purulent otorrhea, anterior displacement of the pinna with postauricular swelling		+	CT: Postauricular abscess, petromastoid opacification, bony erosion	–		Mastoid surgery	Pale granulation tissue, bony erosion, necrotizing granulomatous inflammation	+	Anti-TB therapy	Improved
Din et al. (2022) [214]	4 y/M	Otalgia, otorrhea/4 days	Purulent otorrhea, anterior displacement of the pinna with postauricular swelling		+	CT: Postauricular abscess, petromastoid opacification, bony erosion, intracranial involvement	+		Mastoid surgery	Pale granulation tissue, bony erosion, necrotizing granulomatous inflammation	+	Anti-TB therapy	Improved
Din et al. (2022) [214]	4,5 y/M	Otalgia, otorrhea/30 days	Purulent otorrhea, anterior displacement of the pinna with postauricular swelling, cholesteatoma	Intracranial extension	+	CT: Postauricular abscess, denuded ossicles, petromastoid opacification, bony erosion, intracranial involvement	–		Mastoid surgery	Pale granulation tissue, bony erosion, necrotizing granulomatous inflammation, destructive cholesteatoma	+	Anti-TB therapy	Improved

Author(s) (publication year)	Age/sex	Ear–nose–throat symptom on admission/duration of symptoms	Ear–nose–throat examination findings	Tuberculosis at other organ(s)	Presence of hearing loss	Auricular radiology	Presence of tuberculosis contact	Tuberculin skin test	Ear–nose–throat surgery	Auricular tissue pathology	Microbiological evidence of *Mycobacterium tuberculosis*[b]	Agents used for treatment of auricular tuberculosis	Outcome
Hajare et al. (2022) [215]	10 y/F	Painless ear discharge, decreased hearing/1 year Multiple small swelling behind the ear/20 days	Ear pinna pushed downward and forwards, painless multiple discharging sinuses at the postauricular area with an inflammatory swelling, purulent discharge with a small polyp in the canal		+	CT: Soft tissue density filling middle ear and mastoid			Incision and drainage, exploration mastoidectomy	Pale granulation tissues suggestive of tuberculosis		Anti-TB therapy	Improved
Hajare et al. (2022) [215]	13 y/M	Painless swelling behind the ear for 4 months	Soft, firm, well-defined swelling in the postauricular region		+	X-ray: Extensive pneumatization of mastoid with classical haziness suggestive of rarefying ostitis CT: Opacification of the middle ear and mastoid air cells, erosion of mastoid cortex			Incision and drainage, modified radical mastoidectomy	Tubercular granulation tissue		Anti-TB therapy	Improved
Hajare et al. (2022) [215]	14 y/M	Ear discharge/2 years Painful swelling behind ear/10 days	Diffuse swelling behind the ear extending to the neck below the pinna till the angle of the mandible mimicking a Bezold's abscess		+	CT: Soft tissue opacification of mastoid air cells and middle ear cavity with the destruction of middle ear cavity bones			Incision and drainage, modified radical mastoidectomy with tympanoplasty	Extensive pale granulation tissues	+	Anti-TB therapy	Improved
Hajare et al. (2022) [215]	12 y/F	Ear discharge/1 year Multiple discharging sinuses behind and above ear pinna/15 days	Granuloma in the deep part of the external auditory canal		+	CT: Soft tissue density filling middle ear and mastoid			Incision and drainage, exploration mastoidectomy	Fleshy granulations	+	Anti-TB therapy	Improved
Te et al. (2022) [216]	20 m/NR	Otorrhea/8 months Facial nerve palsy, intermittent fever	Pus discharge with polyps and granulation tissue at the tympanic membrane	Lung, brain	+	CT: Soft tissue mass in the middle ear extending to mastoid and into the auditory canal with ossicles destructed, dehiscence lateral semicircular canal and facial canal	–			Chronic inflammation in granulation tissue		INH, RIF, PZA, ETM	Improved
Te et al. (2022) [216]	16 y/NR	Otorrhea, hearing loss/9 months	Multiple tympanic membrane perforations, polyps, and granulations over the tympanic membrane with foul-smelling discharge		+	CT: Soft tissue density in the middle ear, no bony erosion detected	–				+	INH, RIF, PZA, ETM	Improved

[a] *CT* computed tomography, *d* day(s) of age, *ETM* ethambutol, *F* female, *INH* isoniazid, *m* month(s) of age, *M* male, *MDR-TB* multidrug-resistant tuberculosis, *MRI* magnetic resonance imaging, *NR* not reported, *PAS* para-amino-salicylic acid, *PCR* polymerase chain reaction, *PZA* pyrazinamide, *RIF* rifampin, *SM* streptomycin, *TB* tuberculosis, *w* week(s) of age, *y* year(s) of age, (+) yes, (−) no

[b] *Mycobacterium tuberculosis* was demonstrated by direct microscopy and/or culture and/or polymerase chain reaction from ear drainage, gastric lavage, sputum, or cerebrospinal fluid

37.14 Conclusion

Childhood tuberculosis continues to be a public health problem in the twenty-first century. Hearing loss can result from TOM in children and poses a diagnostic challenge. Chronic ear discharge not responding to antibacterial treatment, swelling behind the ear, and facial paralysis should alert the physician as signs of TOM. Pediatricians and otolaryngologists should work in cooperation in the diagnosis and treatment.

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Nontuberculous Mycobacteria Infections in Children and Hearing Loss

38

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38.1 Introduction

Nontuberculous mycobacteria (NTM), also called atypical mycobacteria, environmental mycobacteria, or mycobacteria other than *Mycobacterium tuberculosis*, include all *Mycobacterium* genera except the *M. tuberculosis* complex and *Mycobacterium leprae* [1]. Nontuberculous mycobacteria are a diverse bacterial group that differs from the *M. tuberculosis* complex in terms of virulence, infectivity, growth conditions, and drug susceptibility.

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Since the last century, it has been well known that NTM can cause human diseases, such as lymphadenitis, skin and soft tissue infections, mastoiditis, pneumonia, bone and joint infections, and rarely disseminated disease, especially in immunocompromised conditions and in children [2]. Long-term drug therapy and additional surgical intervention are often required.

This chapter focuses on NTM infections in children and related hearing loss and reviews pediatric patients with NTM otomastoiditis reported in the literature.

38.2 Etiology

Nearly 200 NTM species have been described [3], but fewer than 20 cause human disease [4]. Nontuberculous mycobacteria classification, made in 1959 according to growth rate, colony morphology, pigmentation, catalase activity, and pathogenicity to animal species, is rarely used today [5]. Nontuberculous mycobacteria are traditionally classified according to their growth rate in vitro as "*rapidly growing*" mycobacteria (NTM detectable in 3–7 days) and "*slowly growing*" mycobacteria (NTM detectable after weeks) [5, 6]. Conventional acid-fast staining methods described for *M. tuberculosis* can be used for NTM. Ziehl–Neelsen (EZN), Kinyoun, and fluorochrome dyes are used for direct microscopy. Although most NTM strains grow at 37 °C, some species, such as *Mycobacterium ulcerans* and *Mycobacterium marinum,* can grow at 30–32 °C. In addition, gene sequencing and nucleic acid amplification tests are used for species identification. *Mycobacterium avium* complex (MAC; *Mycobacterium avium*, *M. avium-intracellulare, Mycobacterium chimaera*), *Mycobacterium kansasii, Mycobacterium fortuitum,* and *Mycobacterium abscessus* are most commonly responsible for disease in human [2, 7].

Nontuberculous mycobacteria cause disease at all ages, both pulmonary and extrapulmonary. The pathogenicity varies depending on the type [2, 8]. *Mycobacterium avium* complex and *Mycobacterium scrofulaceum* are most commonly responsible for cervical lymphadenitis in children, and *M. marinum* and *M. ulcerans* frequently cause skin infections [9].

38.3 Epidemiology and Transmission

Some chronic diseases caused by NTM are widespread globally, while certain strains are only rarely recorded in some regions of the world [2]. Some studies have shown that the incidence and prevalence of NTM are increasing [10]. The exact frequency is unknown since NTM disease usually is not routinely reported. Recent studies indicate that the annual incidence is between 0.6–4.5 cases/100,000 children/year [11, 12]. Whereas NTM lymphadenitis is usually seen in healthy children without underlying disease, NTM pulmonary infection is more common in children with chronic lung diseases such as cystic fibrosis (CF), bronchopulmonary dysplasia, and primary ciliary dyskinesia [11]. Disseminated NTM disease almost always

occurs in immunocompromised children [2, 13]. Healthcare-associated infections can also occur with NTM [14].

Nontuberculous mycobacteria species are highly prevalent in soil, water supplies, foodstuffs, and animals [15, 16]. Unlike the *M. tuberculosis* complex, NTM transmission is not person to person but comes from exposure to environmental sources. Bryant et al. [17] reported that *M. abscessus* was demonstrated by whole-genome sequencing to be transmitted from person to person in patients with CF. However, this finding is highly controversial because a common environmental source for human infections could not be ruled out, so this transmission could be possible but still unproven. *Mycobacterium abscessus* is also be found on body surfaces without causing disease. Medical equipment may be colonized by NTM that has not been adequately sterilized [18].

38.4 Pathogenesis and Immunity

An individual acquires NTM from environmental sources. Nontuberculous mycobacteria can cause 4 clinical syndromes in humans:

- Progressive lung disease mostly develops in the elderly and sometimes children as a complication of bronchiectasis or chronic lung disease when the infectious agent is inhaled in aerosol form.
- Superficial lymphadenitis, especially in children in the neck region, occurs after oral ingestion of the agent.
- Disseminated disease often develops following colonization of central venous catheters in severely immunocompromised individuals.
- Skin and/or soft tissue infections occur with the direct entry of bacteria through an open wound in the skin.

Outbreaks have been reported after contamination of tattoo ink [19] or gingival treatment [20]. Some host characteristics predispose to NTM infections. Many species have a unique propensity to infect a particular organ (Table 38.1). Patients with CF are typically predisposed to NTM infection, particularly from the *M. avium* complex and *M. abscessus* [23]. Open fractures, permanent central vein catheters, prosthetic heart valves, tympanic membrane tubes, bronchiectasis, organ transplantation, anti-tumor necrosis factor-alpha (anti-TNF-α) drugs such as infliximab and etanercept used in the treatment of some autoimmune diseases (including rheumatoid arthritis and inflammatory bowel disease) predispose to NTM infections. Interferon-gamma (IFN-γ), interleukin 12 (IL-12), and TNF-α pathways play an important role in the host's immune response to mycobacterial infections [24, 25]. In a group of inherited immune defects known as Mendelian susceptibility to mycobacterial diseases (MSMD), a tendency to severe and systemic mycobacterial infections occurs as a result of various mutations in the IFNγ/IL-12 axis [13].

Their ability to form biofilms [18, 26] and resistance to disinfectants [27] help NTM create infection.

Table 38.1 Infections caused by nontuberculous mycobacteria[a]

Organism	Growth rate (Days)	Most common infections	Uncommon infections
Slowly growing mycobacteria			
Photochromogens, Runyon group I			
Mycobacterium kansasii	10–21	Pulmonary infection Disseminated infection Bone infection	Otitis media and mastoiditis Skin and soft tissue infection Bone infection Cervical lymphadenitis
Mycobacterium marinum	7–14	Skin and soft tissue infection Bone infection	Disseminated infection
Scotochromogens, Runyon group II			
Mycobacterium scrofulaceum	10–28	Cervical lymphadenitis	Pulmonary infection Disseminated infection
Mycobacterium szulgai	12–28	–	Pulmonary infection Disseminated infection Skin and soft tissue infection
Mycobacterium gordonae	10–28	Most common tap water contaminant (nonpathogen)	
Nonchromogens, Runyon group III			
Mycobacterium avium complex (MAC)	10–21	Cervical lymphadenitis Otitis media and mastoiditis Pulmonary infection Disseminated infection	Skin and soft tissue infection
Mycobacterium ulcerans	28–60	Skin and soft tissue infection	Bone infection
Mycobacterium xenopi	14–28	Pulmonary infection	Skin and soft tissue infection Disseminated infection
Rapidly growing mycobacteria			
Runyon group IV			
Mycobacterium fortuitum	3–7	Skin and soft tissue infection Bone infection	Pulmonary infection Cervical lymphadenitis Otitis media and mastoiditis Catheter infection Disseminated infection

(continued)

Table 38.1 (continued)

Organism	Growth rate (Days)	Most common infections	Uncommon infections
Mycobacterium abscessus	3–7	Skin and soft tissue infection Otitis media and mastoiditis Pulmonary infection Bone infection	Cervical lymphadenitis Disseminated infection
Mycobacterium chelonae	3–7	Skin and soft tissue infection Disseminated infection	Pulmonary infection Cervical lymphadenitis Otitis media and mastoiditis Catheter infection

[a]Adopted and modified from Ref. [5, 6, 21, 22]

38.5 Pathology

The histological appearances of the lesions caused by *M. tuberculosis* and NTM are usually not distinguishable from each other. Hydrophobic mycolic acid in the cell wall may prevent mycobacteria from being visible by Gram staining; however, mycobacteria may appear as Gram-positive rods. Nontuberculous mycobacteria are also not easily visualized with EZN staining [28]. The classic pathological lesion is granuloma formation. Suppurative, noncaseous, irregularly circumscribed granulomas or chronic inflammatory changes are often in NTM infections. Histological features reflect the patient's immune status. The inflammatory response is usually minimal in patients with untreated HIV and disseminated NTM infection [29, 30].

38.6 Clinical Manifestations

38.6.1 Lymphadenitis

Lymphadenitis is the most common manifestation of NTM infection in children and is usually seen in healthy young toddlers, most often 1–5 years of age [4, 31]. In high-income countries with low tuberculosis prevalence, most unilateral, chronic neck, and submandibular lymphadenitis occur with NTM, most often with MAC. In a minority of patients (5%), the NTM infection is localized to the lymph nodes of the thorax, primarily paratracheal or mediastinal.

Patients with NTM lymphadenitis usually do not have any significant complaints or symptoms. Painless or slightly painful lymphadenopathy begins to fluctuate over time, and the overlying skin turns red-purple and may fistulize the skin. Lymphadenitis sometimes resolves spontaneously with fibrosis and calcification without draining outside.

38.6.2 Skin and Soft Tissue Infections

Nontuberculous mycobacterial skin and soft tissue infections can result from localized or disseminated infections in patients of all ages [32]. After trauma and surgery, *M. marinum, M. ulcerans, M. fortuitum, M. chelonae, and Mycobacterium goodii* are responsible for skin and soft tissue infections. Diagnosis is made by demonstrating the organism in a skin nodule, wound or abscess fluid, or biopsy material. Nontuberculous mycobacteria in the immunocompetent host usually enter the skin infection site after local trauma. In an immunocompromised host, skin lesions primarily develop after the hematogenous spread of disseminated disease. Skin lesions can range from progressively ulcerating erythematous papules and nodules to cellulitis to ecthyma. The wound may begin as painless papules or clusters of bumps and progress to a reddish plaque. Regional lymphadenitis or constitutional symptoms are rare. Serious NTM diseases such as tenosynovitis and joint and bone infection are infrequent.

Buruli ulcer develops by *M. ulcerans* and occurs mainly in sub-Saharan Africa. Infection is usually acquired from insects or mosquitoes at the river and seaside. The initial lesion progresses slowly over months, transforming into a painless ulcer, usually on the arm or leg's extensor surface, and often eventually causing severe limb deformity. About 15% of *M. ulcerans* infections end in osteomyelitis [28].

Cellulitis, abscess, or catheter-related infection can develop with NTM, often with penetrating injuries, tattoos, cosmetic procedures [19], or bacteria-contaminated multi-dose vials and surgical materials.

38.6.3 Pulmonary Infection

Nontuberculous mycobacteria-associated lung infection typically occurs in adolescents and young adults with compromised host defenses [33]. The findings are not easily differentiated from other pulmonary problems in patients with CF, chronic obstructive pulmonary disease, human immunodeficiency virus (HIV) infection, and other immunodeficiency syndromes. The most encountered NTM are MAC, *M. abscessus*, *M. chelonae,* and *M. fortuitum* in patients with pulmonary disease. Pulmonary NTM infection is rare in children without CF.

38.6.4 Disseminated Infection

Disseminated NTM infection is rare in healthy individuals. However, patients with underlying malignancy, congenital or acquired cellular immunodeficiency, IFNγ/IL-12 axis disorder [13], organ and stem cell transplant [34], and those who use long-term corticosteroid or cytotoxic chemotherapy [35] are prone to severe, life-threatening disseminated NTM disease, and they often exhibit skin

lesions as an early sign. *Mycobacterium chelonae* and *M. abscessus* are the most common causative agents, and less frequently, MAC, *Mycobacterium haemophilum*, *M. kansasii*, *M. fortuitum,* and *Mycobacterium simiae* can be encountered [21, 36].

Patients with AIDS and those with congenital immunodeficiencies, including severe combined immunodeficiency (SCID), develop disseminated MAC infection, especially in parallel with low CD4+ lymphocyte levels. Disseminated MAC infection in children with AIDS is mostly associated with fever, weight loss, night sweats, and gastrointestinal complaints [37].

38.6.5 Miscellaneous Infections

Nontuberculous mycobacterial infections have been reported in almost every organ system. Miscellaneous NTM infections mainly include parotitis, otomastoiditis, choroiditis, ocular disease, panniculitis, synovitis, osteomyelitis, genitourinary tract infection, and catheter- and prosthetic device-related infections. Both slowly and rapidly growing NTM can play a role in etiology [2, 21].

38.7 Complications

Suppuration and fistula development at the operation site, healing with scar tissue, and facial nerve injury may develop in children undergoing surgical intervention for NTM cervicofacial lymphadenitis [31]. Skin infections of NTM may leave undesirable cosmetic scars. Pulmonary infection unresponsive to antibiotics can progress to lobectomy, bronchiectasis, chronic obstructive airway disease, and chronic respiratory problems [2]. A potential exists for prolonging chronic infection due to ineffective treatment and the development of adverse side effects of antibiotics used in all NTM infections.

38.8 Differential Diagnosis

Tuberculosis should be considered in the differential diagnosis of all clinical forms of NTM disease. Pneumonia with NTM may be confused with atypical bacterial infections, chronic lung diseases, bronchiectasis, neoplasms, and connective tissue diseases [38]. Acute bacterial adenitis, cat-scratch disease, infectious mononucleosis, toxoplasmosis, brucellosis, tularemia, malignant tumors, and cystic hygroma should be listed in the differential diagnosis of NTM lymphadenitis [31]. Lymph nodes are usually larger, grow faster, and become softer, painful, and reddened in acute bacterial lymphadenitis. Fever is also a prominent symptom, and the white blood cell count and C-reactive protein level are typically elevated in pyogenic bacterial adenitis.

38.9 Laboratory Findings

Complete blood count in NTM lymphadenitis is usually within normal limits. The erythrocyte sedimentation rate may be increased. Except for pulmonary disease, findings on a chest radiograph are normal in most cases. Tuberculin skin test (TST) may be negative or positive. The interferon-gamma release assay (IGRA) tests are helpful in the differential diagnosis because the assay gives less cross-positivity than TST [39].

38.10 Diagnosis

The diagnosis of NTM lymphadenitis should be supported by a histopathological examination of the lymph node. Granulomas occur with or without caseification. A definitive diagnosis is made by tissue culture and molecular assay for NTM. Compared to lymph node culture, polymerase chain reaction (PCR) has a higher sensitivity [39]. Nontuberculous mycobacteria isolation from respiratory specimens is essential for the definitive diagnosis of pulmonary disease. Due to the widespread environmental presence of NTM, the agent should be isolated in at least two sputum cultures for diagnostic purposes [8]. The definitive diagnosis of disseminated NTM disease is based on demonstrating the causative agent in the blood, bone marrow, liver, lymph nodes, or other normally sterile body sites.

38.11 Treatment

No definitive and evidence-based recommendations exist for NTM infection treatment. Since the treatment of NTM infections is prolonged and challenging, it is recommended to consult a specialist. Surgical intervention and combining multiple antimycobacterial drug regimens are required for appropriate treatment (Table 38.2) [2, 6, 21, 22, 41]. Many NTM strains are resistant to the first-line antituberculosis drugs used to treat *M. tuberculosis* complex diseases. An antimicrobial susceptibility test is essential for selecting an effective drug combination. Significant differences are known between in vitro drug sensitivity and response to in vivo treatment, possibly explained by the synergism of antituberculosis drugs.

Classified as slow-growing mycobacteria, *M. kansasii*, *M. marinum*, *Mycobacterium xenopi*, *M. ulcerans,* and *Mycobacterium malmoense* are generally susceptible to rifampin and ethambutol. *Mycobacterium avium* complex mycobacteria are usually resistant to these drugs individually but susceptible when used in combination and have variable sensitivity to macrolides. Among rapidly growing mycobacteria, *M. abscessus* is highly resistant to antituberculous agents and generally has mechanisms of inducible macrolide resistance; *M. fortuitum* and *M. chelonae* are relatively less resistant. Multidrug therapy is required to prevent the development of resistance [2, 6, 21, 22, 40, 41].

Table 38.2 Treatment of infections caused by nontuberculous mycobacteria[a]

Organism	Disease	Treatment
Slowly growing mycobacteria		
Mycobacterium avium complex *Mycobacterium haemophilum*	Lymphadenitis	Complete removal of lymph nodes; clarithromycin or azithromycin + ethambutol and/or rifampin/rifabutin if incomplete removal or disease recurs
	Pulmonary/disseminated infection	Clarithromycin or azithromycin + ethambutol and rifampin/rifabutin (+ amikacin/streptomycin in severe disease) Lung resection if unresponsive to drug therapy
Mycobacterium kansasii	Pulmonary/disseminated infection	Rifampin + ethambutol + isoniazid Rifampin resistance: Susceptible 3-drug regimen of clarithromycin or azithromycin, moxifloxacin, ethambutol, sulfamethoxazole, or amikacin/streptomycin
	Bone infection	Surgical debridement and long-term treatment with rifampin + ethambutol + isoniazid
Mycobacterium marinum	Skin infection	Minor wounds are not treated For moderate wounds; rifampin, trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline Large wounds may require additional surgical debridement
Mycobacterium ulcerans	Skin and bone infection	Streptomycin (intramuscular) + rifampin for 8 weeks Necrotic tissue should be surgically removed
Rapidly growing mycobacteria		
Mycobacterium fortuitum	Skin infection	Initial treatment for the severe disease is amikacin + meropenem (intravenous) followed by clarithromycin, doxycycline or trimethoprim-sulfamethoxazole, or ciprofloxacin based on in vitro susceptibility testing Surgical debridement may be required
	Catheter-related infection	Catheter removal and amikacin + meropenem (intravenous), then clarithromycin, trimethoprim-sulfamethoxazole or ciprofloxacin based on in vitro susceptibility testing
Mycobacterium abscessus	Middle ear infection, skin infection	There is no reliable antimicrobial therapy due to variability in drug sensitivity Clarithromycin or azithromycin and amikacin + cefoxitin or imipenem/meropenem as initial therapy Surgical debridement may be required
	Pulmonary infection (esp. in cystic fibrosis)	Clarithromycin or azithromycin, amikacin and cefoxitin or imipenem/meropenem based on susceptibility testing in severe disease Most isolates have very low tigecycline MIC Surgical resection of the lung may be required

(continued)

Table 38.2 (continued)

Organism	Disease	Treatment
Mycobacterium chelonae	Catheter-related infection, prosthetic valve endocarditis	Catheter removal, debridement, foreign body removal, valve replacement and tobramycin (initial) + clarithromycin or azithromycin, meropenem, and linezolid
	Disseminated skin infection	Tobramycin and meropenem or linezolid (initially) + clarithromycin or azithromycin

[a] Adopted and modified from Ref. [2, 6, 40]

38.11.1 Lymphadenitis

Removal of the entire necrotic inflamed lymph node is recommended for NTM adenitis, as far as complete excision may be performed. If the lymph node diseased with NTM is not surgically removed, antimicrobial therapy is suggested rather than observation [42]. Nontuberculous mycobacterial lymphadenitis may resolve spontaneously; however, monitoring without treatment, complete recovery usually takes 9–12 months. Also, antimicrobial therapy is generally preferred over observation because the risk of fistula formation is lower [42]. Because MAC is the most common cause of NTM lymphadenitis, treatment with clarithromycin, rifabutin, and/or ethambutol is appropriate [2, 6, 40].

Drainage by incision or needle may cause permanent sinus tract and is not recommended [2].

38.11.2 Skin, Soft Tissue, and Bone Infections

Skin and soft tissue NTM infections in children are suggested to be treated with antimicrobial therapy rather than observation. For localized, nonulcerated skin and soft tissue infections, "clarithromycin or azithromycin" plus either "a fluoroquinolone, doxycycline (≥8 year) or trimethoprim-sulfamethoxazole" are recommended while waiting for the culture result about NTM type is obtained. Spontaneous resolution may take up to 12 months in case of no treatment [43].

The optimal therapy for *M. marinum* infection is uncertain due to the lack of controlled studies. Dual therapy with clarithromycin or azithromycin combined with ethambutol or rifampin is most commonly recommended [33]; however, improvement may not be achieved in some patients, or the infection may recur. It is recommended to add rifampin as the third agent in patients with bone or joint involvement [2]. Surgical wound debridement may be required for those with localized extensive deep infections. The initial antibiotic regimen can be adjusted based on the culture and antibiotic susceptibility results.

Buruli ulcer caused by *M. ulcerans* is treated with surgical intervention and skin graft, but the infection may recur. Systemic therapy with

trimethoprim-sulfamethoxazole, minocycline, streptomycin, rifampin, dapsone, or clozapine may be used; however, the clinical response is poor in chronic ulcerative lesions [44]. Antibiotic therapy is recommended not for less than 8 weeks, which may limit the need for surgical treatment. Physiotherapy should not be neglected to avoid contractures after surgical intervention of the limbs.

In skin and soft tissue infections due to *M. fortuitum*, *M. chelonae*, and *M. abscessus*, drainage of the abscesses and removal of foreign bodies are necessary before adding appropriate antimycobacterial drugs. *Mycobacterium fortuitum* is generally sensitive to oral antibiotics such as clarithromycin, doxycycline, minocycline, sulfonamides, and fluoroquinolones; however, resistance to macrolides may develop rapidly [45]. Skin and soft tissue infections with *M. abscessus* can be treated with a macrolide such as clarithromycin or azithromycin, and an intravenous drug such as amikacin, cefoxitin, imipenem, ciprofloxacin, or linezolid as initial therapy [2, 40]. Duration of treatment should be individualized according to host characteristics, clinical response to treatment, and degree of infection. The recommended time for severe disease, including bone infection, is at least 6 months.

38.11.3 Pulmonary Infection

In patients with pulmonary symptoms, nodules, cavities, or multiple bronchiectasis on a chest radiograph or computed tomography, in addition to excluding other possible diagnoses and NTM in sputum taken at two separate times or in bronchial lavage fluid or findings of mycobacterial infection on the histopathological specimen is the indication for therapy [12]. If excluding the diagnosis of *M. tuberculosis* disease is not possible as the causative agent of pulmonary disease at the beginning, it is reasonable to give empiric treatment with isoniazid, rifampin, ethambutol, pyrazinamide, and a macrolide, azithromycin, or clarithromycin until discrimination by culture is available [2, 46].

Treatment regimens for pulmonary NTM disease in children are not well established. Empiric treatment for suspected NTM pulmonary disease is not recommended [2]. Patients with mild complaints may be observed without treatment. For patients with more severe clinical and radiographic findings or permanently positive culture results, the choice of drugs to be used in the treatment should be decided according to the culture and antibiotic susceptibility results. An initial regimen with rifampin, ethambutol, clarithromycin, or azithromycin combination is used [6, 46]. If macrolide resistance is in question, adding isoniazid and moxifloxacin to the combination instead of macrolides is preferred [47]. Amikacin inhalation may also be applied. Azithromycin is administered once daily, increasing adherence, and is generally preferred to clarithromycin for pulmonary NTM disease [46]. Antibiotic treatment should be continued for at least 12 months [2, 46]. Sputum culture conversion to negative is expected in 3–6 months. Expert opinion should be taken for resistant infection.

38.11.4 Disseminated Infection

Initial treatment of disseminated NTM infection in patients with AIDS includes a multidrug regimen with clarithromycin or azithromycin plus ethambutol with the addition of a third drug such as rifabutin or amikacin [2, 6, 48]. Symptomatic improvement can be seen after 2–3 weeks to 2 months. Blood cultures should be repeated to prove that the bacterial load has decreased [2]. Once clinical improvement is observed, treatment should be continued for the patient's life or until adequate immune reconstitution ensues [2, 6].

Device removal is essential for patients with infection associated with a central venous catheter or prosthetic devices such as a ventriculoperitoneal shunt or intraperitoneal dialysis catheter. The choice of drugs and duration of treatment that constitutes combination antimicrobial therapy are based on the agent, in vitro susceptibility tests, and the degree of immunosuppression. It is not unusual for new skin lesions to appear during successful treatment of disseminated disease, which may be due to immunological response. For *M. chelonae*, the culture of a biopsy specimen from a newly emerged lesion is expected to be sterile after 4–6 weeks of treatment [2, 6]. To achieve culture negativity, it usually takes 3–4 months to treat M. abscessus infection.

Prophylactic therapy against MAC is recommended with clarithromycin or azithromycin for HIV-infected adults and adolescents with CD4+ T lymphocyte counts <50 cells/mm^3 [49]. Before initiating preventive therapy, active MAC, *M. tuberculosis,* and other mycobacteria diseases should be excluded. *Mycobacterium avium* complex prophylaxis with clarithromycin (15 mg/kg/day divided into two doses, maximum 500 mg/day, every other day) or azithromycin (20 mg/kg, maximum 1200 mg/dose once a week) is also recommended in HIV-infected children with profound CD4+ T lymphocytopenia [2]. Deep CD4+ T lymphocytopenia is defined as CD4+ count <50/mm^3 for children over 6 years of age, <75/mm^3 for 2–6 years, <500/mm^3 for 1–2 years, and <750/mm^3 for <1 year old [50].

Patients with IFNγ/IL-12 axis disorder and disseminated MAC infection should be treated with rifampin or rifabutin plus ethambutol plus clarithromycin or azithromycin for at least additional 12 months after sputum cultures become negative [2, 51]. To prevent relapse once the clinical disease has resolved, extended prophylactic treatment with clarithromycin or azithromycin is recommended [51]. In addition, the need for interferon supplementation is determined by the specific genetic defect.

38.12 Prognosis

Antibiotic susceptibility results of isolate and underlying problems such as the host's immune status and chronic lung disease are the most important determinants of the prognosis of NTM infections [52, 53].

38.13 Prevention and Control

Care should be taken so that surgical wounds, injection sites, and intravenous catheters do not contact tap water to prevent healthcare-associated NTM infections. Tap water should not be used for cleaning medical devices such as endoscopes and cardiac surgery instruments [2]. For the prevention of MAC lung infection in severely immunocompromised AIDS patients, prophylactic agents such as clarithromycin or azithromycin should be ordered [54].

38.14 Nontuberculous Mycobacterial Otomastoiditis in Children

Ear infections with NTM are increasing gradually due to factors such as the relative decrease in incidence of tuberculosis with better control, the increase in the HIV epidemic, the more frequently performed ear surgery, and the improved physicians' awareness [55, 56]. Table 38.3 refers to the epidemiological and clinical data of 86 pediatric patients with nontuberculous mycobacteria otomastoiditis (NTM-OM) presented in the literature to date [57–82].

38.14.1 Etiology

Many NTM can cause otitis and mastoiditis in humans. The first case report of ear infection associated with NTM was published in 1976 [83]. *Mycobacterium fortuitum* was isolated in a long-standing ear discharge in an adult male patient with hearing loss (HL), fullness in the ears, and a middle ear ventilation tube for 2 years. The first pediatric otological infection with NTM that appeared in the literature was a chronic recurrent middle ear infection in a 10-year-old boy with *M. fortuitum*, which was complicated by hydrocephalus, subdural empyema, an abscess in the posterior fossa, and HL [57].

De novo acute mastoiditis, first seen with *M. avium*, has been reported in an 8-month-old infant who underwent mastoidectomy for recurrent middle ear infections, subperiosteal abscess, and aural polyp [58].

The first report of *M. chelonae* as the causative agent of ear infection was an article describing a nosocomial outbreak among patients, primarily children, who had tympanotomy tubes and were treated for perforated tympanic membrane [60]. *Mycobacterium abscessus* and *M. kansasii*-associated otomastoiditis were also first published in children in 1994 [62]. With the development of microbiological methods such as mycobacteria growth indicator tube (MGIT) and nucleic acid amplification tests, NTM are successfully isolated in more patients as a cause of chronic otomastoiditis.

According to analysis based on case series and case reports, NTM-OM with *M. abscessus* is most common in children and constitutes nearly half of the cases (Table 38.3).

Table 38.3 Epidemiological and clinical data of pediatric patients with nontuberculous mycobacteria (NTM) otomastoiditis in the literature[a]

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Dalovisio (1981) [57]	10 Y/M	Chronic recurrent otitis media	Otitis media		Yes/ persisted	CT: Right cerebellopontine angle mass		Mastoidectomy, craniotomy, and partial resection of the abscess		*Mycobacterium fortuitum*	Erythromycin, isoniazid, kanamycin, doxycycline, ethionamide, amikacin	11 mo
Wardrop (1984) [58]	8 m/M	Fever, otorrhea, postauricular edema without fluctuance	Polyp in the external auditory canal, perforated tympanic membrane	No	No	X-ray: Cloudy mastoid air cells with early coalescence	TST (+)	Incision and drainage of the subperiosteal abscess, mastoidectomy	Caseating mastoid granulomas	*Mycobacterium avium*	No treatment, spontaneous healing	–
Kinsella (1986) [59]	5.5 m/F	Otitis media and otorrhea	Mastoiditis	Yes	Yes/ persisted	CT: Subacute mastoiditis (destruction of bony air cells of left mastoid with thinning and destruction of mastoid cortex)	TST (+) NTM skin test (+)	Mastoidectomy	Necrotizing granulomas with AFB	*Mycobacterium avium-intracellulare*	Rifampin, streptomycin	1 month
Lowry (1988) [60]	Case series of 14 children out of 17 total (range 10 m–56 Y) Mean age 2.5 Y Index case: 20 m/M	Chronic otorrhea	Tympanic membrane tube and/or perforation in all cases Abundant granulation tissue, nonhealing mastoidectomy incision in 6/17 cases	Yes, in 9 cases	Not reported		Index case: TST (+)	Tympanoplasty or mastoidectomy or external canal debridement in 6 cases	Granulomas with AFB Index case: AFB	*Mycobacterium chelonae* subspecies *abscessus*	Erythromycin	Mean 21 wk. (range 9–40 wk)

Moerman (1993) [61]	9 Y/F	Recurrent otomastoiditis	Thickened tympanic membrane, polypoid mass in the external ear	Yes	Yes	CT: Polypoid mass in the external ear canal	TST (−) NTM skin test (+)	Cleaning of mastoid	Tuberculoid granulation tissue with epithelioid and Langhans cells	Not reported	Isoniazid, rifampin	2 mo
Moerman (1993) [61]	8 Y/M	Pressure on the affected ear and head	Indurated bulging tympanic membrane	Yes	Yes	CT: Chronic mastoiditis with polypoid tissue	TST (−)	Cleaning of middle ear and mastoid	Granulomatous tissue with epithelioid and Langhans cells	*M. Fortuitum*	Isoniazid	10 mo
Moerman (1993) [61]	7 y/M	Recurrent otitis media and mastoiditis, cholesteatoma	Perforated and draining tympanic membrane	Yes	Yes			Mastoidectomy	Granulomatous tissue with epithelioid and Langhans cells	*M. Chelonae*	Trimethoprim and sulfamethoxazole, Roxithromycin	Not reported
Nylén (1994) [62]	6 y/M	Recurrent serous otitis media	Perforation and secretion in left ear and polyp	Yes	Yes/ persisted	CT: No air in the mastoid system and middle ear, filled with granulomatous tissue		Mastoidectomy, curettage	Granulomatous process, epithelioid-cell granulomas with giant cells, partly of Langhans' type	*Mycobacterium abscessus*	İmipenem, amikacin, ciprofloxacin, clarithromycin	2.5 mo
Nylén (1994) [62]	9 Y/M	Recurrent otitis media and secretion from the left ear, acute mastoiditis	Polyp in ear canal, thick and red tympanic membrane	Yes	Yes/ persisted	CT: No air in the mastoid system and middle ear, filled with granulomatous tissue		Curettage	Chronic inflammation	*Mycobacterium kansasii*	Isoniazid, rifampin, pyrazinamide	7 mo
Nylén (1994) [62]	10 Y/M	Recurrent otitis media, chronic otorrhea	Polyps in the ear canal, chronic secretion	No	Yes/ persisted	CT: No air in the mastoid system and middle ear, filled with granulomatous tissue		Mastoidectomy, curettage	Granulation tissue	*M. Chelonae*	Clarithromycin, rifabutin, ethambutol, topical amikacin	13 mo

(continued)

Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Franklin (1994) [63]	1 Y/F 1 y/M 2 y/M 3 y/M 4 y/F 6 y/M	Recurrent otitis media in all cases	Otorrhea in all cases	Yes, in all cases	Not reported			Tympano-mastoidectomy in 5 cases Tympanoplasty in 1 case Debridement in 1 case		*M. Abscessus*	Erythromycin, clarithromycin	Not reported
Stewart (1995) [64]	7 m/F	Otorrhea and postauricular mass	Granulation tissue covering the tympanic membrane, an erythematous, nontender, nonfluctuant mastoid mass		Yes/ persisted	CT: Soft tissue filling the mastoid cavity and middle ear, and a mass overlying the mastoid; bony destruction	TST (+)	Mastoidectomy	Necrotizing granulomatous inflammation with Langerhans' giant cells	*M. avium*	No treatment, spontaneous healing	–
TerKonda (1995) [65]	2 y/M	Persistent otorrhea and otitis media	Bulging tympanic membrane	Yes	Yes/ persisted	CT: Mastoid and middle ear disease		Tympano-mastoidectomy	Granulomatous inflammation	*M. avium-intracellulare*	Ciprofloxacin, rifampin	7 mo
TerKonda (1995) [65]	3 y/M	Chronic otorrhea	Thickened tympanic membrane, thick, green-white secretion	Yes	Yes/ improved	CT: Mastoid and middle ear disease		Tympano-mastoidectomy	Polypoid granulation, granuloma	*M. Fortuitum-chelonei* complex	Ciprofloxacin, erythromycin	12 mo
TerKonda (1995) [65]	5 y/M	Otalgia	Lobulated lesion occluding tympanic membrane, clear drainage	Yes	Yes/ persisted	CT: Mastoid and middle ear disease		Tympanotomy, mastoidectomy	Necrotizing granulomatous inflammation, giant cells of Langhans' type	*M. avium-intracellulare*	ETM, clofazimine, clarithromycin	12 mo

Plemmons (1996) [66]	14 y/F	Persistent otitis media	Drainage of serous fluid	Yes	Not reported			Mastoidectomy, debridement	Granulation tissue	*M. Fortuitum*	Clarithromycin	12 mo
Avery (1996) [67]	3 y/F	Recurrent otitis media and chronic otorrhea	Attic retraction pocket cholesteatoma, purulence with a thickened tympanic membrane, and protruding granulation tissue	Yes	No	X-ray: Partial opacification of the mastoid air cells		Mastoidectomy with middle ear debridement plus myringotomy	Granulomatous inflammation with caseous necrosis, AFB	*M. Cheonae*	Imipenem, cefoxitin	6 mo
Ferguson (1996) [68]	5 y/M	Recurrent otitis media and chronic otorrhea	Drainage from the middle ear	Yes	Not reported					*M. Abscessus*	Clarithromycin	4 mo
Liening (1997) [69]	14 y/F	Otorrhea, recurring otitis media	Otitis media and externa, perforated tympanic membrane	Yes	Not reported			Tympano-mastoidectomy	Acute and chronic inflammation with focal granulation tissue and multinucleated giant cells	*M. Fortuitum*	Clarithromycin, amikacin, trimethoprim-sulfamethox-azole, hyperbaric oxygen therapy	12 mo
Aarem (1998) [70]	2.5 y/M	Chronic mastoiditis	Acute mastoiditis, fluctuant retro-auricular swelling, perforated tympanic membrane, granulation tissue	Yes	Yes/ persisted		TST (−) NTM skin test (+)	Mastoidectomy	Granulomatous inflammation with noncaseous necrosis	*M. Chelonae* subs. *Abscessus*	Clarithromycin, ciprofloxacin, ethionamide	2 mo

(continued)

Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Flint (1999) [71]	3 y/F	Chronic otorrhea and cervical adenopathy	Polyp protruding from the ventilation tube with aural discharge	Yes	Yes/ persisted	CT: Opacification of the mastoid and middle ear, abscesses deep to the sternomastoid muscle, and in the retropharyngeal soft tissues		Removal of the polyp, incision, and drainage of the abscesses; mastoidectomy and modified radical neck dissection	Caseous necrosis consistent with a mycobacterial infection	*M. avium-intracellulare*	Ethambutol, clarithromycin	6 mo
Flint (1999) [71]	7 y/M	Recurrent otitis media, persistent otorrhea	Mastoid filled with rubbery granulation tissue	Yes	Yes/ returned to normal	CT: Soft tissue in the mastoid and the middle ear		Tympanoplasty and exploration of mastoid	Necrotizing and non-necrotizing granulomata	*M. Chelonae*	No treatment, spontaneous healing	–
Flint (1999) [71]	9 y/M	Chronic otorrhea	Nonhealing postauricular wound after mastoidectomy	Yes	No			Mastoidectomy with tympanoplasty		*M. Chelonae*	Clarithromycin, clofazimine	6 mo
Flint (1999) [71]	12 y/M	Chronic otorrhea	Granulation tissue in the mastoid and middle ear	Yes	Yes/ persisted			Mastoidectomy, debridement		*M. Chelonae*	Clarithromycin, ciprofloxacin	3 mo
Trupiano (2001) [72]	8 y/M (died)	Chronic otorrhea, complicated by intracranial and disseminated infection, underlying common variable immunodeficiency syndrome	Erythematous tympanic membrane with a thick, green, purulent exudate; ipsilateral seventh nerve palsy			CT: Dural-based mass overlying the left temporal lobe associated with the left petrous bone		Mastoidectomy	Fibrohistiocytic reaction with mild acute and chronic inflammation and multiple AFB; definitive well-formed granulomata not identified	*M. avium-intracellulare*	Postmortem diagnosis and no treatment	–

Muller (2006) [73]	18 m/F	Recurrent otorrhea; acute otitis media and externa, perichondritis, mastoiditis	Displacement of the auricle, swelling behind the ear; the external auditory canal was swollen and filled with an odorless mucopurulent discharge	Yes	No	CT: Filling of the mastoid with intact auditory ossicles		Mastoidectomy	Granulomatous necrotizing inflammatory reaction and AFB	*M. avium-intracellulare*	Clarithromycin, rifabutin	6 mo
Linmans (2008) [74]	4.5 y/M	Persistent otorrhea	Draining ventilation tube	Yes	Yes/ returned to normal	CT: Soft tissue in the right middle ear and mastoid cavity	TST (−)	Tympanoplasty		*M. Abscessus*	Clarithromycin	4 mo
McAvoy (2009) [75]	9 y/M	Headache, fever, myalgia, photophobia, recurrent cholesteatoma	Mastoid fluid	Yes	Not reported	MRI: Osteomyelitis of the pyramidal portion of the temporal bone with meningeal enhancement (intracranial empyema and meningitis)	TST (−)	Tympano-mastoidectomy with excision of aural polyps Retromastoid craniectomy	Granulomas with central necrosis surrounded by chronic inflammation are composed predominantly of lymphocytes, also epithelioid histiocytes, and multinucleated giant cells	*M. Fortuitum/ Mycobacterium peregrinum*	Rifampin, clindamycin, azithromycin, doxycycline, meropenem, hyperbaric oxygen therapy	4 mo
Ingen (2010) [76]	2 y/M	Chronic otorrhea, tympanic membrane perforation, fever	Mastoiditis	Yes	Yes/ persisted	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[b]		Surgery and delayed wound healing, retro-auricular abscess drainage		*M. Abscessus*	Rifampin, ethambutol, ciprofloxacin, clarithromycin	4 mo

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Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Ingen (2010) [76]	3 y/M	Chronic otorrhea, tympanic membrane perforation	Mastoiditis	Yes	Yes/ returned to normal	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery		*M. Abscessus*	Clarithromycin	5 mo
Ingen (2010) [76]	4 y/M	Chronic otorrhea, tympanic membrane perforation, fever	Mastoiditis	Yes	Yes/ returned to normal	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery		*M. Abscessus*	Clarithromycin	3 mo
Ingen (2010) [76]	4 y/M	Chronic otorrhea, tympanic membrane perforation	Mastoiditis	Yes	Yes/ persisted	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		–		*M. Abscessus*	Clarithromycin	8 mo
Ingen (2010) [76]	5 y/M	Chronic otorrhea	Mastoiditis	Yes	Yes/ returned to normal	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		–		*M. Abscessus*	Clarithromycin	4 mo

Ingen (2010) [76]	5 y/F	Chronic otorrhea, tympanic membrane perforation, vertigo	Mastoiditis, lymphadenitis	Yes	Yes/ persisted	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery		*M. Abscessus*	Clarithromycin	1 mo
Ingen (2010) [76]	6 y/F	Chronic otorrhea, otalgia, fever, tinnitus, vertigo	Mastoiditis, lymphadenitis	Yes	Yes/ persisted	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery and delayed wound healing, retro-auricular abscess drainage		*M. Abscessus*	Ciprofloxacin, clarithromycin, meropenem	6 mo
Ingen (2010) [76]	10 y/F	Chronic otorrhea, tympanic membrane perforation, fistula	Mastoiditis	Yes	Yes/ returned to normal	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery and delayed wound healing		*M. Abscessus*	Ciprofloxacin, clarithromycin, meropenem	6 mo
Ingen (2010) [76]	10 y/F	Chronic otorrhea, tympanic membrane perforation, vertigo	Mastoiditis, lymphadenitis	Yes	Yes/ returned to normal	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Chain reconstruction		*M. Abscessus*	Ciprofloxacin, clarithromycin	2 mo
Ingen (2010) [76]	12 y/M	Chronic otorrhea, tympanic membrane perforation, otalgia, fistula, seventh nerve palsy	Mastoiditis, lymphadenitis	Yes	Yes/ persisted	CT was performed in 5 patients of 10 case series. CT findings were not specified on a case-by-case basis[a]		Surgery and delayed wound healing, radical debridement, cervical lymph node excision, chain reconstruction		*M. Abscessus*	Clarithromycin, moxifloxacin	1 mo

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Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Pelkonen (2011) [77]	5 y/M	Recurrent otitis media, left-sided auricular proptosis, fever	Postauricular erythema and tenderness, granulation on the auditory canal, and polyps on the tympanic membrane	Yes	Yes	CT: Opacification of the left middle ear and mastoid ear cells, destructive changes of mastoid septations, and external mastoid cortex. MRI: Subperiosteal abscess and a reactive inflammatory thickening of temporal lobe dura	TST (−) TBSpot™ negative[c]	Tympano-mastoidectomy	Granulation tissue, AFB	*M. Abscessus*	Clarithromycin, amikacin	6 mo
Lefebvre (2015) [78]	2 y/M	Recurrent otitis media, chronic bilateral painless otorrhea	Tympanic membrane granulation tissue	Yes	Not reported	CT: Bilateral opacification of the mastoid air cells and no cholesteatoma		No		*M. Abscessus/ bolletii/ massiliense complex*	Clarithromycin, linezolid, topical boric acid	3 mo
Lundman (2015) [79]	10 y/M	Persistent otorrhea, otalgia	Secretion, polyps, mastoiditis	Yes	Yes/ persisted	CT/MRI: Bone destruction		Mastoidectomy	Granulomas with necrosis, multinuclear giant cells, histiocytic Infiltrates	*M. Abscessus*	Clarithromycin, amikacin, linezolid	10 mo
Lundman (2015) [79]	8 y/F	Persistent otorrhea	Secretion, polyps, mastoiditis	Yes	Yes/ returned to normal	CT/MRI: Bone destruction		Mastoidectomy	Necrosis without granulomas, histiocytic Infiltrates	*M. Abscessus*	Amikacin, clarithromycin, tigecycline	11 mo

Lundman (2015) [79]	4 y/M	Persistent otorrhea	Secretion, polyps, mastoiditis	Yes	Yes/ returned to normal	CT: Bone destruction		Mastoidectomy		*M. Abscessus*	Amikacin, clarithromycin	7 mo
Lundman (2015) [79]	12 y/M	Persistent otorrhea	Secretion, polyps	Yes	Yes/ persisted			Mastoidectomy		*M. Abscessus*	Amikacin, clarithromycin, linezolid	5 mo
Lundman (2015) [79]	7 y/M	Persistent otorrhea	Secretion, mastoiditis	Yes	No	CT/MRI: Bone destruction		Mastoidectomy	Granulomas with necrosis, histiocytic infiltrates	*M. Abscessus*	Ethambutol, rifampin, azithromycin	12 mo
Lundman (2015) [79]	9 y/M	Persistent otorrhea	Secretion, tympanic membrane perforation	Yes	No				Chronic suppurative inflammation, histiocytic infiltrates	*M. Abscessus*	Clarithromycin, doxycycline	4 mo
Lundman (2015) [79]	3 y/F	Persistent otorrhea	Secretion, polyps, mastoiditis	Yes	No			Mastoidectomy		*M. Abscessus*	Clarithromycin	7.5 mo
Lundman (2015) [79]	8 y/M	Persistent otorrhea	Secretion, polyps	No	No					*M. Abscessus*	Clarithromycin	6 mo
Lundman (2015) [79]	3 y/M	Persistent otorrhea	Secretion, polyps	Yes	No	CT/MRI: Bone destruction		Mastoidectomy, lymph gland removal	Granulomas with necrosis, multinuclear giant cells	*M. Abscessus*	Amikacin, clarithromycin	10 mo
Lundman (2015) [79]	14 y/M	Persistent otorrhea	Secretion, polyps	Yes	Yes/ returned to normal	CT/MRI: Bone destruction		Mastoidectomy	Granulomas with necrosis, multinuclear giant cells, histiocytic infiltrates	*M. Abscessus*	Clarithromycin, ciprofloxacin, amikacin, ethambutol	13 mo

(continued)

Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Lundman (2015) [79]	4 y/M	Persistent otorrhea, known IgA deficiency	Secretion, polyps	Yes	No			Mastoidectomy		*M. Abscessus*	Local steroid, antibiotic	Not reported
Lundman (2015) [79]	6 y/F	Persistent otorrhea	Secretion, polyps, seventh nerve paralysis	Yes	Yes/ persisted	CT/MRI: Bone destruction		Mastoidectomy	Granulomas with necrosis, multinuclear giant cells, histiocytic infiltrates	*M. Fortuitum*	Amikacin, ciprofloxacin, tigecycline, moxifloxacin	20 mo
Lundman (2015) [79]	6 y/M	Persistent otorrhea	Secretion, polyps	Yes	Yes/ returned to normal	CT: Bone destruction		Mastoidectomy	Granulomas with necrosis, multinuclear giant cells	*M. Fortuitum*	Clarithromycin, amikacin	6 mo
Lundman (2015) [79]	6 y/M	Persistent otorrhea	Secretion, polyps, mastoiditis	Yes	Yes/ returned to normal	CT: Bone destruction		Mastoidectomy	Granulomas with necrosis, multinuclear giant cells	*M. avium complex*	Azithromycin, rifampin	9 mo
Lundman (2015) [79]	1 y/F	Known IL-12/ IFNg deficiency	Mastoiditis	No	No	CT/MRI: Bone destruction		Mastoidectomy		*M. avium complex*	Clarithromycin, ethambutol, rifampin	13 mo
Myojin (2018) [80]	10 y/M	Recurrent otitis media	Otorrhea	Yes	Yes/ improved	CT: Space-occupying lesions in the ear and mastoid cavity		Tympanoplasty and mastoidectomy	Focal fibrosis without caseous necrosis	*M. Abscessus*	Clarithromycin, amikacin, tigecycline, linezolid	6 mo

Wijk (2019) [81]	7 y/M	Otalgia, otorrhea	Perforations of tympanic membrane		Yes/ improved	CT: Opacification of the mastoid cavity and the middle ears. MRI: Restricted diffusion in the mastoidectomy cavity, consistent with pus		Mastoidectomy		*M. Abscessus*	İmipenem, tigecycline, clofazimine, azithromycin, minocycline, topical imipenem-tigecycline	11 mo
Wijk (2019) [81]	7 y/M	Otorrhea	Central tympanic membrane perforation and thickened middle ear mucosa		Yes/ persisted	CT and MRI: Contrast-enhancing opacification of the right middle ear and the mastoid				*M. Abscessus*	İmipenem, tigecycline, clofazimine, azithromycin, topical imipenem-tigecycline	2 mo
Wijk (2019) [81]	9 y/F	Otorrhea, submandibular lymphade-nopathy	Central perforation and thickened middle ear mucosa, otorrhea		Yes/ persisted	CT: Opacification of the entire middle ear and mastoid with osseous destruction of the petrous apex and cortical interruption of the mastoid bone. MRI: This area was continuous with a retropharyngeal abscess		Tympanoplasty		*M. Abscessus*	İmipenem, tigecycline, clofazimine, azithromycin, topical imipenem-tigecycline	8 mo

(continued)

Table 38.3 (continued)

The first author of reference (Publication year)	Age/Sex	Symptom on admission	Ear examination	Ventilation tube	Hearing loss/ Outcome (if specified)	Radiology	Skin test	Surgery	Pathology	Type of NTM	Antibiotics after NTM isolated (not necessarily used together)	Total period of therapy after NTM isolated
Wijk (2019) [81]	15 y/F	Otorrhea	Otorrhea with a tympanostomy tube	Yes	Yes/ persisted	CT: Mucosal swelling in the left middle ear and mastoid		Tympanoplasty, mastoidectomy		*M. Abscessus*	İmipenem, tigecycline, clofazimine, azithromycin, topical imipenem-tigecycline	6 mo
Sédillot-Daniel (2020) [82]	4.5 y/F	Chronic otorrhea	Post-tympanostomy-otitis	Yes	Not reported	CT: Fluid-filled mastoid air cells		Mastoidectomy, masto-tympano-plasty		*M. Abscessus complex*	Cefoxitin, amikacin, clarithromycin, linezolid, topical boric acid	228 d
Sédillot-Daniel (2020) [82]	3 y/F	Chronic otorrhea	Post-tympanostomy otitis	Yes	Not reported	CT: Fluid-filled mastoid air cells		Myringotomy		*M. Abscessus complex*	Cefoxitin, amikacin, clarithromycin, linezolid, topical boric acid	87 d
Sédillot-Daniel (2020) [82]	6 y/M	Acute otorrhea	Post-tympanostomy otitis	Yes	No	CT: Fluid-filled mastoid air cells				*M. Abscessus complex*	Clarithromycin, amikacin, linezolid, topical boric acid	112 d
Sédillot-Daniel (2020) [82]	4 y/M	Chronic otorrhea, recurrent fever	Post-tympanostomy otitis, recurrent fever	Yes	No	CT: Fluid-filled mastoid air cells		Myringotomy		*M. Abscessus complex*	Clarithromycin, amikacin, linezolid, topical boric acid	97 d

Sédillot-Daniel (2020) [82]	2 y/F	Chronic otorrhea	Post-tympanostomy otitis	Yes	No	CT: Fluid-filled mastoid air cells, bony destruction		Myringotomy		*M. Abscessus complex*	Azithromycin, clarithromycin, cefoxitin, amikacin, linezolid, topical boric acid	91 d
Sédillot-Daniel (2020) [82]	1 y/M	Chronic otorrhea, fever	Acute mastoiditis, left sigmoid thrombosis, left cervical adenitis	No	No	CT: Fluid-filled mastoid air cells, bony destruction		Myringotomy, subperiosteal abscess drainage and excision, mastoidectomy		*M. avium complex*	Cefotaxime, ciprofloxacin (ear drop), amikacin, moxifloxacin, rifabutin, clarithromycin, azithromycin, ethambutol	202 d
Sédillot-Daniel (2020) [82]	5 y/M	Chronic otorrhea	Post-tympanostomy otitis	No	No	CT: Fluid-filled mastoid air cells		Ventilation tube removal		*M. Abscessus complex*	Cefoxitin, amikacin, clarithromycin, linezolid, topical boric acid	113 d
Sédillot-Daniel (2020) [82]	2 y/M	Chronic otorrhea	Post-tympanostomy otitis, acute mastoiditis	Yes	No	CT: Fluid-filled mastoid air cells, bony destruction		Mastoidectomy		*M. Abscessus complex*	Amikacin, cefoxitin, clarithromycin, linezolid, ciprodex	170 d

[a] *AFB,* indicates acid-fast bacilli; *CT,* computerized tomography; *d,* days; *F,* female; *M,* male; *mo,* months; *MRI,* magnetic resonance imaging; *NTM,* nontuberculous mycobacteria; *TST,* tuberculin skin test; *wk,* weeks test

[b] CT findings in 5/10 cases: mucosal swelling in 5, fluid in the mastoid in 4, and bone erosion of the mastoid in 2

[c] TBSpot™, in vitro lymphocyte stimulation test with *Mycobacterium tuberculosis* antigens

38.14.2 Epidemiology and Transmission

Otomastoiditis due to NTM is very rare. Between 1972 and 2020, only 89 NTM-OM cases were described in medical literature, most seen in children [79]. No case of otomastoiditis with NTM infection was documented in any of the 365 patients aged 1–95 years, followed for more than 20 years in a tertiary hospital [84]. No ear infection was reported in a study notifying the epidemiology of NTM in children of all ages between 2000 and 2010 [10].

Nontuberculous mycobacteria are frequently found in tap water, swimming pools, and soil. Their presence has been demonstrated in the pharyngeal secretions of healthy individuals [61]. Pool and lake swimming history may be obtained from NTM-OM patients [67, 77]. Contamination of materials and instruments used for ear examination may result in patient-to-patient transmission [60]. Outbreaks have been reported due to contaminated tap water in the tub used for intra-auricular suctioning [60].

Inoculation occurs when NTM, common in the environment, is acquired in the oropharynx and transmitted to the middle ear through the Eustachian canal or retrograde through the tympanostomy tube [61, 83]. Patients with an ear tube may be referred due to NTM-OM after water leaks into the ear while bathing in a hot tub [65]. Transmission from patient to patient has been reported through poor disinfection and sterilization of devices during the examination [60]. Infection into the middle ear can spread by aerosol inhalation of water contaminated with mycobacteria during showering and retrograde propagation through the Eustachian tube while coughing or sneezing [62]. Blood-borne spread from a previously unrecognized primary focus is infrequent in the immunocompetent individual [62]. No direct transmission from NTM-OM patient to another has been reported [70, 85–87].

While NTM-OM is usually seen in healthy children aged 10 years and younger (Table 38.3), it has been reported rarely in adulthood [83, 88–91]. Nontuberculous mycobacterial OM may occur more frequently in children because age-specific environmental exposure is more intense, such as swimming and playing in a sandbox in the playground [76]. A clonal relationship between the causative mycobacteria has been suggested since NTM-OM is also seen in siblings [76]. Acute bacterial mastoiditis is most common at 2–3 years, while NTM-OM develops later, around 5 years of age [91].

38.14.3 Pathogenesis and Immunity

The conditions that pave the way for the development of the NTM-OM are the deterioration of the integrity of the tympanic membrane and the formation of its undesirable connection with the external environment. Risk factors that increase the development of NTM-OM are as follows [60, 63, 65, 70, 76, 79, 81–83, 88–92]:

- ≥3 months of ear discharge
- Recurrent or chronic middle ear infection

- Presence of tympanostomy tube or foreign body
- Repeated examination or aspiration of the external ear canal
- Perforation of the tympanic membrane due to infection or injury
- Ear surgery
- Use of ear drops containing steroids
- Systemic or intranasal steroid use (in adults)
- Presence of cochlear implant (in adults)
- Immunodeficiency

Even a minute NTM inoculum can settle on previously damaged tissue and initiate infection [62]. Biofilm formation on a synthetic material, such as a tympanostomy tube, probably plays a role in the infection associated with NTM chronic otitis media [4, 36, 82]. In a case–control study examining an outbreak of otitis media with *M. chelonae*, mycobacteria were not isolated from patients with intact tympanic membranes, pointing to the role of a ruptured tympanic membrane in the pathogenesis [60].

Although NTM tends to cause disseminated disease in secondary immunodeficiencies such as HIV infection or AIDS, no HIV-infected or AIDS case developing NTM-OM has been reported. However, NTM-OM patients with common variable immunodeficiency (CVID) [72], IgA deficiency, and IL-12/IFNg deficiency [79] have been reported. Otomastoiditis may also be seen in normal individuals with no underlying disease by rapidly growing NTM, such as *M. chelonae, M. abscessus,* and *M. fortuitum* group [93].

38.14.4 Pathology

Since diagnosing NTM-OM is challenging, pathological examination provides valuable support for the diagnosis (Table 38.3). The middle ear and mastoid cavity are filled with whitish granulation tissue [58–60]. Granulation tissue is frequently detected in samples of adult patients [83, 88, 93].

Histological findings are indistinguishable from tuberculosis [58]. Pathological examination reveals granuloma and caseation in some cases [58, 72]. There was no definitive well-formed granuloma formation in the NTM-OM case with CVID mentioned above [72].

Acid-resistant bacteria can be seen in materials taken from ear structures, which helps predict the etiologic microorganism [60, 67, 72, 73, 77, 93].

38.14.5 Clinical Manifestations

Symptoms of NTM-OM in children do not differ from *M. tuberculosis* disease with clinical presentation features (Table 38.3). Mild tension and ear discharge without significant pain are the most common complaints. The child with NTM-OM may be febrile [76, 82]. In most NTM-OM cases, ear discharge continued for an average of

4.5 months [60]. Continuous unilateral persistent perforation, recurrent otitis media, and polyps in the external auditory canal should be warning signs for NTM-OM [61, 62]. Ear discharge persisting even for years and not responding to treatment in adults is typical for NTM-OM [83, 88, 91, 94].

Multiple perforations of the tympanic membrane, classic in tuberculous otitis, have been reported less frequently in NTM otitis [65]. Postauricular edema and fluctuance may be seen, and the mastoid cavity, antrum, and middle ear can be filled with granulation tissue on examination [58, 65, 95]. The tympanic membrane may be thickened [61, 62, 65, 67]. The auricle may be displaced upwards due to swelling [70], and bone destruction may develop behind the ear [56].

In patients with NTM-OM, infection in the ear may be bilateral; second ear involvement may co-occur or arise later under inappropriate treatment [67]. Refractory ear discharge that does not regress with standard treatment of antibiotic-containing ear drops is a common complaint [71, 73, 74, 76, 78, 79, 88]. *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* may cause co-infections in cases with chronic NTM-OM [58].

38.14.6 Complications

The following complications may develop during NTM-OM in children (Table 38.3):

- Facial nerve palsy [61, 72, 76, 79]
- Outer ear infection and perichondritis [73]
- Intracranial infections such as meningitis and empyema [57, 75]
- Sigmoid vein thrombosis [82]
- Hearing loss [59, 61, 64]

Complications of NTM-OM occur less frequently in adults than in children. Facial nerve palsy reported at 9.1% in an adult NTM-OM case series [88] may improve after treatment [96, 97]. Sigmoid sinus thrombosis progressing to intracranial structures developed in an adult patient with chronic NTM-OM [93].

38.14.7 Differential Diagnosis

The etiological investigation is essential in long-standing middle ear infections and/or HL and necessary to identify unusual causes [62]. Middle ear infection and mastoiditis with NTM should be distinguished from other infectious and noninfectious conditions, including other granulomatous diseases, foreign body reactions, sarcoidosis, tuberculosis, syphilis, lymphoma, carcinoma, and vasculitis diseases such as Wegener's disease, periarteritis nodosa, systemic lupus erythematosus [61, 64].

In the first decades of the twentieth century, the frequency of chronic ear infections caused by tuberculosis was reported as 15.4% [98]. The incidence has gradually decreased with advances in the diagnosis and treatment of tuberculosis: In a

series of 3750 tuberculosis patients in India, only six patients had tuberculous otomastoiditis [99]. It is challenging to distinguish between *M. tuberculosis* and NTM infections by their clinical and histological features. Culture methods are helpful in the differential diagnosis because NTM grow more rapidly in culture than *M. tuberculosis* [5, 61, 100]. In patients with middle ear mycobacterial infection, the absence of lung involvement increases the probability of NTM being the causative agent of ear infection [60]. Also, NTM-OM can be distinguished from tuberculosis infection by a moderate response to the TST (<15 mm) and usually a negative interferon-gamma release assay result, absence of fever, malaise, weight loss, also exposure history to an adult with pulmonary tuberculosis, and a normal chest film [64, 70].

38.14.8 Laboratory Findings

Microscopy and culture methods, histopathological examination of tissue, radiological work-up, and skin tests are used for diagnosis (Table 38.3). Mastoid air cells are cloudy on the mastoid bone roentgenogram [58]. Computed tomography can show the mastoid system filled with granulomatous tissue [62], subperiosteal abscess, and adjacent temporal lobe dura thickening and enhancing [77].

Tuberculin skin test [58], and a skin test with NTM antigens, a historical practice not done today [59, 70], or both skin tests may be positive [61].

38.14.9 Diagnosis

Mycobacteria culture from tissue biopsy is required for definitive diagnosis (Table 38.3). The culture should be incubated for at least 4 weeks.

Acid-resistant bacteria can be found in ear fluid [76] or tissue removed by mastoidectomy [67]. *Mycobacterium abscessus* and *M. chelonae* are common in dust, soil, and water and can be mistaken for harmless contaminants, as Gram-positive rods resembling diphtheroids appear on Gram staining [62, 68, 101]. Nontuberculous mycobacteria are easily isolated in culture and should be differentiated according to growth characteristics [2, 5, 100]. In addition, because mutations in the *rpoB* gene, encoding the β subunit of RNA polymerase, are strongly associated with RIF-resistant phenotypes, *rpoB* gene sequencing using molecular methods can help determine which species of NTM is the cause of otomastoiditis [62, 76, 102].

Nontuberculous mycobacterial infection may be superimposed on a pre-existing chronic or recurrent middle ear infection [96]. Appropriate bacterial culture should also be done because patients may have co-infection with other organisms such as *P. aeruginosa*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*, coagulase-negative staphylococci (CONS), *Proteus* spp., *Acremonium* spp. [65], and *Candida* spp. [82].

Infection caused by NTM should be considered in a child with an ear tube and chronic unilateral ear discharge, mild pain, pressure sensation, cholesteatoma, facial nerve palsy, and granulomatous inflammation refractory to antibiotic therapy [61, 67, 88].

38.14.10 Treatment

Nontuberculous mycobacterial OM is usually chronic and progressive. A combination of medical treatment and surgical intervention is recommended in NTM mastoiditis (Table 38.3) [61, 83, 88].

Surgical management includes ventilation tube removal, tympanoplasty, mastoidectomy, subperiosteal abscess drainage, and removal of eroded bone, granulation tissue, and polyps [58, 64, 74, 76, 79, 81, 82, 88]. Multiple surgical debridement may be required due to the regeneration of granulation tissue, separation of postoperative wound edges, and fistula development [63, 65, 67, 72, 76, 79, 81, 82]. Surgical intervention was performed up to four times in some reported cases for complications such as the intracranial spread of otomastoiditis, abscess formation in the temporal lobe [79], or biofilm formation in the ventilation tube [82] in the literature.

Treatment of chronic otitis media caused by NTM is often problematic as antibiotic resistance is high [67, 79–81]. Usually, long-term antibiotherapy is needed. Most NTM that cause otomastoiditis are resistant to antituberculous drugs, and their susceptibility may vary by species [65, 79, 89, 103, 104]. However, in rare cases, improvement was observed with antituberculous medications [62]**.** Since diseases caused by *M. tuberculosis* are also included in the differential diagnosis of NTM infections, it may be reasonable to initiate antituberculous therapy until culture results are obtained [2, 58, 64, 105]. Appropriate antibiotic therapy should be tailored according to the drug susceptibility test results of the mycobacterium. Avoiding treatment with a single drug is recommended, as there is a risk of developing drug resistance [6, 70].

Generally, *M. marinum* and *M. kansasii* are susceptible to isoniazid, rifampin, and pyrazinamide. However, tissue culture and drug susceptibility tests are required for other NTM due to their variable susceptibility characteristics for appropriate treatment selection [2, 6, 61]. Amikacin, cefoxitin, and doxycycline are usually active in vitro against *M. fortuitum* and *Mycobacterium chelonae* [57]. Erythromycin and amikacin were beneficial in treating a case with *M. fortuitum* mastoiditis [106]. *Mycobacterium avium* may be susceptible to cycloserine, ethionamide, or streptomycin [58, 59, 107], but the susceptibility pattern may change over time [108]. However, virtually all cases of MAC infection are treated with azithromycin, ethambutol, and rifampin. Some patients may improve with mastoidectomy alone [64]. *Mycobacterium abscessus, M. fortuitum,* and *M. chelonae* are resistant to all first and most second-line antituberculous drugs [89, 103]. *Mycobacterium chelonae* was often susceptible to cefoxitin, ciprofloxacin, and erythromycin in previous reports [60, 67]; however, an increased resistance ratio has been recorded in recent studies [109–111]. It should be kept in mind that the antibiotic susceptibility pattern for each NTM is not uniform and may vary from center to center and over time, which needs the decision of treatment to be individually evaluated.

Many strains of *M. abscessus* are susceptible to amikacin, clarithromycin, and azithromycin [103, 109–111]. Patients with good responses to clarithromycin/

azithromycin were reported [68, 70]. In some patients with OM, *M. abscessus* can develop secondary resistance with clarithromycin therapy [76]. Two of three *M. abscessus* subspecies, accounting for 88% of the isolates in the United States of America, have inducible clarithromycin/azithromycin resistance because of mutations in the erm gene. Many *M. abscessus* isolates have inducible clarithromycin/azithromycin resistance. The laboratory needs to check for this by analyzing the erm gene directly or holding the drug susceptibility result for clarithromycin/azithromycin for 2 weeks to be sure inducible resistance is not detected. According to a meta-analysis, antibiotic treatment for *M. abscessus* OM should be continued for at least 6 months with 3 drugs [91].

Tigecycline is a new choice in extensive-resistant *M. abscessus* infection [109, 111] and is used as salvage therapy in adults [80]. Tigecycline was used for a pediatric patient with chronic otitis media caused by *M. abscessus* multidrug-resistant and not responding to repeated treatment [80]. It was well tolerated except for the side effects of nausea and vomiting. In a few children, the tigecycline ear drops with imipenem were successful in avoiding nausea and vomiting side effects of intravenous tigecycline [81].

Ventriculoperitoneal shunt placement was required for hydrocephalus that developed after chronic, recurrent middle ear infection, subdural empyema, and abscess caused by *M. fortuitum* in a 10-year-old boy [57]. Intraventricular amikacin was applied in addition to systemic therapy since eradicating the mycobacteria was difficult.

Cases reports exist where hyperbaric oxygen therapy was used for complex patients, such as failure to respond to long-term antibiotic treatment [69] and the development of intracranial empyema [75].

Boric acid has bacteriostatic and fungistatic effects, also easy to use at a low cost, and was previously used to treat chronic suppurative otitis media [78]. It does not stimulate antibiotic resistance and provides symptomatic relief in patients. In children with chronic suppurative NTM-OM, boric acid was used with a mean duration of 78 days as systemic treatment and did not cause ototoxicity. Boric acid was used for a mean duration of 78 days concurrently with systemic antibacterial therapy in children with chronic suppurative NTM otomastoiditis. Clarithromycin/azithromycin and/or amikacin and/or cefoxitin and/or linezolid were used in the antibiotic combination regimen for an average of 21 weeks, and no patient developed ototoxicity [82].

As a general rule, medical treatment for NTM-OM should be given until 2–3 months after being apparently disease-free [61, 70, 74, 82]. Treatment with multiple antibiotics rather than one should continue for at least 6 months [79]. Recovery duration may vary between 1 and 24 months [96]. The most significant symptom that predicts the duration of antibiotic treatment is otalgia [91]. During treatment, repeated ear examination, repeat cultures for bacteria and fungi, and monitoring antibiotic resistance in culture growth are essential [2, 67, 79, 81].

38.14.11 Prognosis

The current treatment approach can achieve successful outcomes in most NTM infections [2, 6]. However, after inadequate therapy, NTM may still be isolated in culture, and the infection improves over a more prolonged duration [68]. Nontuberculous mycobacterial mastoiditis may also recur if antibiotic-resistant [70, 91]. Immunodeficiency should be investigated in patients with chronic and recurrent middle ear infections [62].

38.14.12 Prevention and Control

Otological examination materials must undergo a high-level disinfection and sterilization process to prevent pathogen transmission [60, 112]. **Tap water should never be used for otological procedures.** A genetic predisposition to NTM infections has been identified [13, 113].

38.15 Nontuberculous Mycobacterial Infections in Children and Hearing Loss

Hearing loss may develop in children with NTM-OM (Table 38.3). Few papers have comprehensive information on HL as a complication of auricular NTM infection. The present data suggest that HL is associated with recurrent otitis media, chronic mastoiditis, the operation (mastoidectomy in most cases) performed as a part of therapy, or the undesirable effects of antimicrobials (such as amikacin) used for the treatment of NTM infection.

Hearing loss is most common between the ages of 3 and 10, a critical period for learning difficulties. A previously placed ventilation tube for facilitating the drainage of the middle ear fluid of chronic otitis media was present in 85% of the reported cases with HL and NTM ear infections (Table 38.3) [57–82]. The male-to-female ratio of HL related to NTM infection is notified around 3:1 (Table 38.3) [57–82]. Hearing loss due to NTM-OM can also occur in adults [88, 89, 94, 114]. *Mycobacterium abscessus* is most isolated in those patients with auricular NTM infection complicated with HL (Table 38.3) [57–82, 91].

Hearing loss associated with NTM ear infection may be conductive or sensorineural, usually mixed [88]. Impaired hearing is due to polypoid masses filling the ear canal, tympanic cavity, mastoid cells, and thickened tympanic membrane. Surgical resection of bony structures of the mastoid further contributes to the outcome of an auditory compromise. Hearing loss may also develop due to neurological damage resulting from intracranial infection, a complication of chronic otitis media [57]. The audiogram should be performed as early as possible to reveal the impact on hearing and plan appropriate treatment [82].

Clarithromycin/azithromycin and aminoglycosides, the main components of combination antibacterial therapy for NTM, have side effects such as a decrease or

loss of hearing [57, 79, 95, 115, 116]. Hearing loss was reported in 7% of 47 pediatric patients treated for NTM lymphadenitis at a pediatric tertiary care facility over 12 years, at an average of 3 months after using clarithromycin [117]. Another child with NTM lymphadenitis also had HL after taking clarithromycin for 15 weeks and recovered 4 weeks after the drug was discontinued [118]. As for treating other NTM infections, monitoring HL with an audiogram is recommended in those receiving macrolides [39].

Gradenigo syndrome, an urgent clinical condition characterized by chronic suppurative otitis media, headache, facial nerve weakness, and diplopia due to the sixth cranial (abducens) nerve palsy, develops due to petrous apicitis, and patients may also have HL. Gradenigo syndrome has rarely been reported in adult patients with NTM-OM [90, 119]. Treatment should be continued for at least 4–6 months in patients with Gradenigo syndrome.

Hearing impairment due to NTM-OM may be reversible entirely or partially (Table 38.3) [65, 71, 79, 91], and the patient may need a hearing device.

38.16 Conclusion

Nontuberculous mycobacteria are among the emerging pathogens of the last century. Nontuberculous mycobacteria infections are characterized by variable clinical presentations, nonstandardized antibiotic combination treatment, and/or surgical intervention. Hearing loss may develop as a result of NTM ear infection directly or due to the side effects of drugs used for NTM disease. The prognosis of HL due to NTM is favorable if the patient can continue the treatment patiently.

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Cat-Scratch Disease in Children and Hearing Loss

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Soner Sertan Kara, Emin Sami Arısoy, and Armando G. Correa

39.1 Introduction

Cat-scratch disease (CSD), a zoonotic disease worldwide, causes significant acute and chronic health problems. Several clinical manifestations of CSD have been reported in humans for more than a century. Until 1993, human diseases caused by *Bartonella* species have not been well-described [1]. *Bartonella* spp. were first recognized as a causative agent of endocarditis. With the advances in serological and molecular tests, expansion of up to 30 *Bartonella* spp. has been detected [2]. *Bartonella bacilliformis, Bartonella henselae,* and *Bartonella quintana* are the most common species causing human disease. *Bartonella henselae,* the causative agent of CSD, is the most common species of *Bartonella*-associated infection in children. *Bartonella clarridgeiae* has also been reported in some cases [3].

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The typical clinical presentation of *Bartonella* infections is CSD. Polymorphic cutaneous lesions generally arising at the site of inoculation, visceral organ (liver, spleen) involvements, ocular manifestations including papillitis, optic neuritis, retinochoroiditis, neuroretinitis, and Parinaud's oculoglandular syndrome, neurological manifestations such as encephalopathy, transverse myelitis, radiculitis, and cerebellar ataxia, and musculoskeletal involvements, including myalgia, arthralgia, neuralgia, arthritis, tendinitis, and osteomyelitis may be seen as clinical manifestations. Additionally, *Bartonella* infections should be considered in the differential diagnosis of fever of unknown origin and prolonged fever in childhood.

Cat-scratch disease is usually a self-limited infection, often called "typical CSD," which presents lymphadenopathy with little or no systemic symptoms. The disease is usually acquired with domestic or wild cats' scratches. Generally, a localized crust or pustule, in addition to fever and lymphadenopathy, is experienced 1–3 weeks after the exposure. Other more complicated manifestations, including involvements of the central nervous system (CNS), bones, heart, or eye may be encountered in some patients.

39.2 Etiology and Transmission

Bartonella is the only *genus* in the family Bartonellaceae and is closely related to the genera *Brucella* and *Agrobacterium*. The members of the genus *Bartonella* are pleomorphic, intracellular, relatively fastidious, and gram-negative coccobacilli. Whole-genome sequencing has shown that *Bartonella* includes similar but reduces chromosomal elements of *Brucella melitensis* [4]. Even with optimal conditions, it takes 1–6 weeks to grow culture [5]. So, routine cultures have a low yield, and molecular methods are increasingly applied.

Domestic house cats, especially the kittens, constitute the primary reservoir for *B. henselae* and cat flea *Ctenocephalides felis* from cat-to-cat transmission [6]. Cats serve as a reservoir even if they are asymptomatic. Worldwide, *B. henselae* is identified endemically. Serological evidence suggests that domestic cats are infected in all parts of the world. The infection is more prevalent in warmer and humid climates, where the flea population is denser [7]. Infrequently, dogs have also been reported as a source of infection. Although cat ownership and contact with a cat are accounted for CSD transmission, individuals without a history of scratching a cat were also shown to be seropositive [8]. Cat-to-cat transmission is mostly by flea bite. Although transmission to humans is mostly via either a scratch or bite from a kitten, patients rarely get the disease through contact with mucosal surfaces or cat fleas [5, 9].

39.3 Epidemiology

Bartonella henselae infection and CSD are seen worldwide. It is assumed that the prevalence of the infection is higher than it has been detected. The infection's seroprevalence is variable, ranging from 0.7 to 57.0% [10]. In a study, only 15% of the

general population had seropositivity (≥1:64) for *B. henselae* immunoglobulin (Ig) G [8]. The true incidence is unclear as B. henselae infections are not reportable by the governments. In the United States of America (USA), an estimated 22,000 ambulatory patients are diagnosed with CSD annually, while the hospitalization rate is 0.42–0.86 per 100,000 individuals [5]. Nelson et al. [11] reported the highest CSD incidence in children aged 5–9 years and women. Surprisingly, veterinary personnel do not have an increased prevalence of infection than the general population [12]. The only possible way for *B. henselae* to transmit from human to human is organ transplantation, as reported in a liver transplant patient [13].

39.4 Pathogenesis and Pathobiology

The lipopolysaccharide structure on the outer membrane of *Bartonella* spp. has a diminished endotoxic activity, letting them escape from the toll-like receptors and evading the host's innate immune system relatively easily. Additionally, some strains have other abilities, such as dampening the host inflammatory response by means of the overproduction of the anti-inflammatory cytokines evading the immune system with the help of flagella [14]. After bloodstream infection, the *Bartonella* genus display sequential tropisms toward endothelial cells and erythrocytes and can persist as intraerythrocytic parasites in the host [15]. Erythrocytes, endothelial cells, and bone marrow have been speculated to be the primary niches in both incidental and reservoir hosts during the nonbacteremic phase of infection [16]. Additionally, *Bartonella* spp. can cause a unique host response, angiogenesis, performed through vascular endothelial growth factor and endothelial cell proliferation [14]. The severity of the clinical picture depends on the immune status of the host and the infecting species. Several virulence factors involved in the pathogenesis may result in an exaggerated or aberrant inflammatory response, contrary to asymptomatic cases.

39.5 Clinical Manifestations

Bartonella henselae infection may be asymptomatic. Host factors such as young age and immune status are critical. The clinical findings highly depend on the immune status of the patient. However, the inoculum size, source of infection, and strain specificity are also related to the clinical presentation and disease severity [17]. Among seropositive participants, 11% reported having an apparent febrile illness and 4.5% lymphadenopathy [17].

Generally, symptomatic patients have a benign and self-limiting clinical course. 4 to 9.6% of patients develop serious manifestations requiring hospital admission [10]. Typically, immunocompetent patients usually present with CSD. The cat-scratch disease generally affects children and young adults, presenting as an acute, benign, and self-limited disease lasting 2–8 weeks. Fever, malaise, fatigue, headache, or sore throat can accompany [17].

39.5.1 Typical Cat-Scratch Disease (Lymphadenopathy)

The "typical" CSD is the most common form. After entrance at the scratch site, in 7–12 days, single or more erythematous papules or nodules appear and may be seen for about a few weeks [18]. In this stage, it is hard to diagnose unless knowing the history or see any sign of cat scratching. Although the lesion generally regresses spontaneously, the infection may progress to tender, warm, erythematous, and indurated lymphadenopathy in 2–4 weeks [5, 19]. Mild constitutional symptoms, such as low-grade fever, loss of appetite, emesis, headache, malaise, and fatigue can accompany [18]. Typically, a solitary lymph node is involved. Axilla is the most common site; the cervical, submandibular, and inguinal nodes follow [5, 18]. The lymphadenitis mostly regresses in 4–6 weeks without any treatment. Suppuration occurs in 20–30% of the patients, sometimes with fistulas to the skin surface. Surgical drainage is required in approximately 10% of cases [20]. Ultrasonographic examination reveals hypoechoic and highly vascularized multiple or solid lymph nodes with increased echogenicity of the surrounding soft tissues. Diagnostic evaluation requires total excision of lymph nodes in prolonged cases and for differential diagnosis. A granulomatous reaction, microabscesses, and local necrosis are determined in histopathological examination of inflamed lymph nodes.

39.5.2 Hepatosplenic Cat-Scratch Disease

Hepatosplenic CSD, which generally accompanies systemic CSD, is one of the rare atypical clinical presentations of CSD. It constitutes less than 10% of the cases, with a tendency to occur mostly in children [21, 22]. Patients experience prolonged fever concomitantly abscesses in the liver and/or spleen. Prolonged fever, abdominal pain, arthralgia, headache, constitutional symptoms, and lesions on abdominal imaging, such as ultrasound, computed tomography (CT), or magnetic resonance (MR) imaging, should raise suspicion in differential diagnoses about hepatosplenic CSD [23]. Fever can last for weeks. Abdominal pain is seen in the periumbilical and/or upper quadrant regions as an episodic dull pain or intermittently [23]. Hepatomegaly without splenomegaly is more frequently seen than hepatosplenomegaly and splenomegaly. Some patients can have lymphadenopathy.

Laboratory examination reveals increased leukocyte and thrombocyte numbers and acute phase reactants. Some patients can experience elevated transaminase levels [22]. On the other hand, patients may not experience organ enlargement or increased transaminase levels. Imaging reveals mostly solitary, sometimes multiple hepatosplenic abscesses with a dimension smaller than 2 cm, so-called microabscesses [22]. The diagnosis can be challenging. In addition to serological tests, a biopsy can help physicians by showing granulomatous lesions in visceral organs [24].

39.5.3 Disseminated Cat-Scratch Disease

Disseminated CSD is also known as systemic CSD. Although immunocompromised children are more prone to this clinical situation, it may also be seen in immunocompetent individuals [25]. Fever, multiple hepatosplenic abscesses, pericardial effusion, and coronary artery dilatation were reported in otherwise healthy children. Cat-scratch disease has been reported as one of the most common reasons for fever of unknown origin, even without a cat exposure history [26]. Children may present with prolonged fever, as in hepatosplenic CSD [23]. Hepatosplenomegaly due to granulomatous lesions in the liver or spleen and increased acute phase response are encountered. Endocarditis is another clinical presentation that may accompany with systemic CSD. Especially, the presence of an existing valvular disease increases the risk of this complication [27]. *Bartonella* spp. is one of the most frequent reasons for endocarditis with negative blood cultures in children [28].

39.5.4 Other Unusual Manifestations of Cat-Scratch Disease

Patients with CSD may present atypical manifestations. The disease can be severe, complicated, and challenging to diagnose, mainly in immunocompromised patients. Atypical presentations may involve skin, eyes, heart, nervous system, liver, spleen, or musculoskeletal system, with a prevalence of 5–20% [29]. The average atypical CSD annual incidence was reported as 0.7 cases per 100,000 population [29]. The atypical CSD has an increased risk than the typical presentation for hospitalization and a propensity for adolescent female patients [30].

One of the most frequent and serious atypical presentations of *Bartonella* spp. infections is neurological manifestations [31]. The incidence is 2% among infected patients. Encephalopathy comprises 90% of these cases, occurring 1–6 weeks after the lymphadenopathy [31]. Central nervous system imaging is generally normal. Cerebrospinal fluid examination reveals normal findings or mild pleocytosis and elevated protein levels. A cat exposure history and determination of anti-*B. henselae* antibodies in serum help in diagnosis. Encephalopathy occurs with or without lymphadenopathy. In the course of the disease, almost always, a complete resolution of symptoms occurs within 1 year [31].

Patients can experience other uncommon neurological involvements such as neuroretinitis, cerebellar ataxia, hemiparesis, myelitis, abductor nerve palsy, and aphasia, generally concomitantly with encephalopathy [31]. Peripheral facial nerve palsy due to reactive granulomatous lesions resulting from the host's immune reaction to *Bartonella* infection is a probable complication [19].

Eye involvement is the most frequent atypical presentation of *Bartonella* spp. infections [29]. Although it is not certain why patients with CSD develop eye pathology, the major histocompatibility human leucocyte antigen (HLA) B27 may predispose patients to this condition [32]. Several proposed mechanisms, such as neuroretinitis, edema, and compression by granuloma, have been accused of ocular involvement in CSD.

Parinaud's oculoglandular syndrome (POGS) is a type of CSD in which unilateral granulomatous follicular palpebral or bulbar conjunctivitis and/or skin infection is seen together with ipsilateral preauricular, cervical, or submandibular lymphadenopathy [33]. A cat bite, contact near or directly into the eye, or the patient's self-inoculation can cause the pathogen's entry. Redness in the eyes, epiphora, and foreign body sensation are common symptoms. Diagnosis may be challenging, as some cases can present without a trauma history or other constitutional symptoms [34]. Fortunately, serious retinal, ocular, orbital complications are not encountered during POGS. However, many other inflammatory ocular conditions, including neuroretinitis, multifocal retinitis, uveitis, optic neuritis, retinal detachment, iridocyclitis, and retinal artery occlusion, may happen during *Bartonella* infections.

The inflammation of the optic nerve and retina, called neuroretinitis, is the most common posterior segment complication of CSD. Severe cases can complicate macular hole development [35]. Multiple superficial retinal infiltrates, known as acute multifocal retinitis, can occur after flu-like symptoms with a low prevalence. Due to ocular involvement, retinal artery occlusion can also be seen with or without neuroretinitis [36]. Retinal and choroidal involvement during CSD is more detrimental than neuroretinitis.

Another uncommon complication of CSD is musculoskeletal manifestations. They are unusual in CSD so the diagnosis can be blinded. Myalgia and/or myositis, arthralgia and/or arthritis, back pain, tendinitis, or osteomyelitis may be encountered [37]. One of the rarest musculoskeletal complications of CSD is osteomyelitis, which mainly affects children and young adults. The mainly affected bones are the vertebrae, pelvic bone, and ribs [38]. Bone pain, inflammatory signs, and symptoms are nonspecific. A physician can suspect CSD if a history of cat scratches or a typical lymph node disease and splenic or hepatic lesion co-exist. Musculoskeletal complications have a favorable prognosis, as mainly reversible and rarely debilitating symptoms are encountered in these patients [39].

Maculopapular rash, erythema nodosum, erythema multiforme, cutaneous vasculitis, urticarial eruptions, and papulo-edematous and purpuric lesions can accompany CSD as dermatological presentations [37]. The histopathologic appearance of cutaneous lesions can be similar to that of lymph nodes, including granuloma formation and a central necrotic area surrounded by lymphocytes and histiocytes [40]. Because host immunity plays a critical role, immunocompetent patients generally have granulomatous and suppurative reactions, while immunocompromised patients present vascular proliferative responses [27]. Vascular proliferative disorders such as bacillary angiomatosis on the skin, subcutaneous tissue, or peliosis in the liver or spleen can be encountered primarily in immunocompromised patients [1]. These lesions present with a verrucous, papular, or plaque-like appearance, which can be misdiagnosed as Kaposi sarcoma in human immunodeficiency virus (HIV)-infected patients. Vasculitis can eventually result in dermal lesions, cerebral infarction, and splenic infarction in children with CSD.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory immune response that results in multiorgan failure and mortality. It

presents with fever, hepatosplenomegaly, lymphadenopathy, neurologic symptoms, and skin rash and is divided into two groups primary and secondary. Secondary HLH is induced mainly by infections, autoimmune diseases, and malignancies. Cases associated with *B. henselae* have also been reported [41–43]. As with other reasons, treatment should include the definitive treatment of CSD and immunosuppressive and chemotherapeutic options.

39.6 Cat-Scratch Disease in Children and Hearing Loss

Hearing loss (HL) is a rare and extraordinary involvement during a *Bartonella* spp. infection. None of the current infectious diseases textbooks and online medical reference sites involving *Bartonella* infections yield any information about the association between CSD and HL [5, 18, 44, 45]. Additionally, case reports or studies presenting neurological involvement of CSD did not have any data about HL [29, 37, 46–49]. In the literature, only in the study of Carithers and Margileth [31] was reported a case with profound HL lasting for 8 months, along with transient hemiplegia, aphasia, and bilateral sixth nerve palsy. Unfortunately, the authors did not give additional details about the course or the patient's prognosis.

39.7 Laboratory Findings and Diagnosis

To be suspicious of CSD is mandatory when a history of cat contact is known. Clinical presentations such as fatigue, insomnia, memory loss, fever of unknown origin, or small vessel disease should consider the presence of *B. henselae* disease. Routine laboratory tests are unremarkable except for occasionally elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Hepatic involvement in disseminated disease can cause an elevation in transaminase levels.

Bartonella species are difficult to culture as they are fastidious. A positive culture requires an enriched medium for growth up to 6 weeks for incubation [50]. Measuring specific IgM and IgG levels with several methods, including indirect immunofluorescence antibody (IFA) and enzyme-linked immunoassay (ELISA) assays, is widely used. However, serological tests alone are insufficient for the diagnosis as low titer *Bartonella* IgG antibodies can be found in approximately 9% of asymptomatic healthy people [37]. These tests show variability in sensitivity and specificity, so they should be interpreted together with compatible clinical findings.

Any positive IgM titer or an IFA IgG titer over 1:256 is diagnostic for an active or recent infection. In contrast, an IFA IgG titer below 1:64 is significant to rule out a current *Bartonella* infection [37]. A seroconversion, a fourfold increment in the IgG titers between acute and convalescent serums, is diagnostic. A negative test result cannot rule out CSD if symptoms are compatible with the disease. Positive titers may not decrease for up to 6 months. Some handicaps can be encountered while interpreting the serological tests. The false-positive result rate is high in the general population. *Bartonella henselae, B. quintana,* and other *Bartonella* spp. can

cross-react, and immunocompromised patients, such as those with HIV infection, can have false-negative test results [37].

The histologic examination of any tissue specimen, such as a lymph node, can give clues for diagnosis. Necrotizing, granulomatous tissue, or microabscesses are seen on tissue samples. A vascular proliferative pattern is found as the infection spreads due to increased immunosuppression or disseminated disease [50]. Warthin–Starry silver impregnation stain can show the microorganism, especially in the early stages of lymphadenopathy [50]. Additionally, molecular detection of bacterial deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) is commonly used. Real-time PCR is a reliable alternative, especially in the acute phase of infection [50]. However, it is not feasible for all *Bartonella* spp. diseases such as eye disease.

39.8 Differential Diagnosis

The differential diagnosis of fever and subacute or chronic lymphadenopathy includes several causes, such as typical bacterial (e.g., *Streptococcus pyogenes* or *Staphylococcus aureus*), mycobacterial (nontuberculous mycobacteria and *Mycobacterium tuberculosis*), and viral (e.g., cytomegalovirus [CMV], Epstein-Barr virus [EBV], HIV) infections, toxoplasmosis, nocardiosis, brucellosis, tularemia, anthrax, histoplasmosis, plague, coccidioidomycosis, and malignancies such as lymphoma.

The differential diagnosis of skin eruptions and regional lymphadenopathy includes fungal infections, leishmaniasis, and nocardiosis.

Cat-scratch disease can also be encountered in transplant recipients [51]. Symptoms compatible with typical CSD or fever of unknown origin necessitate investigation for CSD. In addition, the differential diagnosis of atypical presentations, including vasculoproliferative lesions, bacillary angiomatosis, and peliosis, include pyogenic granuloma and neoplasms, such as Kaposi sarcoma and angiosarcoma.

39.9 Treatment and Prognosis

39.9.1 Lymphadenitis

In most immunocompetent patients, typical CSD presents as self-limited lymphadenopathy, which resolves spontaneously in 2–4 months, with supportive treatment, without any antibiotics [5, 18, 44]. Aspiration of purulent material can relieve symptoms of painful suppurative lymph nodes. Excisional biopsy for chronic lymphadenopathies can be preferred to rule out other causes.

However, some authors suggest treating even mild-to-moderate cases with antibiotics to shorten the duration of symptoms and prevent complications [44]. As *Bartonella* spp. require several weeks to yield visible growth, and currently, there

are no standardized susceptibility testing methods as there is contradiction between in vivo and in vitro susceptibilities [18]. In vitro susceptibility tests show that *Bartonella* spp. are susceptible to macrolides (clarithromycin and azithromycin), tetracyclines, rifampin, ciprofloxacin, and aminoglycosides [5, 18, 32]. There is a lack of controlled studies concerning the treatment of CSD. Azithromycin (12 mg/kg/day, maximum 500 mg/day, once a day, per oral) for 5 days, clarithromycin (15 mg/kg/day, in 2 divided doses, maximum 500 mg/dose, per oral), rifampin (20 mg/kg/day, in 2 divided doses, maximum 300 mg/dose, per oral), or trimethoprim–sulfamethoxazole (8–10 mg/kg/day based on trimethoprim component, in 2 divided doses, maximum 160 mg trimethoprim/dose, per oral) for 7–10 days are suggested for the initial options [44, 52].

39.9.2 Disseminated and Hepatosplenic Cat-Scratch Disease

As in typical CSD, well-designed, prospective, randomized, and controlled studies evaluating antibiotic treatment for the disseminated or hepatosplenic CSD do not exist [23, 44]. A delay in diagnosis and immunosuppressive conditions, such as primary or secondary immunodeficiencies, may result in a progression and complicated disease. Rifampin (20 mg/kg/day, in 2 divided doses, maximum 300 mg/dose, per oral) alone or with either azithromycin (12 mg/kg/day, maximum 500 mg/day, once a day, per oral) or gentamicin (5–7.5 mg/kg/day, in 2–3 divided doses) can be preferred [5, 18, 44]. Trimethoprim–sulfamethoxazole plus rifampin plus gentamicin can also be used [5, 18, 44]. The duration of the treatment is generally 14 days.

The patient can be followed-up using CRP and ESR levels and clinical response, as it is not helpful to follow the antibody titers. In severe cases, corticosteroids can be added to alleviate symptoms. No additional imaging is necessary if the patient recovers completely.

39.9.3 Neurological and Ocular Involvement

The cases with neurological and ocular involvement are expected to be more complicated. There is a debate about the choice of antibiotic treatment and dose and duration because even some CSD-associated neuroretinitis cases were reported to gain spontaneous visual recovery [53].

In the literature, no antibiotic treatment, combination antibiotic treatment (doxycycline plus rifampin or ciprofloxacin), steroids plus antibiotics, or steroids alone were reported as the treatment options retrieved mostly from case reports or case series, in which an evident superiority over the others was able to be shown [53, 54]. However, treatment with antibiotics and corticosteroids was associated with better visual acuity outcomes [55]. Doxycycline plus rifampin or "rifampin plus azithromycin or trimethoprim–sulfamethoxazole" can be used for 4–6 weeks in patients with neuroretinitis 10–14 days in patients with Parinaud's oculoglandular disease or other neurologic involvements such as encephalitis [32].

Adjunctive prednisolone is generally recommended for patients with neuroretinitis [32].

39.10 Prognosis

Generally, a sequela is not experienced in patients with CSD. Antibiotics are usually effective even for complicated and invasive forms of the disease, although prolonged courses are needed. *Bartonella* spp. have been reported as a bacterial cause of encephalitis and resultant convulsions, even in immunocompetent individuals [56]. Encephalopathy, a most serious complication of CSD, occurs 1–6 weeks after the onset of lymphadenopathy in 5% of patients [18]. Luckily, the clinical survey is good, with improvement rapidly and spontaneously. Relapses can be seen primarily in immunocompromised patients [31, 45].

39.11 Prevention

Abstaining from touching cats, especially for immunosuppressed patients, is a simple control method to prevent infections with *B. henselae.* Also, arthropod control and routine veterinary visits for pets to control flea or tick infestations are necessary. Washing the wound resulting from a cat scratch, bite, or lick can be preventive. Antibiotics are not recommended for pet cats as they cannot eliminate bacteremia [57]. Additionally, if all precautions are taken properly, there is no need to remove the cats even from the house of immunocompromised patients [57]. Unfortunately, there is still an effective vaccine not available.

39.12 Conclusion

Cat-scratch disease is endemic all over the world. People get infected with the causative agent *B. henselae* through scratches from domestic or wild cats. The CSD is usually mild, presenting with lymphadenopathy and little or no accompanying symptoms. Caregivers and physicians generally neglect CSD. However, some patients may suffer atypical and more complicated presentations, such as CNS, skin, bone, heart, or eye involvement.

Hearing loss is an infrequent complication of CSD. Hearing loss was reported in only one patient in the literature [31]. Unfortunately, neither the course nor the prognosis of the patient has been known.

Cat-scratch disease can resolve spontaneously in 2–4 months in most immunocompetent patients. However, antibiotics such as azithromycin, clarithromycin, doxycycline, rifampicin, ciprofloxacin, and aminoglycosides can positively affect the clinical course of the disease. The disease and most of its complications improve without a prominent sequela generally.

Bartonella infections have a broad spectrum of the clinical picture and associated complications, so physicians should keep CSD in mind while evaluating the differential diagnoses of idiopathic conditions.

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Bordetella Pertussis Infection and Hearing Loss

40

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40.1 Introduction

Pertussis, also known as whooping cough, is an acute respiratory disease. The most common causative agent is *Bordetella pertussis*, and less frequently, other types of *Bordetella* may cause similar clinical manifestations and course. The first pertussis epidemic was reported in France by Guillaume de Baillou, and the illness was popularly called "Quinta" or "Quintana." Baillou provided the first detailed clinical

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description of a whooping cough epidemic that occurred in 1578 [1]. Although pertussis affects all age groups, it has a more severe course in children, especially in unvaccinated individuals and infants. Vaccination is the most effective way to prevent pertussis. After whole-cell vaccines were introduced in 1940, the number of pertussis cases decreased. The acellular pertussis vaccine is more commonly used today. *Bordetella pertussis* infection in infants should initially be prevented by vaccination during pregnancy and cocoon strategy. The data on hearing loss (HL) associated with *B. pertussis* are limited.

40.2 Etiology

Currently, 10 species are known in the genus *Bordetella,* which belongs to the family of Alcaligenaceae. While *B. pertussis* is the primary pathogen causing pertussis, *Bordetella parapertussis, Bordetella bronchiseptica,* and *Bordetella holmesii* are the other species that cause a milder clinical disease similar to pertussis. *Bordetella holmesii* may cause bacteremia, endocarditis, septic arthritis, and pertussis-like symptoms and signs [2, 3].

Bordetella pertussis is a gram-negative, motile, aerobic coccobacillus. Humans are the only known host for *B. pertussis*. It is catalase-positive and oxidizes amino acids but does not ferment carbohydrates. The optimum growth temperature is 35–37 °C. Culture is the gold standard for pertussis diagnosis, and a nasopharyngeal sample should be inoculated on a suitable medium such as Bordet–Gengau or Regan–Lowe agar. Culture positivity may vary according to appropriate nasopharyngeal sample collection, stage of the disease, vaccination, and antibiotic use of the patient. Since it contains glycerol, peptones, and horse or sheep blood, *B. pertussis* grows more easily in the Regan–Lowe medium than in the Bordet–Gengau agar [2–4].

Bordetella pertussis contains antigenic and biologically active components. The main ones are filamentous hemagglutinin (FHA), fimbriae (FIM), pertactin, agglutinogens, pertussis toxin (PT), adenylate cyclase toxin (ACT), tracheal cytotoxin (TCT), and dermonecrotic toxin (DNT). Fimbriae and FHA are the two most important adhesins in determining the virulence of *B. pertussis*. So they are also highly immunogenic components of the acellular pertussis (aP) vaccine. Pertactin and PT are other virulence factors responsible for adhesion. Pertussis toxin also prevents neutrophils and macrophages from reaching the respiratory tract mucosa. Adenylate cyclase is another toxin that contributes to the ability of *B. pertussis* to escape host defense by inhibiting neutrophil migration and activation; it also inhibits T-cell activation and chemotaxis [5, 6].

Bordetella pertussis infection, which initially leads to hyperplasia in peribronchial and tracheobronchial lymph nodes, causes necrosis and desquamation in bronchial epithelial cell cilia with tracheal cytotoxin and dermonecrotic toxin [7–9]. Systemic side effects are rare in pertussis. The most common laboratory findings of systemic effects are leukocytosis and lymphocytosis caused by PT. In addition, central nervous system (CNS) involvement and encephalopathy secondary to overexpression of monocyte chemoattractant protein-1 (MCP-1), thought to be due to the

PT effect, have been reported. Less frequently, *B. pertussis* causes pulmonary vasoconstriction, increased vascular resistance due to leukocytosis, pulmonary hypertension, hypoxemia, and hypoglycemia secondary to hyperinsulinism due to pancreatic beta-islet cell stimulation [4, 5, 10].

40.3 Epidemiology and Transmission

Pertussis is one of the common childhood diseases, especially in areas where vaccination is unavailable, or the immunization rates are low. So cases may be seen throughout the year, and pertussis can result in death. But, more often, epidemics occur in late summer and autumn in cyclic periods, usually every 3–5 years. This cyclic period and seasonal feature may not be seen in the areas with high vaccinated rates. However, having pertussis disease or being vaccinated does not provide lifelong immunity.

Bordetella pertussis is transmitted from person to person by respiratory droplets caused by coughing, less frequently by sneezing, and by spending a long time in the same closed environment. It can also be transmitted through hands or the environment contaminated with the respiratory secretions of a sick person. Pertussis is a highly contagious disease; one sick person (R0) can infect up to 12–17 people. In the household setting, the attack rate in susceptible persons can reach 70–100%. An individual infected with *B. pertussis* is most contagious in the catarrhal and early paroxysmal stages [2, 11, 12]. In particular, *B. pertussis* is transmitted to infants from older siblings, parents, or caregivers with mild clinical symptoms or asymptomatic [2, 11, 12].

Pertussis is seen worldwide and is more common in girls, American Indians, Alaskan Natives, Hispanics, and Caucasians [13]. In the pre-vaccine period, pertussis was seen more frequently in the 1–10 year age group and caused more deaths than scarlet fever, measles, and poliomyelitis in those younger than 1 year [14, 15]. After using the whole-cell vaccine, the case numbers decreased significantly, and the age range of the disease changed. After introducing pertussis vaccines in the United States of America (USA) in the 1940s, annual cases have dropped from over 100,000 to 10,000 [11]. The annual number of cases reported in 2019 was approximately 18,000 [11]. Children younger than 1 year are the age group with the highest annual incidence/100,000. In vaccinated areas, pertussis incidence and the death rate due to pertussis are most common in infants younger than 1 year and 3 months, respectively [16].

The European Centre for Disease Prevention and Control (ECDC) pertussis surveillance report includes data from 30 European countries from 2014 to 2018 [17]. Within the scope of this report, 35,627 cases were detected in 2018, the lowest number of cases in the previous 5 years reported by 30 European countries. Seventy-two percent of these cases were reported by Germany, the Netherlands, Norway, Spain, and the United Kingdom (UK) [17].

While pertussis still severely affects children younger than 6 months, there has been an increase in infection rates in adolescents and adults over the past decade.

Sixty-two percent of pertussis cases reported in 30 European Union/European Economic Area (EU/EEA) countries in 2018 were over 14 years; 54% of reported pertussis cases in the USA were over the age of 11 years. Adolescents and adults with undiagnosed pertussis are an important reservoir for infection in infants and children [17].

According to the World Health Organization (WHO) data, approximately 81% (105 million) of infants worldwide received 3 doses of the diphtheria–tetanus–pertussis (DTP3) vaccine in 2021 [18]. In 2021, 18.2 million infants did not receive the DTP vaccine, and 6.8 million were partially vaccinated. Of the 25 million, more than 60% of these infants live in 10 countries: Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Myanmar, Nigeria, Pakistan, and the Philippines [18]. Although the global target is to achieve at least 80% DTP3 vaccine in every district of the world, this is still not reached [2, 11, 16, 18]. Infants younger than 6 months or unvaccinated and people aged >65 years are the groups with high morbidity and mortality for pertussis disease. Adolescents and adults with underlying diseases such as asthma and chronic obstructive pulmonary disease also are at increased risk for severe pertussis [19, 20].

40.4 Pathogenesis, Immunity, and Pathology

After *B. pertussis* enters the body via respiratory droplets, it secretes many active biological components. *Bordetella pertussis* attaches to the upper respiratory tract and tracheal ciliated epithelium, and then, local tissue damage and systemic disease occur [14]. Pertussis infection begins by *B. pertussis* attaching to the ciliated epithelium of the respiratory tract with adhesins such as FIM, lipopolysaccharide (LPS), and PT. Fimbria, one of the adhesin proteins, is thought to affect pathogenesis because *B. pertussis* colonization is not seen in the respiratory tract epithelium in people with antibodies to FIM [5, 11, 21]. Pertussis toxin stimulates leukocytosis and causes pulmonary hypertension due to obstruction in the pulmonary arteries. While PT prevents the migration of macrophages and lymphocytes to the infection site and intracellular killing, ACT also prevents phagocytosis. Tracheal cytotoxin and DNT cause local damage to the respiratory tract mucosa. The virulence determinants and their impacts are shown in Table 40.1 [2, 3, 5, 14, 22].

Data on pertussis pathology are limited. In the study by Paddock et al. [22], necrotizing bronchiolitis, intraalveolar hemorrhage, and fibrinous edema were found in the histopathological examination of the materials of 15 infants younger than 4 months who died due to pertussis. In addition, leukocyte clusters were detected in the pulmonary arteries and lymphatic vessels, and *B. pertussis* was detected extracellularly in the trachea, main bronchi, bronchiolar cilia, bronchial epithelium, and intracellularly in the alveolar macrophages by immunohistochemical staining. Cranial and hepatic involvement may occur due to anoxic damage. Cortical atrophy and cerebral hemorrhage may also be seen.

Table 40.1 Biologically active and antigenic components of *Bordetella pertussis* have a role in human infection or disease[a]

Component	Characteristics
Pertussis toxin (PT)	A classic bacterial toxin with an enzymatically active A subunit and a B oligomer-binding protein; effects in an animal model system include histamine sensitization, promotion of lymphocytosis, stimulation of insulin secretion, and adjuvant and mitogenic activity; the envelope protein is also an important adhesin; it adversely affects host immune cell function
Adenylate cyclase toxin (ACT)	Calmodulin-activated RTX family toxin with dual adenylate cyclase and hemolysin activity[b]; acts as an antiphagocytic factor during infection
Fimbriae (FIMs)	Serologic types 2 and 3; antibody to specific types causes agglutination of the organism; organisms may contain FIM 2, FIM 3, FIMs 2 and 3, or neither form
Filamentous hemagglutinin (FHA)	220-kd surface-associated and secreted protein; highly immunogenic
Lipopolysaccharide (LPS)	An enveloped toxin with activities similar to endotoxins of other gram-negative bacteria; a significant cause of reactions to whole-cell pertussis vaccines; antibody to LPS causes agglutination of the organism
Autotransporters	
Pertactin (PRN)	69-kd outer-membrane protein that allows the organism to resist neutrophil-mediated clearance; antibody to pertactin causes agglutination of the organism
Vag8	95-kd outer-membrane protein
BrkA	73-kd surface-associated N-terminal passenger domain with 30-kd outer-membrane C-terminal protein; confers serum resistance and protection against antimicrobial peptides in *B. pertussis*
SphB1	Subtilisin-like Ser protease or lipoprotein required for FHA maturation
Tracheal colonization factor (i.e., *tcfA* gene product)	60-kd secreted protein

kd indicates kilodalton

[a]Adopted and modified from Ref. [1, 2, 4, 6, 17]

[b]RTX family: A toxin superfamily is a group of cytolysins and cytotoxins produced by bacteria. The name RTX (repeats in toxin) refers to the glycine- and aspartate-rich repeats at the C-terminus that facilitate toxin export

40.5 Clinical Manifestations

The incubation period is often 7–10 days (range: 5–21 days) [2, 11]. The patient's clinical status varies according to age, vaccination status, whether or not they had pertussis previously, and the underlying disease. The classical pertussis consists of three phases; catarrhal, paroxysmal, and convalescent. While classical disease findings are seen in unvaccinated children under 10 years of age, the clinical picture may be atypical in adolescents, adults, and vaccinated individuals. Paroxysmal

cough, inspiratory whooping, and posttussive vomiting are the most common findings of pertussis disease [5, 6].

At the end of the incubation period, the catarrhal stage begins with a serous nasal discharge and cough gradually increasing. Fever is usually absent or in subfebrile degrees. The catarrhal stage usually lasts 1–2 weeks [2, 3, 5, 12].

In the paroxysmal stage, cough gradually increases in frequency and severity, and coughing attacks with breathing efforts begin to develop. The cough is dry and repetitive. Coughs occur 5–10 times or more in succession. Cough attacks may start spontaneously or with external stimuli, and cyanosis may occur during and after coughing. These paroxysms are associated with the accumulation of thick and viscous mucus plugs in the airways and are not related to the production of purulent sputum. Attacks may end with the expulsion of thick and viscous mucus plugs. Complications often occur during coughing attacks. Attacks are usually more frequent and severe at night. Along with the coughing spells, sweating, the prominence of protruding eyes, lacrimation, outthrust of the tongue, salivation, and the appearance of petechiae on the face are seen in children [3–5]. The paroxysmal stage lasts up to 2–8 weeks. Especially in the first 2 weeks of this stage, the cough gradually increases, continues for 2–3 weeks in a similar severity, and begins to decrease in the following weeks.

Whooping occurs secondary to forced inspiration during coughing attacks at a rate of 79% in unvaccinated children, while it is between 22 and 44% in vaccinated children and is common under 1 year of age [14, 23]. In studies, specificity of posttussive vomiting under 12 years of age was determined as 66% and sensitivity as 60% for pertussis [24]. Although the cough gradually decreases in the convalescent stage, it lasts longer than 4 weeks and may extend up to 112 days [25]. Increased cough attacks may be observed secondary to upper respiratory tract infections [2, 3, 5].

Atypical clinical presentations are related to the patient's age and vaccination status. The pertussis disease is milder in vaccinated individuals. The catarrhal phase may be short or asymptomatic in children younger than 4 months. In the paroxysmal stage, the cough may not be paroxysmal. There may be vomiting, cyanosis, swelling of the eyes, and bradycardia. Also, apnea, seizure, respiratory distress, pneumonia, pulmonary hypertension, hypotension, shock, renal failure, and death may occur.

Distinguishing pertussis from other respiratory diseases in infants may be challenging, but its early recognition reduces morbidity and mortality. In one study, paroxysmal cough, vomiting after coughing, prolonged coughing, apnea, cyanosis, seizures, leukocytosis, and lymphocytosis were more common in pertussis than in other upper respiratory tract infections [26].

Adolescent and adult patients have a milder clinical picture than infants. In older children, pertussis-related prolonged cough is the most common clinical manifestation. Sometimes, the only symptom in adolescents and adults may be a prolonged cough, and classical findings such as paroxysmal character, whooping, and vomiting after coughing may not be seen. Other findings may include episodes of expectoration, nonspecific upper respiratory infection symptoms, sore

throat, and sweating. Patients with wheezing have been reported. It should be kept in mind that pertussis may occur in adults when a cough lasts longer than 2 weeks [27].

40.6 Complications

Complications are more common in infants. Apnea, pneumonia, weight loss due to feeding difficulties, posttussive vomiting, seizures, encephalopathy, pneumothorax, epistaxis, subconjunctival hemorrhage, rectal prolapse, rib fractures, urinary incontinence, subdural hematoma, intracranial hemorrhage, and death may occur. Apnea is more common in patients younger than 6 months and may start spontaneously or after coughing. Sometimes, apnea may be the only sign of pertussis in infants. Primary *B. pertussis* pneumonia may be associated with leukocytosis (>60,000 white blood cells/mm^3), pulmonary hypertension, and mortality in infants. Tachypnea, fever, increased breathing between paroxysms, and absolute neutrophilia are signs of secondary bacterial pneumonia. Pulmonary hypertension leads to the dilation of the right ventricle and respiratory failure in young infants, a usually fatal complication of pertussis. A chest radiograph is generally normal or nonspecific findings of atelectasis, and perihilar infiltration may be seen in the uncomplicated disease. The relationship between pertussis and sudden infant death syndrome is also known [2, 3, 5, 19, 28].

40.7 Bordetella Pertussis Infection and Hearing Loss

Hearing may be affected by congenital or acquired infections in children. The literature has limited data on the relationship between *B. pertussis* and HL. Catlin et al. [29] reviewed HL related to infections. The pertussis-related data in this article were based on the National Census of Deaf Persons (NCDP) report of the National Association of the Deaf in 1971. In the NCDP report, 28% of all causes of HL were a result of an infection, including meningitis (9.7%), rubella (5.2%), scarlet fever (6.2%), measles (4.3%), and pertussis (2.6%) [30].

In the following years, few reports of HL associated with pertussis were published. In the study of Williams et al. [31], examining the epidemic in the borders of West Glamorgan between 1977 and 1979, HL was reported as a complication in 5 of 2295 patients with clinical whooping cough. Pearson et al. [32] screened adults aged 61–63 years in 1000 families to evaluate whether childhood infections at an early age are a preventable risk factor for HL detected in adulthood. Childhood infection records from birth up to their fifth year of life of 296 patients followed up and audiometrically measured within the scope of this study were accessed; 136 (46%) of them had pertussis in childhood. It was found that those with tonsillitis, bronchitis, ear discharge, or at least two severe respiratory tract infections had more HL. Still, no increase in HL was detected due to a bacterial or viral factor such as pertussis.

The aim of the study by Schubert et al. [33] under the title of "diphtheria and hearing loss" was to evaluate the relationship between HL due to infections. Schubert et al. evaluated whether the HL developed due to inflammation after viral or bacterial infections, primarily diphtheria, pertussis, meningitis, and toxin-related inflammation. In the study, 3753 adults were assessed, and no correlation was found between pertussis and HL [33].

The literature search through the internet and PubMed did not reveal an additional study or case report regarding pertussis-related HL, except for the above-mentioned reports [29–33]. On the other side, in only one of the leading textbooks of infectious diseases, deafness has been mentioned as a complication of pertussis, without a reference [2]. Apart from this, none of the other current infectious disease textbooks or Uptodate® present any information about pertussis-related HL [3, 5, 6, 12, 34, 35].

Related to this context, in a study planned concerning vaccine-related HL after a case that developed tinnitus and HL on the sixth day after the trivalent inactivated influenza vaccine, post-vaccine HL was evaluated between 2007 and 2013 [36]. A total of >20 million vaccinations were administered in the group, and sensorineural HL (SNHL) was evaluated after vaccination. The acellular pertussis vaccine was also assessed in the study, and no association was found between HL and vaccination [36].

Macrolides, including erythromycin, azithromycin, and clarithromycin, generally used for pertussis treatment, are ototoxic [37]. Therefore, HL may be indirectly associated with these antibiotics used in the treatment rather than pertussis. A systematic review examining the relationship between macrolides and SNHL emphasized that even oral forms at standard doses can cause SNHL [38]. However, in a recent meta-analysis, Alsowaida et al. [39] concluded that although the frequency of SNHL was higher in people who have received macrolides compared with controls, overall, no relationship was found between macrolide antibiotics and SNHL.

40.8 Differential Diagnosis

Bordetella parapertussis, B. bronchiseptica, and *B. holmesii* are other *Bordetella* species that can cause paroxysmal cough. *Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia pneumoniae,* and *Mycobacterium tuberculosis* are other bacterial agents that cause prolonged cough and whooping cough-like clinical picture. Among the viral agents, respiratory syncytial virus, adenovirus, parainfluenza viruses, influenza A and B viruses, rhinovirus, and human metapneumovirus can cause whooping cough. Pertussis can also be confused with foreign body aspiration, reactive airway disease, gastroesophageal reflux, aspiration pneumonia, and allergic or infectious sinusitis. Pertussis may also present similar clinical manifestations to other respiratory tract infection agents. *Bordetella pertussis* co-infections with other agents may occur. And less frequently, *B. pertussis* is detected in patients hospitalized for bronchiolitis. Smoking and

angiotensin-converting enzyme inhibitors, especially in adolescents and adults, may also cause paroxysmal cough [2, 3, 5, 40–42].

40.9 Diagnosis and Laboratory Findings

The non-specificity of the early signs of pertussis and the difficulty of clinical diagnosis in vaccinated and older children make the early diagnosis of the disease challenging. The presence of classical findings such as paroxysmal cough, whooping, posttussive vomiting, normal findings on physical examination, and absence of other symptoms, including fever, rash, or myalgia, suggest the diagnosis of pertussis.

Diagnosing pertussis is generally based on a clinical and laboratory combination. More often, in the first 3 weeks of coughing, samples taken from the nasopharynx with calcium alginate or Dacron swabs are added to Regan–Lowe or Bordet–Gengou agar or modified Stainer–Scholte broth within 7–10 days, and growth occurs with high specificity in patients who have not taken antibiotics. In addition, molecular tests and serology can also be used for pertussis diagnosis. Nucleic acid amplification tests such as polymerase chain reaction (PCR) are widely used because they give rapid results, have higher sensitivity than culture, and are not affected by antibiotic use.

Immunoglobulin (Ig) A and IgG against PT is the preferred serological test with the highest sensitivity and specificity. An increase in antibody titers measured at 2-week intervals or the first high value of antibody titers supports pertussis diagnosis. Immunoglobulin G antibody against PT, the most standardized serological test, becomes positive in the middle of the paroxysmal phase, showing a previous infection as a value >90–100 IU/mL. Serological tests should not be applied in patients vaccinated against pertussis within the last year because vaccine-induced IgG may cause false-positive results [2, 5, 43].

The Centers for Disease Control and Prevention (CDC) has established a standard case definition for monitoring pertussis surveillance set for public health reports and is not intended to determine clinical diagnosis or treatment. Probable or definitive case definitions are made using clinical, laboratory, and epidemiological data (Table 40.2) [2, 3, 5, 11].

40.10 Treatment

Antimicrobial therapy is necessary for the treatment and eradication of *B. pertussis*. It is thought to be more effective on clinical response when antibiotic treatment is initiated in the catarrhal or early paroxysmal stage. However, a Cochrane analysis concluded that antimicrobial therapy does not affect the clinical response, particularly when treatment started in the paroxysmal stage [2, 3, 5, 44, 45]. However, antimicrobial therapy started in the early period reduces the contagiousness even though it does not affect the disease's clinical course [2, 5].

Table 40.2 Centers for Disease Control and Prevention (CDC) case definition for pertussis, 2020[a]

Clinical criteria In the absence of a more likely diagnosis, a cough illness lasting ≥2 weeks, with at least one of the following signs or symptoms:
• Paroxysms of coughing, OR • Inspiratory whoop, OR • Posttussive vomiting, OR • Apnea (with or without cyanosis)
Laboratory criteria Confirmatory laboratory evidence:
• *Isolation of Bordetella pertussis from a clinical specimen* • Positive polymerase chain reaction (PCR) for *B. pertussis*
Epidemiologic linkage Contact with a laboratory-confirmed case of pertussis
Case classification
Probable: • In the absence of a more likely diagnosis, an illness meeting the clinical criteria **OR** • Illness with cough of any duration, with • At least one of the following signs or symptoms: – Paroxysms of coughing, OR – Inspiratory whoop, OR – Posttussive vomiting, OR – Apnea (with or without cyanosis) **AND** • Contact with a laboratory-confirmed case (epidemiologic linkage)
Confirmed: Acute cough illness of any duration with • Isolation of *B. pertussis* from a clinical specimen, **OR** • PCR positive for *B. pertussis*

[a]Adopted from Ref. [2, 3, 5, 11]

A reasonable guideline is to treat persons older than 1 year within 3 weeks of cough onset, infants younger than 1 year, and pregnant women, especially near term within 6 weeks of cough onset [11].

If pertussis is suspected, especially in infants younger than 4 months, treatment should be started without delay and followed up by hospitalization. Traditionally, erythromycin for 14 day was the first drug recommended for treating pertussis. However, using other macrolides, such as azithromycin and clarithromycin, has come to the fore because erythromycin causes drug interactions in adults and hypertrophic pyloric stenosis in infants younger than 1 month, and gastrointestinal side effects. Studies have shown that azithromycin and clarithromycin are more effective in nasopharyngeal eradication of *B. pertussis* with shorter-term use than erythromycin. Trimethoprim-sulfamethoxazole and fluoroquinolones are also used in treatment. However, strains resistant to fluoroquinolones have been identified. Drugs used in patients with pertussis are shown in Table 40.3 [2, 5, 44, 46].

Table 40.3 Recommended oral antimicrobial treatment and postexposure prophylaxis for pertussis by age group[a]

Age group	Primary agents			Alternate agents
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX
<1 month	Recommended drug; 10 mg/kg/day in a single dose for 5 days	Not preferred; Use if azithromycin is unavailable; 40 mg/kg/day in 4 divided doses for 14 days	Not recommended	Contraindicated for infants aged <2 months (risk for kernicterus)
1 through 5 months	10 mg/kg/day in a single dose for 5 days	Not preferred; Use if azithromycin or clarithromycin is unavailable; 40 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated for infants aged <2 months; for ≥2 months, TMP 8 mg/kg/day (SMX 40 mg/kg/day), in 2 divided doses for 14 days
Aged ≥6 months	10 mg/kg on day 1 (maximum 500 mg), then 5 mg/kg/day (maximum 250 mg) on days 2 through 5, in a single dose	40 mg/kg/day in 4 divided doses for 7–14 days (maximum 2 g/day)	15 mg/kg/day in 2 divided doses for 7 days (maximum 1 g/day)	TMP 8 mg/kg/day (SMX 40 mg/kg/day) in 2 divided doses for 14 days (maximum TMP 320 mg/day, and SMX 1600 mg/day)
Adults	500 mg on day 1, then 250 mg/day on days 2 through 5, in a single döşe	2 g (base)/day in 4 divided doses for 7–14 days	1 g per day in 2 divided doses for 7 days	TMP 320 mg, and SMX 1600 mg/day, in 2 divided doses for 14 days

TMP-SMX indicates trimethoprim-sulfamethoxazole (cotrimoxazole)
aAdopted and modified from Ref. [1, 6, 7, 35]

Due to ineffectiveness, ampicillin, cephalosporins, and tetracyclines are not recommended for treating or providing prophylaxis for *B. pertussis* infection. Since *B. pertussis* is frequently detected by molecular methods, antibiograms are not performed routinely, and no results support an increase in macrolide resistance. There are reports of quinolone resistance and sporadic case reports of macrolide resistance from some countries [5, 46–48].

It is important in treating pertussis to avoid triggers that provoke coughing attacks and have adequate nutrition and fluid support. Oxygen support should be provided to patients with respiratory distress and pneumonia. In severe cases, mechanical ventilator support, pulmonary artery vasodilators, and extracorporeal membrane oxygenation (ECMO) support may be required. Exchange transfusion may be needed in cases with hyperleukocytosis due to higher mortality. Among other treatments, corticosteroids, antihistamines, antitussives, and salbutamol are thought to have no significant effect in the treatment of pertussis [2, 5, 43, 49].

40.11 Prognosis

The prognosis of pertussis is related to the severity of the disease, the patient's age, and vaccination status. Considering the rate of infants hospitalized because of pertussis in pediatric intensive care units (PICUs), it was reported that 41.8% were younger than 6 weeks and unvaccinated, 46.7% were between 6 weeks and 6 months and partially vaccinated, and 11.5% were fully vaccinated patients over 6 months old [50]. Maternal vaccination protects the infant from pertussis at a high rate in the first 2 months of life [51, 52]. Morbidity and mortality are particularly higher in neonates and infants, also related to vaccination rates.

Serious complications such as apnea, pneumonia with leukocytosis, pulmonary hypertension, seizures, encephalopathy, pneumothorax, and subdural hematoma may be seen in unvaccinated and young children and determine the prognosis [2, 5]. Leukocytosis, concurrent viral infection, and severe pulmonary hypertension are poor prognostic factors in patients followed up in the PICU with the diagnosis of pertussis [53]. Infants requiring mechanical ventilation because of respiratory failure have a worse prognosis than those needing mechanical ventilation because of apnea [54].

In children who develop seizures and encephalopathy, neurological problems such as subsequent intellectual impairment may occur in the future [2, 55].

More widespread vaccination, improved healthcare conditions, better access to health facilities, and availability of PICUs and mechanical ventilation have reduced infant mortality rates. No evidence suggests that people with pertussis have impaired respiratory function later in life [5].

40.12 Prevention and Control

Immunization is the most effective and only tool for preventing pertussis. Although acquiring pertussis naturally produces antibodies, it is unclear how long the protection lasts. The American Academy of Pediatrics (AAP) recommends completing the vaccination with tetanus, diphtheria, and acellular pertussis (TDaP) combination vaccine for children younger than 7 years, or tetanus, adult diphtheria, and adult acellular pertussis (Tdap) combination vaccine for children 7 years and older, adolescents, and adults, even in case of pertussis [12].

The vaccine against pertussis was first developed with the whole cell of *B. pertussis*. Whole-cell pertussis (P) vaccine was first used in 1940. In the following years, cases of encephalopathy, coma, and death were reported related to the whole-cell pertussis vaccine [56–58]. The British Medical Research Council investigated the protection of pertussis vaccines by testing different vaccines in the 1940s and 1950s [59]. The National Childhood Encephalopathy Study emphasized that the risk of neurological involvement with tetanus, diphtheria, and whole-cell pertussis (DTP) vaccine was very low [60]. In another study conducted in Canada between 1993 and 2002, no evidence of vaccine-related neurologic involvement was reported [61].

Centers for Disease Control and Prevention 1978–1981 data reported that post-vaccine adverse events were rarer than complications after primary pertussis infection. In general, after the pertussis vaccine became widespread after 1940, complications decreased with the reduction of the disease [29]. However, because of the reactogenicity of whole-cell pertussis vaccines, acellular pertussis (aP) vaccine studies were started [62]. In 1997, the whole-cell pertussis vaccine was started to be replaced by acellular pertussis vaccines in several countries. The acellular pertussis vaccines contain antigens such as inactivated PT, filamentous hemagglutinin, fimbrial proteins, and pertactin. Acellular pertussis vaccines are also protective against *B. parapertussis*. Although whole-cell pertussis vaccines have more extended protection, acellular pertussis vaccines are preferred because of the side effects of the whole-cell vaccine. Whole-cell vaccines stimulate cellular immune response via T helper (Th)-1 and Th-17, while acellular vaccines stimulate cellular response via Th-2 [2, 3].

Although vaccination with TDaP can be started at 6 weeks, the recommended application is at 2, 4, 6, and 15–18 months of age. The fifth dose is recommended in the preschool period at 4–6 years. There should be a minimum of 4 weeks between the first 3 doses and 6 months between the third and fourth doses. A booster dose of Tdap is recommended in adolescents 11–12 years of age. Due to the high amount of PT in DTaP, it should not be applied to children over 7 years old; the Tdap vaccine should be preferred. If Tdap is given to children younger than 7 years old as the first 3 doses, it should be considered invalid, and revaccination with TDaP should be started. If 4 and 5 doses were given as Tdap, there is no need for a repeat. A single dose of Tdap should be administered to children over 7 years of age who have not completed or are not known to have completed their primary immunization. However, Td may be used if necessary for tetanus or diphtheria. Until the age of 7 years, tetanus and diphtheria vaccine doses should not exceed 6 [2, 3, 12].

Post-DTaP reactions begin a few hours after vaccination and generally resolve within 48 hours. Most commonly, there may be redness, swelling, induration, and numbness at the injection site. Restlessness, vomiting, loss of appetite, crying attacks, and subfebrile fever may be seen. Prolonged crying (≥3 h), seizure, hypotonic–hyporesponsive episode, and temperature of 40.5 °C (104.8 °F) rarely have been reported after DTaP. Contraindications for DTaP are severe allergic reactions and unexplained encephalopathies within 7 days after vaccination [2, 3, 5, 6, 12].

Pertussis-related severe illness and death often occur in the first few months of life. Therefore, cocoon and pregnancy vaccination strategies have been developed to prevent the transmission of *B. pertussis* to infants. Parents are known to be significant sources of infection for infants, and vaccination of household members is recommended to protect unvaccinated infants. The cocoon strategy aims to reduce the risk of family members acquiring pertussis to protect infants, especially unvaccinated children younger than 6 months, aiming to vaccinate people who will have close contact with infants under 12 months of age at least 2 weeks before contact [2, 3, 12, 63].

In a study of the cocoon strategy in 0 to 3-month-old infants, there was a 70% reduction in pertussis cases [64]. Another study in Austria reported that the risk of

pertussis was reduced by 51% in infants younger than 4 months whose parents were vaccinated [65]. In another study by Kılıç et al. [66], 405 mothers were informed of the cocoon strategy, and the Tdap vaccine was administered to the mothers who agreed to be vaccinated in the first 3 postnatal days. The infants in the study whose mothers were vaccinated had higher pertussis antibody levels and antibody positivity than infants whose mothers were not vaccinated. Vaccination with Tdap within 3 days postnatally has been shown to protect infants against pertussis. However, there are practical and logistical difficulties in achieving all potential infant contacts, such as other family members, and implementing such immunization programs.

Another method planned to reduce the impact of pertussis on infants is to protect newborns by vaccinating mothers during pregnancy and transplacental antibody transmission [12, 67, 68]. In a study investigating the epidemiology of pertussis in people between the ages of 18–44 years old, pertussis surveillance data of pregnant and non-pregnant women were recorded; the annual incidence in pregnant women was found to be 7,7 per 100.000. Whoop, posttusive vomiting, and apnea were more common in pregnant women [69].

Pregnant women with and without prenatal Tdap vaccination were registered in the cohorts of mother–infant pairs in the Medicaid Analytic eXtract (2010–2014) and IBM MarketScan (2011–2015) databases [70]. Investigators found that the risk of pertussis in the first 6 months was reduced by 36% in infants whose mothers received prenatal Tdap vaccination.

Although maternal immunization with Tdap is used as a strategy to protect young infants against severe pertussis infection, few studies have evaluated the long-term adverse health effects of prenatal exposure to the vaccine in children. In a study in which 12,045 (1.9%) infants out of 625,643 live births were exposed to Tdap in utero, Tdap vaccination did not increase the risk of adverse health outcomes in early childhood. These data support the long-term safety of Tdap administration in pregnancy [71].

In the study of Schutter et al. [72], breast milk content and anti-pertussis toxin secretory IgA (anti-PT sIgA) levels were examined according to maternal pertussis vaccination status. When comparing breast milk content of mothers vaccinated with the Tdap vaccine during pregnancy, immediately after birth (cocoon), up to 5 years before birth, and more than 5 years before birth, anti-PT sIgA levels were found to be highest when vaccination was given during pregnancy and immediately after birth (cocoon). Orije et al. [73] reported that maternal Tdap vaccination increases pertussis antibodies in breast milk after preterm and term birth. The authors also emphasized that these high antibody levels provide additional mucosal protection.

Centers for Disease Control and Prevention recommends Tdap vaccination in pregnancy, and one dose of Tdap vaccine should be administered in each pregnancy, preferably between 27 and 36 weeks [74].

Chemoprophylaxis is recommended in addition to immunization to prevent the spread of *B. pertussis*. But some countries do not adopt this recommendation. In most cases, *B. pertussis* is likely to be transmitted before an index case is found, which may reduce the benefit of chemoprophylaxis. However, after exposure to the patient's

secretions, postexposure chemoprophylaxis is recommended for all households and other close contacts. The high-risk individuals are infants, pregnant women, immunocompromised people, and people with cystic fibrosis, chronic lung disease, or respiratory failure. Preferred chemoprophylactic antibiotics, dosages, and duration of chemoprophylaxis are similar to treatment regimens (Table 40.3). An index case is contagious up to 5 days after starting pertussis treatment. Chemoprophylaxis is most effective when started within 21 days of first contact with the index case [2, 3, 5, 12].

40.13 Conclusion

Pertussis is an acute respiratory tract infection that may cause hospitalization and death, often in infants younger than 6 months. The incubation period of pertussis is usually 7–10 days. Classical pertussis disease consists of catarrhal, paroxysmal, and convalescent phases. Paroxysmal cough, inspiratory whooping, and posttussive vomiting are the most common findings of pertussis disease. The clinical presentation of the disease varies according to age, underlying condition, and vaccination status. Classical findings such as whooping cough suggestive of pertussis may not be seen in vaccinated children.

Pertussis incidence has significantly decreased after the widespread use of vaccination. This decrease shows the importance of the effect of pertussis vaccination. Vaccination with the TDaP vaccine may be started as early as 6 weeks of age; however, the recommended schedule is at 2, 4, 6, and 15–18 months of age. The fifth TDaP dose is recommended in the preschool period at 4–6 years. A booster dose with Tdap is recommended in adolescents at 11–12 years.

Pertussis can be prevented by childhood vaccination, vaccination in adolescence, cocoon strategy, and widespread vaccination during pregnancy. Antimicrobial therapy is recommended for the treatment and eradication of *B. pertussis*. Azithromycin, clarithromycin, erythromycin, and trimethoprim-sulfamethoxazole are used in pertussis treatment and postexposure chemoprophylaxis. The prevention of infection in high-risk groups is optimized by starting chemoprophylaxis within 21 days after contact with the index case.

A literature search has not revealed any data about a definite relationship between pertussis and HL.

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Diphtheria and Hearing Loss

41

Ahu Kara Aksay, Dilek Yılmaz Çiftdoğan, and Tobias Tenenbaum

41.1 Introduction

Diphtheria is a serious bacterial infection that is the result of the causative bacterium *Corynebacterium diphtheriae*. Hippocrates first announced diphtheria in the fifth century B.C., and *C. diphtheriae* was described in 1882 [1]. Although rare, it has been reported that other *Corynebacterium* species (*C. pseudotuberculosis*, *C. hemolyticus*, and *C. ulcerans*) can cause a similar disease [2]. Clinical features vary from mild to severe. *Corynebacterium diphtheriae* frequently causes respiratory diseases like membranous nasopharyngitis, obstructive laryngotracheitis, or bloody nasal discharge. Less frequently than respiratory tract disease, diphtheria also causes cutaneous, conjunctival, vaginal, or otic involvements [3].

There are many complications of diphtheria, including death. The widespread complications include myocarditis, otitis, neuritis, and respiratory failure [1]. The disease has been controlled in resource-rich countries with high diphtheria immunization rates due to the rare circulation of toxigenic strains. Diphtheria continues to

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be endemic in many low-income countries, with poor socioeconomic conditions and inadequate immunization rates [1].

41.2 Etiology

Corynebacterium diphtheriae is an aerobic, mostly nonmotile, non-capsulated, pleomorphic gram-positive bacillus. Non-toxin-producing strains of the four subtypes of *C. diphtheriae* (*C. d. belfanti*, *C. d. mitis*, *C. d. gravis*, and *C. d. İntermedius*) are usually expected to cause mild illness, rarely causing membranous pharyngitis [4]. Toxigenic strains produce an exotoxin composed of a catalytically active A fragment that mediates intracellular toxicity and a B fragment responsible for receptor binding [3].

41.3 Epidemiology

Corynebacterium diphtheriae is found in nature, such as in humans, plants, water, and soil. Although humans are assumed to be the unique reservoir of this pathogen, rare cases of diphtheria in animals have been reported [5, 6]. *Corynebacterium diphtheriae* is spread from person to person through droplets such as sneezing or coughing. The disease may also occur from touching infected open wounds and ulcers. Patients are typically not contagious 48 h after starting antimicrobial therapy [3].

Diphtheria is a worldwide disease. The infection most frequently occurs in the spring or winter months. This infectious disease is now endemic in some countries with poor socioeconomic conditions and low immunization rates. In high-income countries, the transmission of *C. diphtheriae* is mostly by travel to endemic regions such as South America, Central America, Asia, and Eastern Europe or laboratory obtaining [7]. Severe disease is more common in unvaccinated or inadequately vaccinated people. Fully vaccinated individuals possibly have slight symptoms or carriers [3]. The estimated case-fatality rate for this infectious disease is 5–10% [1]. The fatality rate is much higher (20%) in children under 5 years old [1].

Over the past 20 years, better living standards, universal immunization programs, rapid diagnosis, and treatment through improved diagnostic methods have caused a reduction in the world [1]. At the beginning of the twentieth century, up to 200,000 cases and 15,000 deaths were reported yearly. In contrast, diphtheria cases decreased to 19,000 with the introduction of vaccines containing diphtheria toxoids in the 1940s. Then a faster decline was achieved by implementing national vaccination programs that included diphtheria toxoid vaccines [1].

41.4 Pathogenesis

Corynebacterium diphtheriae causes a local inflammatory reaction in the respiratory mucosa or superficial skin layers. The organism's main virulence factor is a 62-kDa polypeptide exotoxin. In the early stage of respiratory diphtheria, a thick, grey, and necrotic pseudomembrane composed of bacteria, inflammatory cells, fibrin, and epithelial cells is formed [8, 9]. The pseudomembrane is adherent and difficult to remove. The toxin causes paralysis of the hypopharynx and palate in the early period [10]. Diphtheria toxin is an ADP-ribosylase toxin that causes a pseudomembrane in the pharynx, myocarditis, delayed peripheral nerve conduction, and acute tubular necrosis by inhibiting protein synthesis, especially in myocardial, peripheral nerve, and renal cells [3]. Cardiomyopathy and neuropathy occur approximately 2–10 weeks after the initial mucosal or cutaneous infection, suggesting that an immune-mediated pathway and toxic tissue destruction may be involved in the pathophysiology [10].

41.5 Clinical Manifestations

The incubation period of this bacteria usually is about 2–5 days, ranging from 1 to 10 days [3]. This infectious disease mainly occurs in two clinical types: (1) Respiratory tract diphtheria (tonsillopharyngeal, nasal, and laryngeal diphtheria) and (2) Cutaneous diphtheria.

41.5.1 Respiratory Tract Diphtheria

The nose, tonsils, and throat are widespread entry routes for *C. diphtheriae*. Two thirds of cases with respiratory tract diphtheria present the symptoms and signs of tonsillopharyngeal type. In one third of the patients, the laryngeal, nasal, and tracheobronchial areas are involved [3].

The disease manifests with a sore throat, fever, difficulty swallowing, fatigue, swollen lymph nodes, and inappetency. Hoarseness may also occur when the larynx is affected [10]. When cervical lymph nodes are involved with underlying soft tissue edema, an appearance called "bull neck" may develop due to profound swelling of the neck. The most distinctive feature of respiratory tract diphtheria is the appearance of the leather-like, adherent pseudomembrane that appears 2–3 days after the disease on the mucous membrane of the upper respiratory tract. This pseudomembrane may be spread into the larynx or trachea and cause airway obstruction. First, establishing an adequate airway and resectioning the pseudomembrane can save the patient's life. The grade of toxin extension is associated with these complications [3, 10].

Symptoms also vary according to other respiratory tracts involved as follows [3, 4, 10]:

- Nasal diphtheria is usually mild and has a serosanguineous/purulent nasal discharge of the nares and upper lip.
- Laryngeal diphtheria often presents with hoarseness and cough.
- Tracheobronchial infection may cause respiratory distress, especially in children with small airways.

41.5.2 Cutaneous Diphtheria

Cutaneous diphtheria may present as an ulcer with a grey membrane. Lesions may not be distinguishable from streptococcal or staphylococcal impetigo with the inspection. *Corynebacterium diphtheria* often coexists with other microorganisms. Lesions are more common in the extremities than in the head and neck region. In this clinical form of the disease, exudate and erythema are first typically present. Less systemic complications are seen in cutaneous diphtheria than respiratory tract diphtheria [3].

41.5.3 Diphtheria at Other Sites

Corynebacterium diphtheriae can cause infections such as purulent or ulcerative otitis externa, conjunctivitis, and ulcerative vulvovaginitis in mucocutaneous sites other than the respiratory tract and skin. *Corynebacterium diphtheriae* can also rarely cause septicemia, often fatal. A few diphtheria cases of endocarditis and pyogenic arthritis have been reported [10].

41.6 Complications

Most complications of diphtheria result from the effects of the toxin. The primary complications are myocarditis, neuroinflammation, and kidney problems such as proteinuria. Myocarditis consists in 10–25% of cases with diphtheria. Myocarditis may be seen as an early or late complication, and its early onset can be fatal.

Neurologic toxicity occurs in approximately 5% of patients [11]. Neuritis most often affects peripheral motor nerves [3, 8, 10]. In the third week of the disease, soft palate paralysis can be seen. After the fifth week, paralysis of the eye muscles, extremities, and diaphragm may occur. Diaphragmatic palsy can lead to secondary pneumonia and respiratory failure. Rarely, in cases, a few weeks after the beginning of the disease, the influenced vasomotor centers may lead to hypotension or cardiac insufficiency [10]. The long period effects of neuropathy on quality of life following diphtheria infection have not been evaluated in detail [12]. Patients diagnosed with diphtheria should be followed up for 3–6 months for possible neurological complications [13].

In addition, otitis media or other short- and long-term complications may develop [14, 15].

41.7 Diphtheria and Hearing Loss

The mechanism and rate of hearing loss due to diphtheria are not clearly known. The severity of hearing loss may depend on the severity of the disease, which varies according to the infecting strain experienced and the clinical type [16].

According to the disease-causing mechanism of *C. diphtheriae*, there are biologically plausible theories that diphtheria may cause hearing loss. First, it may cause neuritis by damaging the eighth cranial nerve responsible for hearing. When the body absorbs the toxin produced by *C. diphtheriae*, it can damage organs far from the infection site, causing clinical manifestations such as cranial or peripheral neuritis. Histological studies have shown significant degeneration of the myelin sheaths and axons of the affected nerves [12]. Paralysis develops as a result of segmental demyelination and axonal damage. It can be thought that diphtheria affects all nerves and the eighth cranial nerve in this way. Second, cranial neuropathies caused by the toxin can lead to ciliary paralysis, affecting hair cells in the cochlea [16].

Numerous experimental studies have benefited from the damaging effect of diphtheria toxin. In these studies, the researchers used diphtheria toxin to impair mice's inner and outer hair cells, causing hearing loss [17–20].

An association between diphtheria and late-onset hearing loss has also been reported. The study of Schubert et al. [16] aimed to determine whether infectious diseases generally experienced in childhood affect hearing ability later in life. The authors concluded that childhood diphtheria is related to hearing loss, especially after 40 years. They interpreted this situation as varying degrees of hearing loss in the later stages of life, with the addition of ototoxic external factors, after the damage to the eighth cranial nerve or the hair cells in the cochlea were affected by diphtheria in childhood. The study concluded diphtheria was related to presbycusis, the gradual loss of hearing in both ears [16].

Apart from sensorineural hearing loss caused by these mechanisms, *C. diphtheriae* can also cause middle ear inflammation (otitis media, especially otitis media with effusion), leading to acute conductive hearing loss [1, 10].

At the beginning of the 1900s, prophylaxis with toxins and antitoxins was attempted. In the 1920s, the diphtheria toxoid was developed [1]. After this development, the diphtheria toxoid vaccine combined with the tetanus toxoid and pertussis vaccine began to be used routinely in the 1940s [1]. Consequently, a decrease in the incidence of diphtheria and its complications, including hearing loss, was observed. It may be supposed that the extreme scarcity of patients with hearing loss associated with diphtheria in the literature is related to the implementation of the diphtheria vaccine in universal immunization programs worldwide.

41.8 Differential Diagnosis

Differential diagnoses of diphtheria should mainly be made with the following diseases [3, 4, 8, 10]:

1. Group A streptococcal tonsillopharyngitis
2. Viral pharyngitis (e.g., adenovirus, Epstein-Barr virus)
3. Vincent's angina
4. Peritonsillar abscess, retropharyngeal abscess
5. Epiglottitis
6. Infective endocarditis
7. Myocarditis
8. Septic shock

41.9 Diagnosis

The case definition of diphtheria is based on clinical and laboratory criteria [1].

41.9.1 Clinical Diagnostic Criteria

The clinical diagnostic criteria in respiratory tract diphtheria are sore throat, fever, and a gray, dense, adherent pseudomembrane on the pharynx. Symptoms typically begin 2–5 days after exposure to bacteria. Besides these respiratory symptoms, absorption and spread of the diphtheria toxin can cause damage to the heart, kidneys, and nervous system [3, 4, 8, 10, 21].

The clinical diagnostic criteria in cutaneous diphtheria are chronic, nonhealing sores or shallow ulcers with a dirty gray membrane; the appearance is relatively nonspecific. Clinical suspicion alone is insufficient in cutaneous diphtheria, and laboratory findings are required for diagnosis [21, 22].

41.9.2 Laboratory Criteria

Corynebacterium diphtheria can be detected by two methods [3, 10]:

1. Demonstration of *C. diphtheriae* by Gram staining or isolation in culture on a swab from the affected area, particularly any ulceration or pseudomembrane. Culture samples are transported in any transport medium at 4 °C. Laboratory staff must be informed about the doubt of *C. diphtheria* in the patients and use selective media for isolation.
2. Histopathologic diagnosis by Albert's stain: The toxin can also be demonstrated by in vivo tests (guinea pig challenge test, rabbit skin test) and in vitro tests (detection of tox gene by enzyme-linked immunosorbent assay [ELISA], polymerase chain reaction [PCR] test) [10].

41.9.3 Classification of Cases

Probable case: A clinically compatible case but not laboratory-confirmed and not associated with an epidemiologically laboratory-confirmed case.

Confirmed case: A clinically compatible and laboratory-confirmed or epidemiologically related to a laboratory-confirmed case [10].

41.10 Treatment

41.10.1 Diphtheria Antitoxin

Diphtheria antitoxin, a hyperimmune antiserum isolated from horses, binds to diphtheria toxin and inactivates it. Human-derived antitoxin may be present in some countries. The antitoxin neutralizes only the circulating toxin and cannot neutralize the toxin already fixed in the tissues. Therefore, antitoxin should be administered in the early period without confirming the culture in cases with clinical findings suggestive of respiratory tract diphtheria. When antitoxin is given in the first 24 h of the disease, the mortality rate decreases below 1% [10].

The antitoxin may be helpful only if systemic toxicity has developed in cutaneous diphtheria. Antitoxin is not recommended for individuals exposed to diphtheria and asymptomatic carriers [10].

The dose of the antitoxin is determined by the toxicity grade, the location and dimension of the pseudomembrane, and the disease duration. The intravenous route is preferred for administration (over approximately 60 min). According to the recommendation of the American Academy of Pediatrics (AAP), antitoxin must be given 20,000–40,000 units (U) for the pharyngeal and laryngeal disease of fewer than 2 days of illness, 40,000–60,000 U for nasopharyngeal disease, and 80,000–120,000 U for more than 3 days of sickness or bull neck [3]. Patients should be tested before antitoxin infusion because of the 10% risk of anaphylaxis or serum sickness. In case of immediate reactions, a desensitization protocol should be applied [3].

41.10.2 Antimicrobial Therapy

Antimicrobial therapy does not replace antitoxin therapy, but should be used to kill the organism and prevent further toxin formation, treat localized infection, and reduce transmission [1]. Antibiotics are also successful in destroying *C. diphtheriae* in carriers. Penicillins, erythromycin, fluoroquinolones, rifampin, tetracycline, clarithromycin, azithromycin, clindamycin, vancomycin, daptomycin, quinupristin-dalfopristin, linezolid, trimethoprim-sulfamethoxazole, and telithromycin have good in vitro activity. However, antibiotics other than penicillin and erythromycin have not been evaluated in clinical infections or carriers [3, 10]. Erythromycin was superior to penicillin in eradicating nasopharyngeal carriage [10].

41.10.2.1 Antimicrobial Therapy of Clinical Diphtheria

Preferred antimicrobials, routes of administration, duration, and doses are as follows [1, 3, 8, 10, 23]:

- Erythromycin: 40–50 mg/kg/day with a maximum of 2 g/day, orally or parenterally, for 14 days
- Procaine penicillin G: 25,000–50,000 U/kg/day divided into two doses, intramuscularly, for 14 days
- Aqueous crystalline penicillin G: 100,000–150,000 U/kg/day divided into four doses, intramuscularly or intravenously, 14 days
- Clindamycin or rifampin can be used in patients allergic to penicillin G or erythromycin

Treatment is usually given for 2 weeks. In patients diagnosed with cutaneous diphtheria, it is recommended to wash the lesion entirely with water and soap. Also, some of these cases which had been diagnosed with cutaneous diphtheria have received it for 7–10 days.

41.10.2.2 Antimicrobial Therapy for Carriers

Oral erythromycin or penicillin G benzathine is given for carries. Erythromycin is given for 10–14 days. A single intramuscular dose of penicillin G benzathine is recommended for carriers (600,000 U for weighing <30 kg and 1.2 million U for children weighing ≥30 kg) [23].

In cases and carriers, repeat cultures should be taken at least 2 weeks after completion of therapy. If the repeat culture result is positive, erythromycin treatment should be given orally for 10 more days, and follow-up cultures should be taken.

41.10.3 Supportive Management

In the acute phase of diphtheria, patients are recommended to rest in bed. Some patients may require respiratory support and airway care.

41.11 Prognosis

Patients with cardiac involvement, especially those with left bundle branch and atrioventricular blocks, have a very poor prognosis with a mortality rate of 60–90% [24–26]. High mortality rates (5–10%) in invasive diseases are known. Especially in the first 5-year-olds, the mortality rate is much higher (20%) [1].

41.12 Prevention and Control

Droplet isolation is recommended for respiratory tract diphtheria, and contact isolation is recommended for cutaneous diphtheria. The current isolation is continued until the patient's two consecutive cultures taken at least 24 h apart are negative [10].

Not all patients develop sustained immunity after diphtheria, so unvaccinated or incompletely vaccinated patients should begin or complete active immunization with the diphtheria vaccine [1, 10].

Public health units must be informed immediately when a diagnosis of diphtheria is suspected or proven in a patient. Close contacts should be identified and monitored for disease during the 7-day incubation period. In addition, cultures should be taken from the throat, nose, and cutaneous lesion. In addition, antimicrobial prophylaxis must be given to the detriment of immunization status. Diphtheria antitoxin must be given once symptoms of the disease are detected. If close contacts of diphtheria patients have an incomplete vaccination history, are unknown, or if more than 5 years have passed since the last dose, contacts should be given a dose of the diphtheria vaccine, and the vaccine series should be completed [3, 10].

41.12.1 Vaccines

41.12.1.1 Preparations

The diphtheria toxoid vaccine is prepared by treating the toxin with formaldehyde. Currently, two preparations of diphtheria toxoids are available.

Pediatric preparations (diphtheria, tetanus, and pertussis [DTP], tetanus and diphtheria [TD], tetanus, diphtheria, and acellular pertussis [DTaP] combined vaccines) contain 6.7 Lf units or more diphtheria toxoid per dose. Adolescent and adult preparations (tetanus and diphtheria [Td], tetanus, diphtheria, and acellular pertussis [Tdap] combined vaccines) contain no more than 2 Lf units of toxoid per dose [8, 27].

41.12.1.2 Vaccine Schedules

- Children (6 weeks to 6 years of age): Five 0.5 mL doses of diphtheria toxoid containing vaccine (DTaP, DTP, DT) [8, 10, 28].
  - The primary series: 2, 4, and 6 months of age
  - The fourth dose: 6–12 months after the third dose
  - A booster dose: Every 4–6 years
- Children (≥7 years of age), adolescents, and adults: Three 0.5 mL doses of diphtheria toxoid-containing vaccine (Td), or Tdap for one of the doses [8, 10, 29].
  - The primary series: Two doses 4–8 weeks apart
  - Third dose: 6–12 months after the second dose
  - A booster dose: Every 10 years (with Td)

A history of a neurological or severe hypersensitivity reaction after a previous dose is considered a contraindication to the diphtheria toxoid vaccine.

41.13 Conclusion

Diphtheria is inevitably important in the medical world because of the high fatality rate and short-term and long-term complications in surviving patients. The mechanism and rate of hearing loss associated with diphtheria are unclear. Although diphtheria toxin damages the eighth cranial nerve as a mechanism of hearing loss, other mechanisms include affecting the hair cells in the cochlea by causing ciliary paralysis and causing otitis media. Since diphtheria is a vaccine-preventable disease, vaccination should be given importance to avoid such complications.

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Brucellosis in Children and Hearing Loss

42

Sevgen Tanır Başaranoğlu, Emin Sami Arısoy, and Ankhi Dutta

42.1 Introduction

Brucellosis is a zoonotic disease caused by *Brucella* spp. It is also known as undulant fever, Mediterranean fever, or Malta fever. It is prevalent in many parts of the world, especially in the Mediterranean countries of Europe, North and East Africa, the Middle East, South and Central Asia, and Central and South America. Brucellosis has also reemerged in Eastern Europe, where the collapse of the former Soviet Union led to social and economic disruption with a decline in veterinary services. The estimated new number of cases is 500,000 annually, associated with significant worldwide effects [1]. It is most often underdiagnosed and commonly stays unreported. Brucellosis is on the list of neglected tropical zoonotic infections of the World Health Organization (WHO). Brucellosis causes multisystem involvement with a variable spectrum of clinical manifestations. The incidence of brucellosis over the years has decreased overall, but remains enzoonotic in some countries. It remains a public health hazard due to increased animal industries, urbanization, and

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a lack of hygienic measures in animal husbandry and food handling [2]. In addition to the high incidence of complications, most authorities consider *Brucella* spp. as a potential biological weapon [3].

42.2 Etiology

The *Brucella* species belong to the alpha-2 (α_2) subdivision of the Proteobacteria and are small, fastidious, gram-negative coccobacilli with 0.5–0.7 μm width and 0.5–1.5 μm length. They are nonmotile, nonspore-forming, lack native plasmids, and have a dominant lipopolysaccharide component on the outer cell membrane. *Brucella* is an aerobic bacterium and has an oxidative metabolism. Carbon dioxide is required in the primary isolation step of *Brucella* species. *Brucella* spp. have catalase enzyme activity, though some biovars show oxidase activity. *Brucella* spp. grow slowly in vitro in media such as trypticase soy, chocolate, and serum dextrose agars. If brucellosis is suspected, the cultures should be kept for 4 weeks since it could slowly grow. Nucleic acid hybridization studies displayed that the different *Brucella* spp. are closely related with 90% similarity, and they may be considered different subspecies belonging to a single species [4].

Brucella—nomen—species currently comprise 12 well-classified species. Among these, *Brucella melitensis* (three biovars), *Brucella abortus* (seven biovars), *Brucella suis* (five biovars), and *Brucella canis* cause most human infections. Three species have been divided into biovars according to the serologic and biologic criteria [5, 6]. Brucellosis in humans is caused by *B. abortus* transmitted from cattle, *B. melitensis* from goats and sheep, *B. suis* from swine, and *B. canis* from dogs. *Brucella abortus* causes most bovine brucellosis as well.

42.3 Epidemiology and Transmission

Brucellosis was first defined in Malta Islands in the 1800s. David Bruce described the causative agent by identifying *B. melitensis* from the liver of a deceased soldier in Malta. *Brucella melitensis*, since then, has been known to cause human disease and high healthcare costs globally [7]. The incidence of brucellosis worldwide ranges from 0.03 to 160 per 100,000 population [8, 9]. Though most animal and human brucellosis cases occur in all the continents except Antarctica, there has been a recent change in geographic distribution, with the emergence of brucellosis in some previous non-endemic areas [10]. Brucellosis can occur at any age, but most frequently in adults and young people [11]. Children present with similar clinical manifestations as adults; however, the diagnosis may be delayed in children due to late recognition of the disease [12].

Generally, human infections are acquired by ingesting unpasteurized cheese and milk or occupational exposure to infected animals, particularly goats, sheep, camels, swine, and cattle. Inoculation through cuts and abrasions in the skin, mucous membranes, and inhalation of contaminated aerosols are other modes of

transmission [13]. Veterinaries, laboratory personnel, ranching, farming and abattoir workers, and meat inspectors have the highest risk of transmission [14, 15]. Brucellosis is a zoonotic disease mostly, with humans being accidental hosts. Rare instances of human-to-human transmission have been documented [16]. In addition, rare instances of mother-to-child transmission by transplacental route [17] or via human milk [18] have been reported. Other less common modes of transmission include blood transfusion, hematopoietic stem cell transplantation, and sexual transmission [19]. As the number of immunocompromised hosts, such as solid organ transplantation, hematopoietic stem cell transplantation, and patients with malignancies have increased, the incidence of brucellosis has increased in these groups. Brucellosis causes adverse pregnancy outcomes, including intrauterine fetal death, spontaneous abortion, premature delivery, low birth weight, and congenital infections [20].

Brucellosis occurs more commonly in temperate and cold climates. However, the incidence of animal brucellosis rises in spring and summer in some parts of the world, as it coincides with the peak period for abortions and parturitions in farm animals. This is more noticeable for ovine and caprine brucellosis than for bovine brucellosis, most probably due to cattle's extended lactation period [21]. However, no seasonal variation is observed in tropical and subtropical areas since animal breeding continues throughout the year.

42.4 Pathogenesis, Immunity, and Pathology

Brucellae are unique in terms of host-microbe interactions. *Brucella* spp. have a predominant intracellular lifestyle in the mammalian host and can overwhelm the host's immune response [21, 22]. Bacteria may enter the host through varied routes such as inhalation, ingestion, and penetration of the conjunctiva or abraded skin.

Most *Brucella* microorganisms are rapidly removed via phagolysosome fusion and enter the intestinal mucosa. After the mucosal invasion, phagocytes ingest the organism by conventional zipper-like phagocytosis using various phagocytosis-promoting receptors by receptor-mediated endocytosis [21]. Following the entry into macrophages and dendritic cells, approximately 90% of the bacteria are killed within the first few hours. The amount of bacteria that survive is 15–30% of the initial population, and they ensure their virulence by diverting endocytic pathway trafficking and replicating in the endoplasmic reticulum with rapid acidification. They form special phagosomes originating from the endoplasmic reticulum called *Brucella*-containing vacuoles. These compartments serve as the main intracellular replication sides. After replication, Brucellae are released from the cell by induced cell necrosis and hemolysins [22]. When they enter the intestinal submucosa, macrophages transport them to the lymphoid tissue. The circulating polymorphonuclear cells and macrophages in the blood contain organisms that use various mechanisms to suppress bactericidal responses. The alternate complement system is not activated [23].

In chronic brucellosis, patients show T-cell anergy and defective T helper (Th) alpha (α)-1 responses, presumably due to the host's cellular immunity modulation by *Brucella* spp. [24, 25]. Patients with chronic brucellosis have a lower percentage of CD4+ T lymphocytes with the interleukin (IL)-2 α receptor (CD25) in the peripheral circulation compared with acute cases. They present a significant reduction in T cells expressing interferon-gamma (IFN-γ).

42.5 Clinical Manifestations

The incubation period for brucellosis is from 5 days to 6 months; however, most people become sick within 2–4 weeks of exposure. Clinical presentations vary in severity and could present as subacute, acute (manifesting in 2–3 weeks), and chronic (recurrent symptoms over 6 months). Fever is the most frequent feature of systemic brucellosis, associated with other nonspecific symptoms like joint pain, sweating, backache, and constitutional symptoms, such as malaise, weight loss, and lethargy.

Osteoarticular involvement is the most widespread complication of brucellosis in children and adults, with symptoms of monoarthritis involving the hip, knee, ankle, and sacroiliac joint being the most common. A common presentation would be a child with a fever who refuses to bear weight on an extremity. Many patients present with signs and symptoms of peripheral arthritis, sacroiliitis, and spondylitis [26, 27]. Peripheral arthritis is frequent and nonerosive, usually involving the hip, knee, wrist, and ankle in acute infection. Spinal involvement may manifest as spondylitis, spondylodiscitis, and discitis [28].

Hematologic abnormalities are frequently encountered in brucellosis [29]. The most frequent laboratory findings are mild leukopenia, anemia, relative lymphocytosis, and thrombocytopenia [30]. Pancytopenia may also be seen in brucellosis, related to hypersplenism and bone marrow involvement. It can also lead to secondary hemophagocytic lymphoproliferative syndrome due to dysregulation of the immune system. Hematological findings typically respond to antimicrobial therapy quickly.

Hepatic involvement is usually in the form of mild transaminitis. Occasionally, liver abscesses, jaundice, ascites, peritonitis, and granulomas in liver tissue may exist [6]. Hepatitis is relatively uncommon, particularly in children with a frequency of less than 1% [31].

Cardiovascular system involvement requires prompt diagnosis and treatment to avoid complications such as myocardial abscess, valve rupture, and sinus of Valsalva fistulas. Endocarditis, pericarditis, myocarditis, and aneurysms of the aorta and cerebral blood vessels are the main cardiac manifestations. The leading cause of mortality in brucellosis is endocarditis, around 1% of all brucellosis cases [32, 33].

Many patients have gastrointestinal complaints like abdominal pain, dyspepsia, constipation, diarrhea, and vomiting. Hepatic abscesses should be suspected in patients with systemic toxicity and persistently elevated liver enzymes. Ocular,

Table 42.1 Clinical manifestations of brucellosis[a]

Systems	Findings
Cutaneous	Palmar erythema, erythematous, papulonodular, and erythema nodosum-like lesions, psoriatic lesions, malar eruption, palmar eczema, purpura, petechiae, leukocytoclastic vasculitis
Ocular	Anterior uveitis and chorioretinitis, optic neuritis, papilledema, keratitis
Respiratory	Bronchitis, pneumonia, pleural effusion; parenchymal granulomas, solitary nodules, miliary mottling
Cardiovascular	Endocarditis, myocarditis, pericarditis, endarteritis, thrombophlebitis; mycotic aneurysms, pancarditis
Hematologic	Leukopenia, anemia, thrombocytopenia, leukocytosis, thrombocytosis, pancytopenia; hypercellularity, hemophagocytosis, and granulomas in the bone marrow; hypersplenism; massive bleeding; capillary leak syndrome
Gastrointestinal	Nausea and vomiting, constipation, diarrhea, and abdominal tenderness; spontaneous bacterial peritonitis; splenic abscess and acute abdominal pain; acute/chronic pancreatitis, intestinal obstruction, colitis, and ileitis
Hepatobiliary	Mild elevation of aminotransferases, liver abscesses, hepatitis including granulomatous forms, cholecystitis, and cirrhosis if left untreated
Genitourinary	Epididymo-orchitis; prostatitis; nephritis; renal and testicular abscesses
Osteoarticular	Sacroiliitis, spondylodiskitis, peripheral arthritis, vertebral osteomyelitis, infection of joint prostheses, paravertebral, epidural, and psoas abscesses
Neurological	Acute meningitis or meningoencephalitis, chronic central nervous system infection (meningoencephalitis, myelitis, cerebellar involvement, cranial nerve palsies), chronic peripheral form (radiculoneuropathy), cerebral abscess, Guillain-Barré syndrome, depression, stroke, polyneuropathy and radiculopathy, paraplegia, sequelae such as walking difficulty, hearing loss, urinary incontinence, visual disturbances, and amnesia

[a] Adapted and modified from Refs. [6, 12]

genitourinary, and cutaneous manifestations can also occur. The main clinical manifestations of brucellosis are listed in Table 42.1.

42.5.1 Neurobrucellosis

Neurobrucellosis is one of the most challenging complications of brucellosis. The term neurobrucellosis includes the involvement of the central nervous system (CNS), coverings, and appendages. The scalp, skull, vertebrae, dura mater, epidural and subdural spaces, brain, and spinal cord may be infectious foci for Brucellae.

The way the *Brucella* bacteria invades the CNS is still unclear, but it is thought that bacteria reach the reticuloendothelial system and enter the circulation [34]. Cytokines and demyelinating immunopathological pathways, along with direct injury by the *Brucella* itself, are thought to be involved in the pathogenesis of neurobrucellosis [35, 36]. The host immunity response initiated by infected macrophages or microglial cells results in a notable increase of pro-inflammatory cytokines, T lymphocyte activation, and increased immune cell recruitment into the

CNS. The release of circulating endotoxins by the microorganism is speculated to be a reason for the neurological manifestations of neurobrucellosis.

Brucellae is isolated from the CSF in a small portion (15–30%) of patients [37, 38]. However, even without a positive culture, high CSF protein count or CSF pleocytosis in a patient with brucellosis indicated neurobrucellosis.

Neurologic complications of brucellosis range between 6.6% and 17.8% [39–42] and can be a late manifestation, especially in adults. In children, a lower incidence, <1–2.2%, has been observed [31, 43]. However, a recent study in Saudi Arabia revealed a higher incidence of neurological complications (3.9%) related to limb weakness, slurred speech, and visual disturbances [44]. Pediatric neurobrucellosis cases most often have an acute presentation [45].

Neurobrucellosis can present with headache, fever, HL, tinnitus, dizziness, speech disorders, and gait abnormalities [46]. Other nonspecific symptoms include weight changes, nausea, loss of appetite, and vomiting. The most common physical findings in neurobrucellosis are meningeal irritation (35%), positive Babinski sign (59%), confusion, and altered mental status at presentation [47, 48]. The symptoms may become apparent abruptly or have a slower onset [49].

Neurobrucellosis can cause encephalitis, meningitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, psychiatric manifestations, and demyelinating syndromes. Demyelination can occur in any part of the CNS. Meningitis (32.6%), encephalitis (14.9%), and hearing loss (HL) (25.8%) are the most common clinical features of neurobrucellosis [50]. In a pediatric study of 74 patients with brucellosis, neurobrucellosis was present in seven (9.4%) patients, of whom two had sensorineural HL (SNHL) [51]. The most common clinical manifestations in this study were meningitis and meningoencephalitis.

The occurrence of basal meningitis may lead to lymphocytic pleocytosis, cranial nerve involvement, or intracranial hypertension [35]. In a cohort of 48 neurobrucellosis cases, the cranial nerves were involved in 19% of patients. Three of the five (10.4%) cases with HL showed notable improvement, while the remaining two presented with persistent SNHL [37]. In another retrospective analysis of neurobrucellosis cases, cranial neuropathy was documented in 71% of patients [52]. Among 17 patients, involvement of the optic nerve was seen in two (12%), the oculomotor nerve in three (18%), the facial nerve in three (18%), the abducens nerve in one (6%), and the vestibulocochlear nerve in seven (41%) patients. The most frequently affected cranial nerve is the eighth, followed by the sixth and seventh. The symptoms associated with these cranial nerves, such as diplopia, visual loss, facial weakness, and HL, may accompany other CNS findings [53–55]. Ototoxic drugs used to treat brucellosis can also contribute to SNHL. Uncommon manifestations are Guillain-Barré syndrome [56, 57], isolated intracranial hypertension [58], papilledema [58], posterior fossa abscess [38, 59], optic neuropathy, diabetes insipidus [60], pituitary abscess [61], cerebral venous thrombosis, and subdural hemorrhage [62]. Periosteal abscesses and lytic and sclerotic lesions of the scalp and calvarium have also been reported [46]. Acute or subacute transverse myelitis is a rare manifestation of neurobrucellosis. It has an incidence of 1–4 per million population, most commonly occurring in the second and fourth decades of life [63, 64].

Psychiatric manifestations, most commonly depression, amnesia, agitation, euphoria, and personality changes, may be seen in patients with neurobrucellosis [65, 66].

Brucellosis can cause vasculitic changes with no predilection for the size or location of vascular structure. Besides vasculitic involvement of the aorta [67], CNS vasculitis is also seen [68]. Endotoxins may lead to arteritis in the endothelium of the cerebral blood vessels, resulting in cerebral ischemia and infarction [47]. Cerebrovascular involvement can be explained by two mechanisms [58]. First, an embolic event from brucellar endocarditis may cause a mycotic aneurysm and result in a rupture of this aneurysm. Second, arteritis with consequent lacunar infarcts, hemorrhages, and venous thrombosis may cause vessel inflammation. Although no controlled trial has supported corticosteroids, the latter mechanism may benefit steroid use in brucellosis. Steroid use has been documented in case reports of brucellosis with demyelinating diseases, cranial nerve involvement, arachnoiditis, cranial nerve involvement, myelopathy, optic neuritis, papilledema, and increased intracranial pressure [64].

In adults, meningitis associated with *Brucellae* has an overall mortality rate of 18% [69]. In studies from other countries, a lower (0–5.5%) mortality rate of neurobrucellosis in the post-antibiotic era has been reported [70]. In Saudi Arabia, a study reported one pediatric death (out of 115) secondary to neurobrucellosis [31]. Adequate antibiotic treatment is believed to result in a good prognosis for neurobrucellosis. Early diagnosis and treatment of neurobrucellosis can prevent mortality, especially in endemic areas.

42.6 Diagnosis and Laboratory Findings

The diagnosis of brucellosis is challenging. A high index of suspicion is crucial for early diagnosis. Since symptoms are nonspecific, a detailed history of travel, recreational activities, occupation, and consumption of raw milk and milk products should be taken. Isolating *Brucella* spp. from blood, bone marrow, or other tissues through cultures ensures a definitive diagnosis. However, the isolation rate in blood cultures varies from 15% to 70%, which may require an extended incubation period [12]. Cultures of bone marrow may facilitate the isolation of species with higher sensitivities [71]. Newer BACTEC systems enable increased sensitivity and may detect *Brucella* spp. within 7 days with no need for prolonged incubation. Detection of microorganisms in CSF is more difficult as the isolation rate can be as low as 10% [33].

Standard agglutination test (SAT), Rose Bengal test and immunoglobulin (Ig) M, and IgG enzyme-linked immunosorbent assay (ELISA) are the main serological tests used in diagnosing brucellosis. These serological assays measure antibodies detected against smooth lipopolysaccharides. These tests are most helpful because they are cost-effective and easy to perform. During the early phase of the illness, serologies may not be positive; however, a fourfold or greater rise in titers for sera collected at least 2 weeks apart suggests a recent *Brucella* infection. The SAT is the

gold-standard test for serologic diagnosis, detecting antibodies against *B. abortus*, *B. suis*, and *B. melitensis* but not *B. canis* or *B. abortus* strain RB51. An SAT titer of ≥1:160 makes a presumptive diagnosis, whereas a titer of 1:320 can be more definitive in endemic areas for brucellosis [72, 73]. Identification of *Brucella* deoxyribonucleic acid (DNA) with polymerase chain reaction (PCR) assay of blood and body tissue samples such as CSF can also confirm the diagnosis; however, it is not yet available in most clinical laboratories.

For the diagnosis of neurobrucellosis, the following criteria are recommended: (1) neurological dysfunction not explained by other neurological diseases, (2) lymphocytic pleocytosis and increased protein in CSF analysis, (3) cerebrospinal fluid culture for *Brucellae* or serological confirmation of positive *Brucella* IgG agglutination titer, and (4) response to antibacterial therapy for *Brucellae* with a significant drop in the CSF lymphocyte count and protein concentration [74].

Imaging studies, especially computed tomography scans and magnetic resonance imaging of CNS, may support the diagnosis of neurobrucellosis. However, imaging studies could be very nonspecific [75]. Neuroimaging findings usually show nonspecific inflammatory processes, as in other bacterial meningitides, and could also demonstrate cranial nerve palsies, demyelination, cerebral atrophy, abscesses, and ventricular dilatation [76]. Imaging studies, especially MRI with and without contrast, help diagnose osteoarticular infections.

42.7 Hearing Loss in Brucellosis

Since the 1970s, reported neurobrucellosis cases with associated SNHL have been increasing, especially in endemic countries. The exact incidence of SNHL caused by brucellosis is unknown. In an analysis of 42 brucellosis patients, Kaygusuz et al. [77] reported 16% HL and 35% of tinnitus. Gul et al. [38] reported that 10% of neurobrucellosis cases had eighth cranial nerve involvement. Isolated hearing impairment may be the sole finding in neurobrucellosis cases [78].

Sensorineural HL has been found to be more common over the age of 30. This is attributed to the chronic course of the disease and more prolonged contact with the pathogen [79]. In patients with acute brucellosis and hearing complaints prior to antibiotic treatment, SNHL was observed in older patients and less commonly in patients younger than 30 years [77]. In a study in the 1980s, SNHL was more prevalent in older patients with dementia and cognitive impairment than in controls; however, a causal relationship could not be confirmed [80].

Although the involvement of the eighth cranial nerve is the most common cranial neuropathy in neurobrucellosis, it is relatively late in the course and mostly accompanied by the involvement of other cranial nerves or other CNS manifestations (meningitis, ataxia [81]). However, acute presentation and isolated involvement of the eighth cranial nerve have been reported [82].

The pathophysiology of SNHL in neurobrucellosis is still uncertain. Meningoencephalitis, or endotoxin-induced vascular compromise caused by Brucella species, may cause involvement of the eighth cranial nerve or central

auditory pathways leading to SNHL [77, 83, 84]. The mechanism could be direct bacterial invasion, hypoxia due to inflammatory edema, or demyelination. This may cause a loss of inner hair cell population, altered synaptic transmission neuronopathy or ganglionopathy at the spiral ganglion cells, a disturbance of transmission in axons from the spiral ganglion to the cochlear nucleus, or defects of the cochlear nucleus and disruption of higher auditory pathways. If audiological tests reveal positive otoacoustic emission (OAE), absent acoustic reflexes, or a reversal of auditory brainstem response, a form of auditory neuropathy can be speculated as the cause of SNHL in neurobrucellosis [85].

Audiometry is the first step in the assessment of HL. Performing BAER or brainstem auditory-evoked potentials (BAEPs) could determine the integrity of primary and secondary auditory pathways between the cochlea and the temporal lobe cortex to evaluate HL in neurobrucellosis further.

42.7.1 Hearing Loss in Children Presenting with Neurobrucellosis

Most data on childhood neurobrucellosis are obtained from case series and case reports from endemic countries. Studies from Türkiye reported that neurobrucellosis comprised 2.2–9.4% of childhood brucellosis, most of whom presented with meningitis or meningoencephalitis [43, 51]. In a series of Iranian children diagnosed between 2011 and 2016, 2 of 43 (5%) patients had neurobrucellosis, but no SNHL was reported [86]. Timely diagnosis of neurobrucellosis is crucial since diagnostic delay in children may result in SNHL, among other complications [87].

42.8 Treatment

Antimicrobial therapy reduces the risk of morbidity, mortality, and risk of complications related to brucellosis. The therapeutic approach for brucellosis aims to concentrate antimicrobials in phagocytes. Treatment consists of a combination of drugs due to the high incidence of relapses and failures with monotherapy. Primary treatment recommendations for different clinical brucellosis forms are listed in Table 42.2. Treatment is based on combination therapy of rifampicin plus doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX), or fluoroquinolones [6, 12, 90]. For uncomplicated brucellosis, the treatment duration is 6–8 weeks. For patients younger than 8 years of age, TMP-SMX with rifampin is preferred. However, doxycycline with rifampin can also be used with close monitoring of side effects. Rifampin and doxycycline are the treatment of choice for all other patients. Treatment duration is typically 6–8 weeks, but can be longer in patients with complicated brucellosis, including neurobrucellosis, depending on treatment response.

Since the SNHL associated with neurobrucellosis is progressive and irreversible, immediate diagnosis and prompt treatment are crucial [91]. The primary drugs of choice that readily cross the blood-brain barrier are TMP-SMX, doxycycline, rifampin, ciprofloxacin, and ceftriaxone. For treating severe infections, including

Table 42.2 Treatment recommendations for different clinical forms of brucellosis[a]

Disease	Drugs	Dose	Duration
Uncomplicated			
	Tetracyclines (preferably doxycycline)	4.4 mg/kg/day (200 mg/day), twice daily, peroral	6 weeks
	Aminoglycosides		
	Streptomycin	30 mg/kg/day, once daily, intramuscular	2–3 weeks
	Gentamycin	5 mg/kg/day, once daily, intramuscular or intravenous	7–14 days
	Rifampin	15–20 mg/kg/day, peroral	6 weeks
	Trimethoprim-sulfamethoxazole (TMP-SMX)	8–10 mg/kg/day, divided in two doses, maximum 160 mg/dose (dosed on TMP component)	6 weeks
World Health Organization (WHO) recommendation [21]	Treatment of uncomplicated cases in adults and children 8 years of age and older: Doxycycline 100 mg twice daily for 6 weeks plus streptomycin 1 g daily for 2–3 weeks. OR Doxycycline 100 mg twice daily for 6 weeks plus rifampin 600–900 mg daily for 6 weeks.		
American Academy of Pediatrics (AAP) Recommendation [88]	For children younger than 8 years: Oral trimethoprim-sulfamethoxazole for 6 weeks plus rifampin for 6 weeks.		
AAP, Nelson's Pediatric Antimicrobial Therapy, 2022 [89]	For children older than 7 years: Doxycycline 4.4 mg/kg/day (maximum 200 mg/day) twice daily, peroral plus rifampin 15–20 mg/kg/day, twice daily, peroral For children younger than 8 years: TMP-SMX (TMP 10 mg/kg/day), twice daily, intravenous or peroral, plus rifampin 15–20 mg/kg/day, twice daily		At least 6 weeks

(continued)

Table 42.2 (continued)

Disease	Drugs	Dose	Duration
Complicated disease (endocarditis, meningitis, spondylitis, and osteomyelitis)	A 3-drug regimen: Gentamicin or streptomycin for 7–14 days plus rifampin for a minimum of 6 weeks plus doxycycline (or TMP-SMX, if doxycycline is not used) for at least 6 weeks. Consider surgical treatment. Gentamicin dose: 6–7.5 mg/kg/day [89].		WHO: Not defined, at least 6–8 weeks, depending on the clinical response [21] AAP: for 4–6 months [88] Nelson's Pediatric Antimicrobial Therapy: Prolonged treatment for 4–6 months and surgical debridement for deep infections [89]

[a] Adapted and modified from Refs. [21, 88, 89]

CNS complications, spondylitis, osteomyelitis, and endocarditis, a three-drug regimen with doxycycline or TMP-SMX with rifampin along with gentamicin is recommended in the first 7–14 days of the therapy regimen. Subsequently, doxycycline or TMP-SMX plus rifampin is advised for 4–6 months [88, 89]. Ceftriaxone-based regimens with shorter courses have also been successful [92].

Clinical response to therapy should be monitored closely to determine the duration of therapy. Surgical interventions for the treatment of the complications should be considered in every phase of brucellosis. Careful monitoring of an infrequent Jarisch-Herxheimer-like reaction, an acute febrile reaction accompanied by myalgia, headache, and a worsened clinical picture lasting less than 24 h, should be undertaken after initiation of antimicrobial therapy. However, this reaction rarely is severe enough to require corticosteroids. Other than that, corticosteroids do not have a proven effect on neurobrucellosis, though their use has been documented in case reports.

42.8.1 Cochlear Implantation for Hearing Loss in Brucellosis

For some patients with profound HL, cochlear implantation is needed. Hearing aids are the primary support for rehabilitating SNHL in neurobrucellosis, too. Guneri et al. [93] reported the first case of successful cochlear implantation in a 32-year-old patient with neurobrucellosis and progressive SNHL, despite hearing aids. Bajin et al. [94] reported a second adult case, a 35-year-old patient with *Brucella* meningitis and profound HL who had cochlear implantation. Cochlear implantation for SNHL after brucellosis-associated meningitis in a 13-year patient also resulted in a favorable outcome [87]. Cochlear implantation is needed for any severe HL, and it is not specific for brucellosis; however, more studies are required to evaluate the impact of cochlear implantation on the prognosis of SNHL in neurobrucellosis.

42.9 Prevention

Prevention efforts in reducing transmission of human brucellosis include reducing direct or indirect exposure to infected animals with brucelloses, such as cattle, goats, swine, and their products. Avoiding contact with infected, predominantly female animals that have been aborted or given birth can prevent transmission. Occupational measures and food hygiene are the mainstays of prevention. Heat-treated milk should be utilized in the preparation of all dairy products. Intake of raw milk and raw milk products should be avoided, and meat should be consumed after adequate cooking. Pasteurization of dairy products for human consumption is also vital in preventing disease. Physicians and health workers should be educated and aware of the transmission methods of brucellosis [2]. Mothers with brucellosis should be advised not to breastfeed their infants until their infection is treated [88]. Breastfeeding infants of mothers diagnosed with brucellosis should be closely monitored for evidence of disease.

42.10 Conclusion

Brucellosis may cause severe disease and multiorgan complications. Clinical manifestations of brucellosis are nonspecific that may delay the diagnosis if the suspicion index is not high. Sensorineural hearing loss is a well-known complication of neurobrucellosis in children and adults. However, the pathophysiology of SNHL in neurobrucellosis is still uncertain. Immediate treatment in patients with brucellosis should be initiated to lessen morbidity, shorten the disease course, and reduce complications, including SNHL. Brucellosis is a public health problem, and prevention is the mainstay of controlling the disease.

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Syphilis and Hearing Loss

43

Tarik Yagci, Rıza Dündar, and Chae-Seo Rhee

43.1 Introduction

The nineteenth century physician, Hutchinson, was the first to describe the conjunction of three congenital abnormalities frequently found in cases of congenital syphilis. This so-called Hutchinson's triad consists of interstitial keratitis, notching of the incisor teeth and deafness [1]. Congenital syphilis was diagnosed by the presence of one or more elements of the triad for many years. A study involving 271 cases of congenital syphilis undertaken by Fiumara and Lessell identified the other highly significant clinical manifestations of the disorder. Symmetrical hydrarthrosis of the knee joints and mulberry molars were noted to be further features of pathognomonic significance [2]. Where the other manifestations of the condition were present, sensorineural auditory impairment was invariable. More recently, serological screening for syphilis has meant clinical signs are less essential in establishing the diagnosis. It has been reported that the fluorescent treponemal antibody test (FTA-Abs) is 100% sensitive and 98% specific. In cases where there is already known to be auditory impairment and a clinical suspicion of syphilis exists, this test has an 11-fold increase in the ability to predict congenital syphilis, compared to its use in the general population [3]. However, no study has so far examined the relationship between the stigmata of congenital syphilis and serological status, which makes assessment of the findings of older studies challenging [4].

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43.2 Pathophysiological Features

Syphilis is the term used to describe infection by the spirochaetic bacterial organism known as *Treponema pallidum*. The name for this genus, i.e. *Treponema*, is derived from Greek τρέπω (trépō = turn) and νῆμα (nēma = thread), and translates as "turning thread". Some other members of the *Treponema* genus are also capable of causing disease, namely *T. pertenue* and *T. carateum* [5].

T. pallidum as the pathogen responsible for syphilis was identified in 1905 by Schaudinn and Hoffman. Then, in 1906, Wassermann introduced a laboratory diagnostic test to confirm cases of symphilis.

The pathogenic members of the *Treponema* genus cause four specific diseases, as follows [5]:

- The sexually transmitted form of syphilis, due to infection by *T. pallidum pallidum*
- Yaws, resulting from infection with *T. pertenue*
- Bejel, a non-sexually transmitted, endemic form of syphilis resulting from infection by *T. pallidum endemicum*
- Pinta, an infection with *T. carateum*

The natural history of untreated syphilis involves three characteristic phases or stages. Once infected, the individual remains infected for life unless successfully treated. The spirochaete invades across mucous membranes or the skin, after which it divides rapidly and is able to disseminate around the body. Spread occurs via the perivascular lymphatic vessels, followed by the bloodstream, prior to manifestation of the clinical features of the primary lesion. The primary lesion is apparent some hours after transmission and is present in the first and second stages of the disorder. Within the lesion, there are numerous infective spirochaetes [5].

The secondary lesion occurs as a result of the immune system's response to the presence of the bacterium in tissues derived from the embryonic ectoderm. These tissues include the central nervous system, mucosae, and skin. The point at which this occurs is between 6 and 12 weeks after inoculation. During this phase of the disease, the bacteria rapidly divide and may become disseminated throughout the whole body. Accordingly, the final, tertiary, stage of syphilis may be observed in any of the organs of the body [5].

Between 1 and 2 months after the secondary lesion appears, it enters a latent stage. For the first year after this occurs (termed the first year of latency), the lesions may become symptomatic again. This recurrence of secondary lesions can only be seen in the first year of latency. Beyond this point, the disease may take two forms: late latent, in which no symptoms are apparent, or tertiary syphilis, in which symptoms do appear. In cases of late latent syphilis, reinfection or relapse are both uncommon [5].

There are a number of different presentations associated with tertiary syphilis. Meningeal syphilis is an uncommon presentation, which may be seen some years after the initial inoculation. A focus of ischaemic damage or a cerebrovascular

accident may result from neurosyphilis at the late stage, since it causes endarteritis in the small calibre cerebral blood vessels. In meningovascular syphilis, any portion of the brain and spinal cord may be involved. Loss of cortical neurones presents as various mental disorders and abnormal neurological findings [5].

For congenital syphilis to occur, the spirochaete must cross the placental barrier. In mothers who have primary or secondary syphilis and remain untreated, there is a 90% risk of this occurring. The foetus may become infected at any point in the pregnancy. Early presenting congenital syphilis presents up to the age of 2 years. Thereafter, if congenital syphilis presents, it is considered late-presenting. The US Centres for Disease Control and Prevention state that syphilis which remains without treatment in pregnant women, particularly first stage syphilis, may cause auditory impairment, neurological abnormalities, abnormal development of osseous tissues, stillbirth, or death of the newborn child [6]. Congenital neurosyphilis may mimic non-accidental injury in its features, causing diagnostic confusion [7].

Infection with *T. pallidum* does not cause abnormalities in organogenesis, since foetal inflammatory responses are not seen before the second trimester, by which point the organs have already formed. However, syphilis can affect any organ or system in the foetus. In cases where infection occurs at an early stage, the presentation is similar to that seen in the second stage of acquired syphilis, since the foetus is reacting to the dissemination of the bacterium across the placental barrier. There is no primary stage defined for congenital syphilis. If congenital syphilis presents in a child above the age of 2 years, it is classified as late-onset. These patients cannot transmit the disease, usually [5].

43.3 Aetiology

Syphilis occurs secondary to infection by the spirochaetic organism, *T. pallidum*. There are two usual modes of transmission, either via the placenta in an infected mother or through sexual contact, but the infection may also occur through contaminated blood or tissues [5].

There are two possibilities for syphilis to occur in a child patient, i.e. congenitally by the bacterium crossing the placental barrier, or as an acquired infection through sexual contact. There is a risk of 50–80% or more of vertical transmission of infection if early syphilis occurs during pregnancy [5].

43.4 Prognosis

Provided treatment occurs early enough and is correctly administered, the majority of cases have an excellent prognosis. Nonetheless, in HIV+ individuals, there is a high risk that syphilis will resist treatment, as indicated by serology. Indeed, the majority of HIV+ patients either do not respond at all or respond insufficiently to treatment of syphilis [5].

43.5 Diagnosis

43.5.1 Serological Investigations

Since the way syphilis presents clinically varies widely, serological investigations play a key part in establishing the correct diagnosis. *T. pallidum* fails to grow on artificial culture media and is not demonstrable by staining with the usual laboratory methods, hence serology plays a major role in confirming the diagnosis and assessing the extent to which the patient responds to antibiotics [5].

There are two kinds of serological investigation suitable for investigating syphilis—the non-treponemal reaginic tests and tests which are specific to treponemal organisms. A positive outcome to the first type calls for verification by the second. The patient may, if clinically necessary, begin treatment prior to confirmatory testing [5].

43.5.2 Non-treponemal Reaginic Serological Testing

The two most common non-treponemal reaginic tests used in routine screening are the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) tests. They benefit from comparable sensitivity, have low associated cost, are straightforward to undertake, and give a quick answer. This type of test is also valuable in assessing how the patient responds to treatment or to see if reinfection has occurred [5].

Non-treponemal reaginic tests quantify immunoglobulins which target either a lipid-containing antigen that is formed as a result of infection or the bacterial antigens themselves. The immunoglobulins of non-specific type are present between 1 and 2 months after inoculation occurs [5].

In 70% of cases, there are immunoglobulins against the pathogen formed under a fortnight after a chance appears and in all cases of secondary or latent syphilis, the serum contains anti-treponemal antibodies. Testing may be falsely negative if undertaken too soon in primary syphilis, during latent acquired syphilis that has lasted a long time, or in the late congenital form of the disease [5].

The titres obtained in serological testing closely match how actively syphilis is progressing, hence they are especially useful for screening purposes. As early syphilis develops, there is an accompanying quadruple or greater elevation in titre. There is invariable positivity in cases of secondary syphilis and the titre is frequently markedly raised, such as 1:32, or higher [5].

There is a 2% risk of false negativity, particularly in cases of secondary syphilis or in pregnant women, due to a prozone phenomenon, whereby a very elevated immunoglobulin concentration in non-diluted test serum can prevent visualisation of a positive test reaction. If there is a clear clinical suspicion of syphilis, such as an infant bearing the stigmata of congenital syphilis, even though serological testing of the mother was apparently negative, the sample will need to be diluted before re-performing the test, in order to exclude the occurrence of the prozone effect [5].

The results of the quantitative serological tests, RPR and VDRL, are generally negative a year after successful eradication of primary syphilis, 2 years after eradication of the infection in secondary or congenital syphilis, and 5 years after adequate treatment of late syphilis. Before negative serology occurs, an ongoing reduction in titre of 75% is evidence of successful treatment. Likewise, if the titre again rises fourfold, the explanation is likely to be either relapse or re-infection, in which case the clinical management will require revision [5].

False positivity of non-treponemal serology may occur when the antigen to which the test responds is present in other tissues. Serological negative occurring under 6 months indicates an acute case, while if seronegativity does not occur within this window, the case is considered chronic. In acute cases, false-positivity potentially arises from other acute events involving the immune system, such as an acute infection with a different bacterium or virus, vaccination, or the early stages of infection with human immunodeficiency virus [5].

False positivity may also occur in chronic syphilitic infections. In such cases, the cause may be intravenous drug administration, autoimmune and connective tissue disorders (in particular, systemic lupus erythematosus), the effects of old age, or hypergammaglobulinaemia. The employment of tests specific for treponemal antigens is generally sufficient to discover whether false positivity has actually occurred [5].

43.5.3 Specific Anti-Treponemal Testing

Specific anti-treponemal tests quantify immunoglobulins targeting *T. pallidum* directly, such as *T. pallidum* immobilisation (TPI), fluorescent treponemal antibody absorption (FTA-Abs), or *T. pallidum* particle agglutination (TPPA). Whenever a non-treponemal reaginic test returns positive, a specific anti-treponemal test should be performed to exclude false positivity [5].

Specific anti-treponemal testing is positive not only in syphilis, but also in other conditions where spirochaetes are involved, namely yaws, pinta, leptospirosis, rat-bite fever, relapsing fever, and Lyme disease. In the latter case, VDRL should have been negative [8].

Seroreactivity on these tests can be demonstrated shortly after infection occurs and, generally speaking, the tests will remain positive for the patient's whole life, even where the spirochaete has been successfully eradicated. There is no relation between this type of serological positivity and how active syphilis is, and the results are not given quantitatively [5].

Immunoglobulin M specific to *T. pallidum* can be measured. At present, polymerase chain reaction amplification of the bacterial DNA is not offered by many laboratories [5].

43.6 Congenital Syphilis

Neonatal exposure to syphilis has frequently been cited as a potential aetiology for deafness of sensorineural type. The Joint Committee on Infant Hearing 2007 Position Statement considers vertically transmitted syphilis to be a risk factor for irreversible congenital, late-onset, or progressive auditory impairment in children [9]. Several review articles focusing on congenital auditory impairment identify syphilis as an aetiological factor in deafness in children [10–12].

It seems that the foetus cannot contract syphilis until the beginning of the second trimester, as the cytotrophoblastic cells form an impenetrable barrier to invasion by *T. pallidum* up to that point. By the sixth month of the pregnancy, the cytotrophoblastic cells are atrophic and no longer prevent the spirochaete from crossing the placental barrier [13]. There is a correlation between the stage of maternal syphilis and the risk of vertical transmission, with the earlier stages (i.e. primary, secondary, or early latent) presenting the greatest danger to the foetus. If the mother is not treated for syphilis, there is an up to 40% risk of miscarriage, stillbirth, premature delivery, or intrauterine growth restriction [12]. In cases where these adverse outcomes do not occur, the rate of vertical transmission in maternal early stage syphilis is 66% [4, 14, 15].

By tradition, the second birthday has been chosen as the point dividing cases of congenital syphilis into early or late-presenting. Neonates with early congenital syphilis may exhibit the stigmata of disease at birth, but the clinical manifestations usually appear somewhat later [13]. The first manifestations of the late-presenting variant of syphilis may appear at any point after the second birthday, right up to when the patient is in his or her 50s. In the 1800s, diagnosis of late congenital syphilis depends on the presence of Hutchinson's triad, namely deafness, notching of the incisors, and interstitial keratitis. The conjunction of these three features is pathognomonic [1]. There are a further two major clinical findings which have a similar pathognomonic status, i.e. the presence of mulberry molars and symmetrical hydroarthrosis [2, 4].

43.7 Pathogenesis

From the beginning of congenital syphilis, the spirochaetic bacterium, *T. pallidum*, is already present in the foetal bloodstream, which means that it can be disseminated into virtually every organ of the foetus. The clinical features arise due to the immune response to this event. Damage to the following organs is the most common and of the highest severity: osseous tissues, liver, pancreas, gut, kidneys, and spleen. The degree of abnormality induced by the disease in different organs may vary considerably, from cases where organ injury is evident only on laboratory or radiological investigations, to fulminant cases with multi-organ damage. Overt indications that the child is infected may be noted in utero, neonatally, or, if treatment has not been administered, at a later stage in childhood [8, 16].

43.8 Clinical Findings

By convention, early congenital syphilis is applied to cases where the stigmata of disease are apparent before the child's second birthday [17]. In the absence of treatment, the clinical features are usually apparent before the age of 3 months, with the peak incidence being before the age of 5 weeks [17, 18].

Between around 60% and 90% of live newborn infants who are affected by congenital syphilis exhibit no signs of the disease at the time they are born [19, 20]. The degree to which physical findings are apparent at birth is influenced by when in the pregnancy the infection was transmitted and what treatment was administered [21]. For infants who do manifest signs, the most frequently occurring findings are the following [16, 19, 22]:

- Hepatomegaly
- Icterus
- Rhinorrhoea (referred to as "snuffles")
- Exanthem
- Tender, enlarged lymph nodes at multiple body sites
- Anomalous development of the skeleton

43.9 Congenital Syphilis and Deafness

The auditory impairment associated with late congenital syphilis, when it presents during childhood, has the following characteristics: acute onset; affects both ears equally; and is profound. There are no associated symptoms of vestibular involvement. This presentation differs from when the condition presents in adulthood, when the associated characteristics are an acute onset (as in children) but usually asymmetrical, of varying intensity, progressing variably, and with frequent symptoms of tinnitus and vertigo [23]. It may be challenging to distinguish between cases where the infection was acquired after birth or before birth, since sensorineural-type auditory impairment is a feature of both types of syphilis [24].

There are data available on how common sensorineural auditory impairment is, but the age ranges involved are sufficiently wide that specific recommendations for when auditory screening should be performed are challenging to make. In a study by Karmody [23], a prevalence for deafness of 12% was reported. The group studied included children with late congenital syphilis and covered the range from birth up to the tenth birthday. According to a study authored by Fiumara, among 271 adults affected by late congenital syphilis, the prevalence of auditory impairment was no higher than 3.3%. However, the study did not report when deafness began, how severe it was, or how it progressed while the patients were still children [2]. According to Tamari [25], the frequency of auditory impairment secondary to late congenital syphilis is 14% in childhood and adolescence. Although the reported data categorised cases using different age ranges, which complicates interpretation, what is clear is that most of the cases of late congenital syphilis reported already had

stigmata of the disease and appropriate treatment had not been undertaken. In the future, studies that employ a prospective design, using serial observations and thus obtaining a longitudinal perspective, will be called for. Besides the diagnosis of congenital syphilis, other data needed for a fuller understanding of the condition will include clinical findings, any serological results, details of pharmacotherapy, and serial audiometric observations.

43.10 Pharmacotherapy

43.10.1 Treating Syphilis in Pregnant Women

Penicillin may be used in any case of syphilis occurring during pregnancy, during all three trimesters [26, 27]. The antibiotic is administered intramuscularly once every week for 3 weeks. The form used is benzathine penicillin at a dose of 2.4 million U each time. A meta-analysis which examined outcomes in pregnant women administered penicillin found that this dosage caused a 97% fall in cases of clinically detectable congenital syphilis, 82% fewer stillbirths, 64% less premature delivery, and 80% reduction in fatal outcomes during the newborn period [5].

There is, unfortunately, no treatment of equal proven efficacy to penicillin for use in patients with an allergy to penicillin. Erythromycin does not consistently prevent congenital syphilis in the same way as penicillin [5].

The penicillin allergy should be confirmed as genuine by demonstrating a wheal and flare on the skin in response to exposure to penicilloyl-polylysine or penicillin G minor determinant mixture. If the allergy is confirmed, the patient will need to be admitted to hospital for a course of desensitisation, so that penicillin treatment of syphilis can go ahead. The Centres for Disease Control and Prevention have issued specific recommendations for this situation [5].

43.10.2 Congenital Syphilis in Neonates

Penicillin G (aqueous or procaine) should be administered for between 10 and 14 days in all cases of congenitally acquired syphilis in neonates, regardless of whether diagnostically confirmed or not. If there is a high degree of clinical suspicion of the disorder or the diagnosis has been confirmed by testing, the use of aqueous crystalline penicillin G is advised. The dose to use is based on chronological age, without factoring in gestational age [5].

The recommendation is for a total daily dose of between 100,000 and 150,000 U/kg, divided into twice or three times daily and lasting 10–14 days. Although some experts advocate the use of procaine penicillin G at a dose of 50,000 U/kg administered intramuscularly, this agent suffers from the major disadvantage that the concentration in cerebrospinal fluid is inconsistent and may be too low for eradication of the spirochaete.

The following points provide evidence to support the diagnosis of congenital syphilis [5]:

- The physical examination or imaging investigations indicate activity of the infection
- On serological testing on non-treponemal type, the titre is a minimum fourfold above that recorded in the mother
- The VDRL test on cerebrospinal fluid is positive; there is leucocytosis or the protein content is abnormally elevated
- There is positivity of immunofluorescence tests for anti-treponemal IgM or of FTA-Abs
- Darkfield microscopy reveals spirochaetes, or treponemal organisms can be demonstrated by staining in placental or umbilical tissues

43.10.3 Congenital Syphilis in Older Infants and Children

For infants above the age of 4 weeks with a diagnosis of congenital syphilis, the treatment consists of aqueous crystalline penicillin (200,000–300,000 U/kg/day, administered intravenously q.d.s as a divided dose, with the course lasting between 10 and 14 days) [5].

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Chlamydia psittaci Infection and Hearing Loss

44

Ali Budak, Cemal Cingi, and Giulio Cesare Passali

44.1 Definition

Psittacosis may also be referred to as "parrot fever". It occurs secondary to infection by the obligate intracellular bacterium, *Chlamydia psittaci*. Morange first coined the term psittacosis in 1892, based on the Greek word for parrot, ψιττακός (psittakos) [1].

C. psittaci causes infections in parrots, parakeets, canaries, and a number of other birds, such as ducks, pigeons, and turkeys. This type of infection may also be referred to as ornithosis, a term denoting an infection from any type of bird (Greek ὄρνις, ὄρνιθος (ornis, ornithos) = bird) [1].

According to the literature, the most widespread epidemic of psittacosis occurred in 1930. At that time approximately 800 patients were infected. It was during the 1930 epidemic that *C. psittaci* was first discovered by multiple European and American laboratories.

Psittacosis is an occupational hazard for certain individuals, whose work brings them into contact with birds. Thus, it may affect employees in zoos, pet shops, or

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those working in poultry rearing or animal husbandry. Although the disease rarely passes directly between human hosts, such transmission may occasionally occur. Cases of psittacosis where the transmission was from human to human exhibit more severe features than cases where the infection was acquired from birds [1].

44.2 Epidemiology

The usual way that the bacterium is transferred to a human host is by inhaling bacteria contained in the dried bird faeces. This dust may be aerosolised when birds move their wings in a cage, or through dust generated by the birds' feathers. The infection may also be transmitted when the bird's cage is cleaned [2, 3]. Some other routes for the spread of infection have also been noted. These include being bitten by a bird, humans touching their mouths to the bird's beak, or simply being in proximity with infected birds, such as following a visit to an aviary. Nearly every bird species kept as a pet may harbour *C. psittaci*, although the psittacines are those that present the highest risk. Infections passing from pigeons, doves, or mynahs are less common. An Italian study of cases of psittacosis ($n = 76$) found that the majority originated from poultry birds [4]. There have been a number of outbreaks linked to avian abattoir workers, the highest risk being in those involved in removing the slaughtered chickens' internal organs. In a proportion of these cases, psittacosis was sufficiently severe to require admission to intensive care [5].

Direct person-to-person transmission of psittacosis seldom occurs, but has occasionally been reported. A Swedish case involved a patient with severe infection. Psittacosis occurred by human-to-human transmission in ten contacts. One of the cases was in a patient on the same ward as the original patient. Seven cases occurred in healthcare employees from the same hospital [6, 7]. One Chinese outbreak was linked to a factory processing duck meat. The first cases were contracted from the ducks, but later these infected workers transmitted psittacosis to their contacts. Some tertiary transmission was also observed. Some individuals were found to carry the infection without showing symptoms, and transmission from infected healthcare personnel was also identified. Epidemiological understanding of psittacosis has greatly increased thanks to metagenomic analyses, and this now puts psittacosis in the category of biosecurity hazards [8].

Despite the fact that cases may occur at any life-stage, the disease has a predilection for young adults or those in middle age. It has been reported by numerous studies that men are more at risk then women. Men may have a higher degree of exposure to infected birds, but this gender-bias has not been replicated in all the case series reported [9, 10].

After infection with *C. psittaci*, the severity of ensuing illness varies. A number of pet-owning households were examined after being exposed to a batch of pet birds in which *C. psittaci* infection was detected. An acute infection of the respiratory tract was noted in 11% of owners and their households. Some 30% of the households had members with clinical evidence or positive serology confirming psittacosis. Among infected individuals, the resulting disease was frequently mild or

produced no symptoms [11]. Nonetheless, a fatal outcome in some cases has been reported, albeit infrequently [2, 12].

44.3 Pathophysiological Features

The main route by which *C. psittaci* organisms invade the human is via the respiratory tract. The patient becomes infected after aerosolised bird excrement or respiratory secretions from infected birds enter the tract. The bacterium can attach itself to the epithelium of the airways, following which there is haematogenous spread to the reticuloendothelial system. When the organism again re-enters the bloodstream, there is spread to the pulmonary tissues [1].

The infection may be transmitted to humans who come into contact with infected avian species. Some cases have occurred following attempted resuscitation of birds by breathing into their beaks. Even a relatively brief contact with an infected avian species, as may occur when visiting a pet shop, may be sufficient to provoke symptomatic psittacosis [1].

44.4 Aetiology

There are four known species within the genus *Chlamydia*, all of which are obligate intracellular parasites. These species are *C. trachomatis*, *C. pneumoniae*, *C. psittaci,* and *C. pecorum*. The characteristics shared by every member of the *Chlamydia* genus are as follows: possession of an envelope that does not contain peptidoglycans and stains negatively on Gram staining; bearing a lipopolysaccharide antigen that is unique to the genus; and the need to utilise ATP produced by the host for the bacterium to synthesise its own proteins. The genus has a developmental cycle not shared by other genera. There are two forms of *C. psittaci*. The extracellular form has very little metabolic function (the so-called elementary body) and is responsible for infection. The non-infectious form is intracellular and has an active metabolism. The latter form is also known as the reticulate body. The elementary bodies measure between 200 and 400 nm in diameter. They bind to the host cell membrane, with entry into the host cell via non-microtubule-dependent endocytosis. The elementary body remains wrapped in membrane inside a phagosome, which does not then fuse with a lysosome, as would normally be expected. Within the phagosome, the elementary body develops into a reticulate body. The reticulate body can then reproduce by binary fission. These divided bacterial cells are the typical intracytoplasmic inclusions seen on microscopy. Around 36 h after this transformation occurs, the reticulate body re-forms elementary bodies. The pathogen again becomes transmissible at that point. When 48 h have elapsed from the beginning, these elementary bodies may be released *en masse* from the host cell by lysis of the infected cell, or one by one through exocytosis. Infection by the pathogen does not interfere with host cellular replication, and thus only one of the daughter cells may contain the intracytoplasmic inclusions. This phenomenon is likely to explain why chlamydial

species can so easily and characteristically be carried without the host exhibiting any symptoms. Although there are four known members of the genus *Chlamydia*, only three seem to cause disease in human hosts, namely *C. trachomatis*, *C. pneumoniae,* and *C. psittaci*. Humans are the sole infective reservoir for the *C. trachomatis* organism. *C. pneumoniae* is well-adapted to the human host [13], but can also parasitise other hosts, such as koalas or frogs, according to an Australian study. *C. psittaci* is adapted to survive in almost all types of mammal and birds. However, human infection with *C. psittaci* is generally from exposure to a bird rather than a mammal. The fourth member of the genus, *C. pecorum*, has recently been recognised as a distinct species. It causes bovine and ovine infections, but so far appears unable to infect humans [14].

Psittacosis is a disease resulting from infection with *C. psittaci*. This pathogen is an obligate intracellular parasite. It is often found in psittacine avian species, as well as poultry. Because of their occupational exposure, psittacosis may occur in poultry farmers, pet shop employees, and veterinary surgeons. After initial infection, the disease may recover, only to then relapse [1].

The nature of psittacosis as a disease due to infection by a bacterium means that a single infection typically will not confer long-term complete immunity. However, the likelihood of developing psittacosis a second time has not yet been quantified. In these circumstances, the patient should be encouraged to avoid exposure to birds potentially infected with the pathogen [1].

Another potential source of infection is the laboratory. Infections acquired through contact with laboratories may fail to be reported due to a number of factors, including stigma and anxiety about being disciplined for becoming infected. There are also difficulties in definitively identifying a laboratory source for cases of psittacosis [15].

44.5 History

Psittacosis typically takes between 5 and 14 days to develop following inoculation. The lengthiest incubation period on record is 54 days. The principal presenting features are those of a respiratory tract infection with signs and symptoms of systemic involvement. However, the precise presentation differs from case to case [1]. The following are typical features:

- Systemic features
  - Pyrexia occurs in between 50% and 90% of patients
  - Chills
  - Feeling generally unwell
- Respiratory features
  - Coughing in between 50% and 90% of cases. This is usually a dry cough
  - Pleuritic type chest pain is an unusual symptom
  - Shortness of breath
  - Mild pharyngitis accompanied by pain frequently occurs

  - Nose bleeds are common
- Gastrointestinal symptoms (all are infrequent or rare)
  - Nausea and vomiting
  - Abdominodynia
  - Loose stools
  - Icterus
- Nervous system involvement
  - Headache of high severity frequently occurs
  - Sensitivity to light is also frequent
  - Patients may be either unusually lethargic or agitated
- Cutaneous system
  - An exanthem (especially on the face) known as Horder spots

44.6 Clinical Presentation

The most frequently occurring clinical presentation of psittacosis is with an acute onset of pyrexia, severe headache, and non-productive cough in a young or middle-aged adult. However, infected patients may exhibit no symptoms. There is typically a history of being recently in contact with avian species. While the time from inoculation to symptoms is generally from 5 to 14 days, the incubation period may last up to 39 days [16]. A case series involving 135 patients found that systemic symptoms predominated, with pyrexia present in every case, rigors in 61%, and diaphoresis and muscle aches noted in the majority [9]. Some 82% of these patients complained of cough, but this symptom was only present at a late stage in psittacosis. Around a quarter (24%) of cases featured specific symptoms indicating respiratory involvement, namely, shortness of breath, chest pain, and haemoptysis. There were no indications of respiratory involvement in 18% of cases [2].

Some cases of psittacosis may masquerade as Covid-19. However, according to the authors of a Chinese case series, cases of psittacosis have a more elevated leucocytosis, neutrophilia, and calcium level than is usually the case for Covid-19. Furthermore, the cases of psittacosis tended to affect only one lung, the lesions were less diffuse within the lung, and may, infrequently, provoke a pleural effusion [17].

Headaches are a frequently occurring feature. Headaches are of high severity, often in conjunction with photophobia. In the Chinese case series, lumbar puncture had been performed in a third of the cases, for a clinical suspicion of meningitis [9].

Although less frequently noted, pharyngitis, loose stools, and change in mental state are significant manifestations of psittacosis. Loose stools may occur in up to a quarter of cases, but are rarely severe. Nonetheless, in a minority of cases, diarrhoea is the main presenting complaint [9]. Alteration in mental state occurs in 12% of cases. This may be evident as a range of different alterations, ranging from mild disorientation through to frank evidence of encephalitis [2, 18].

44.7 Laboratory Investigations

Psittacosis may result in any of the following laboratory-detected abnormalities [1]:

- The leucocyte level ranges from normal to slightly elevated.
- Markers of hepatic function are generally slightly raised.
- The erythrocyte sedimentation rate is potentially raised.
- A mild degree of proteinuria (not exceeding 3500 mg/dL) may be noted.
- Although methods exist for culture-confirmation of *C. psittaci*, this option is generally not offered since it presents a hazard to staff working within the laboratory.
- Serology should be conducted in the acute and convalescent stages of the illness. The convalescent stage begins a fortnight after symptomatic onset. An elevation in the titre of at least fourfold confirms the diagnosis of psittacosis. Since complement fixation lacks specificity and cross-reactivity with other members of the *Chlamydia* genus is possible, this is not a useful test in psittacosis.
- Currently, Chlamydial species can be differentiated on the basis of microimmunofluorescent or polymerase chain reaction techniques. PCR is being researched as a potentially highly specific test that can give early warning.
- Enzyme-linked immunosorbent assay (ELISA) and direct immunofluorescence have been utilised on occasion for the diagnosis of psittacosis. They remain, however, at an experimental stage.
- Serology remains an essential element in diagnosing the disease. One disadvantage of these tests is their inability to direct treatment, since specific immunoglobulins do not appear until a late stage in psittacosis.
- The majority of cases receive diagnostic confirmation on the basis of clinical features and the presence of immunoglobulins specific to *C. psittaci* antigens. This is demonstrated by paired sera tested by microimmunofluorescence [19].

For detection of *C. psittaci* in koalas, a more straightforward slide EIA test has been produced. This improved test can give a rapid answer. Slides containing multiple wells are used. Each well contains HeLa 229 cells infected by the specific strain of *C. psittaci* that infects koalas. These cells then present the antigen. The assay then consists of adding koala serum to the slide, followed by rabbit biotinylated immunoglobulin specific for koala antibodies, avidin-biotin-complex reagent, and the substrate [20].

44.8 Imaging Investigations

Chest X-rays have a demonstrable abnormality in approaching 90% of patients infected with *C. psittaci*. The most frequently observed abnormality is a dense infiltrate in the lower lobe on one side (i.e. consolidation). However, the lesions may be present in both lungs, and be nodulary, military, or interstitial in distribution. In rare cases a pleural effusion is noted [1].

The mean point at which chest radiography indicates resolution is 6 weeks after onset, with the range 3–20 weeks [1].

44.9 Medical Therapy

Psittacosis should be suspected in any individual presenting with community-acquired pneumonia and with a history of avian exposure. The principal therapeutic intervention is prescription of antibiotics.

For human patients suffering from psittacosis, the standard methods used for infection control, i.e. prevention of droplet transmission, are adequate. There should be no need for more advanced isolation methods, such as a single room with negative pressure airflow, or respirators [1, 19, 21].

The most suitable antibiotics for treatment of *C. psittaci* infections are the tetracyclines. There are, however, some other potential treatment options. Where there is no laboratory confirmation of the pathogen, clinicians often treat community-acquired pneumonia empirically with macrolides. It is probable that macrolides also effectively treat *C. psittaci* infections [2].

44.9.1 Tetracyclines

Tetracyclines are the first-line treatment. If psittacosis is of no more than moderate severity, an appropriate regimen consists of doxycycline 100 mg b.d., administered by mouth. This treatment generally produces a swift improvement. If the patient is in a critical condition, doxycycline may be administered by the intravenous route. Pyrexia abated in 92% of the patients in a published case series, the effect being apparent within 48 h [9]. Nonetheless, tetracyclines are sometimes ineffective or permit a later resurgence of infection. There are reports indicating the effectiveness of minocycline. Insufficient evidence exists to decide on exactly how lengthy a course of treatment is most effective, but many clinicians opt for a course of between 7 and 10 days when utilising this class of antibiotic.

44.9.2 Macrolides

For cases where a contraindication to tetracyclines exists, the agent usually selected as an alternative is a macrolide antibiotic, e.g. erythromycin or azithromycin. A study of five patients with psittacosis, for whom erythromycin was chosen as pharmacotherapy, reported the outcomes to be comparable to using tetracyclines [22]. Where azithromycin is chosen, the course of treatment may be cut to 5 days as long as there is rapid improvement in the clinical condition.

For paediatric cases where psittacosis is of no greater than moderate severity, macrolides are the first-line treatment. There is little consensus about treating pregnant women. Clinicians often rely on anecdotal experience. Two case reports

describe women infected with *C. psittaci* while pregnant, in whom erythromycin was ineffective. The women did, however, respond to doxycycline after delivery [23, 24]. This evidence has led some experts to propose doxycycline as the first-line treatment for pregnant women. Although azithromycin is effective both in vitro and in animal studies, there is a lack of knowledge about its use in clinical situations. The authors consider azithromycin a suitable agent to use in pregnancy or for a child younger than 8 years old, since doxycycline is generally not advised in these groups. Furthermore, patients generally tolerate azithromycin more easily than erythromycin. This greater tolerability may influence clinicians' preference for azithromycin [2].

44.9.3 Other Agents

Although success has been reported in treating psittacosis with either chloramphenicol or rifampicin, both treatments are associated with a risk of relapse. A study of 13 cases treated with ofloxacin also reported success, but there is a need for more data before deciding on a potential role for quinolones in treating psittacosis [2].

44.10 Auditory Impairment

There is a case report describing auditory impairment of sensorineural type linked to psittacosis, where pneumonia was present. This deafness rapidly resolved when the patient received suitable antibiotic treatment and steroids were commenced at high dose [25].

There is a further case report concerning a female high school student aged 15 years who suffered from uveitis of both eyes of fluctuating intensity, stromal keratitis with proliferating vessels, and auditory impairment in both ears with concurrent tinnitus and disturbed equilibrium. Her death followed 3 years later as a result of endocarditis with valve disease and arteriopathy, which caused sudden cardiac arrest. *C. psittaci* was found within the conjunctival tissues. Serology revealed immunoglobulins specific to the strain of *C. psittaci* with which she was infected at a level of 1/64. The clinical features overall were those of Cogan's syndrome [26].

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Rickettsial Diseases in Children and Hearing Loss

45

Osman Erdogan, Nuray Bayar Muluk, and Kamil Janeczek

45.1 Definition

In terms of phylogeny, the Rickettsiae are located as a group of microbes intermediate between bacteria and viruses, but classified as bacteria. The Rickettsiales order contains the Rickettsiaceae family, which itself includes the Rickettsiae, the tribe consisting of the *Rickettsia* genus. The members of this genus are all obligate intracellular organisms with a coccobacillary morphology that stain gram-negative. Their reproduction depends on eukaryotic host cells. While all members show poor staining characteristics with Gram staining, the Giemsa or Gimenez stains impart a distinctive red colour to these organisms. Rickettsiae are unflagellated and their cell walls do not retain the gram stain. They have a diminutive genome consisting of between 1 and 1.5 million nucleotide pairs [1–3].

There are several diseases that are secondary to infection by Rickettsiae. These diseases fall into three different biogroups [2, 4]:

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45.1.1 Spotted Fever Biogroup (Consisting of 15 Different Rickettsioses)

This biogroup encompasses the following disorders [3]:

- Rocky Mountain spotted fever; an infection due to *Rickettsia rickettsii*
- Rickettsialpox, secondary to *Rickettsia akari*
- Boutonneuse fever, consisting of Kenya tick-bite fever, African tick typhus, Mediterranean spotted fever, Israeli spotted fever, Indian tick typhus, and Marseilles fever

45.1.2 Typhus Biogroup

This group contains diseases that resemble each other but differ in their epidemiological characteristics. The Rickettsial species responsible for these diseases resemble those causing the spotted fevers, but bear different antigens [3]. The diseases in this group are as follows:

- Louse-borne (epidemic) typhus
- Brill-Zinsser disease (the relapsing form of epidemic typhus)
- Flea-borne typhus. Also known as endemic or murine type [3]

45.1.3 Scrub Typhus Biogroup (Tsutsugamushi Disease)

The species responsible for scrub typhus are all classified under the same taxonomic label, *Orientia tsutsugamushi*. These organisms display considerable heterogeneity and are markedly different from the Rickettsia species causing spotted fever or typhus, even though they are within the Rickettsialis order. There are three major serotypes, namely Karp, Gilliam, and Kato [3].

45.1.4 Other Rickettsial or Highly Similar Diseases

Within the preceding decades, descriptions of a number of novel or resurgent rickettsial diseases have appeared in the literature. These include TIBOLA (tick-borne lymphadenopathy), DEBONEL (Dermacentor-borne-necrosis-eschar-lymphadenopathy), and lymphangitis-associated rickettsiosis. DEBONEL is caused by *Rickettsia slovaca*, whereas lymphangitis-associated rickettsiosis is due to *Rickettsia sibricia* [1]. Another member of the *Rickettsia* species, identified as *Rickettisia 364D*, has recently been linked to a Californian case characterised by eschar formation [5, 6].

There are several other rickettsia-like organisms causing disease, which are the subject of other chapters in this volume. These include species of the *Ehrlichia*

genus (including *Ehrlichia ewingii*), which are responsible for human monocytic ehrlichiosis, *Anaplasma phagocytophilum* (which is responsible for human granulocytic anaplasmosis), and organisms of the *Bartonella* genus (infection which causes catscratch disease, relapsing fever, and Trench fever) [3].

Another pathogenic organism that used to be classified among the Rickettsiales, but has now been reclassified, is *Coxiella burnetii* [7]. This pathogen is responsible for Q fever, which has some similarities to other rickettsial diseases, but is discussed elsewhere in this volume [3].

45.2 Pathophysiological Features

The pathogenesis of rickettsial diseases seems to depend on the ability of the bacterium to attach to the vascular endothelial and thereby gain entry into organ tissues. There are adhesins expressed on the bacterial membrane that facilitate phagocytosis of the bacterium by the human cell. When the bacterium has entered the host cytoplasm, two outcomes may occur: (1) the pathogen divides and increases up to the point where the host cell is destroyed (the mechanism in typhus cases), or (2) the bacterium bursts out from the cell, producing damage to the host plasma membrane and causing the cell to absorb water (the mechanism in spotted fevers) [8].

The rickettsial pathogen cannot grow unless it is located within the host cytoplasm. These organisms release phospholipase D and haemolysin C, which damage the membrane of the host phagosome, allowing them to avoid being digested by the host cell [3].

- Rocky Mountain spotted fever (RMSF): In this condition, the bacterium is introduced into the bloodstream via the skin. The pathogen reproduces in the cytoplasm of the endothelial cells of small calibre blood vessels before breaking out into the circulation. There are foci of extravasation into the tissues caused by bacterial reproduction within the endothelium and the infiltration by mononucleocytes of the perivascular space. Although these foci may be found in any organ, their presence is demonstrated best within skin or the adrenal glands. If this pattern of vasculitis occurs in the brain and spinal cord or in cardiac tissues, the host immune response is primarily cellular. This immune reaction then causes further tissue trauma. Hepatic involvement typically results in portal triaditis. As the walls of the blood vessels are obliterated, the physiological response is for thrombocytic aggregation in an attempt to plug the gaps. Thus, a low platelet count is observed, as the thrombocytes are used up. Biochemical abnormalities may also be noted, in particular a low serum albumin and sodium level. The former results from loss via the kidney, less intake, and liver impairment, while the latter is due to loss of sodium ions via the kidney, movement of fluid into the extracellular compartment, and uptake of sodium in place of potassium by the cells [3].
- Rickettsialpox: In this condition, there is a small vessel vasculitis, as occurs with other rickettsial diseases. Although histopathology is seldom needed to confirm

the diagnosis, the appearances are distinctive: there is thrombosis and the capillaries become necrotic, while an infiltrate of mononucleocytes is visible surrounding the vessel [3].

- Boutonneuse fever. The clinical presentation of this disease is explicable as the result of changes in the dermal blood vessels, resembling that seen in cases of RMSF. Dissemination of the pathogen causes the endothelium of capillaries and the smallest calibre arterial and venous vessels to be affected around the body [9]. Furthermore, in some patients, a leucocytoclastic vasculitis has been noted [3].
- Epidemic (louse-borne) typhus. The pathological features resemble those noted in the spotted fevers biogroup. The organisms that cause typhus do not interact with cellular actin to flee the host cell. Instead, they continue dividing within the host cytoplasm up to the point where cytolysis of the endothelial cell occurs and the pathogen is released into the circulation, allowing it to spread around the body [3].
- Brill-Zinsser disease (also termed relapsing louse-borne typhus) also bears similarities in its pathogenesis to the spotted fevers biogroup. One key difference is the apparent ability of the pathogen to enter a dormant condition, probably within the cells of the reticuloendothelial system. When they become active once more, in response to some signal, the nature of which is still mysterious, they begin to reproduce, which then produces a second infection, albeit of lesser severity than the initial episode [3].
- In murine (flea-borne, endemic) typhus, the pathological features resemble those seen in epidemic typhus [3].
- Tsutsugamushi disease (also termed scrub typhus). The pathogenic organism responsible for this disorder, *Orientia tsutsugamushi*, enters the human cell and divides within the cytosolic compartment. It then buds off, wrapped in a portion of host cell membrane, before seeking a neighbouring cell to infect. Analogous to other diseases caused by rickettsiae, there is an accompanying angiitis. There are typically necrosis and inflammation where the mite punctured the skin, while the lymph nodes are enlarged and tender both in the region of the bite and elsewhere on the body [3].
- Q fever. This disease results from direct tissue trauma induced by the causative pathogen, a member of the *Coxiella* genus. The bacterium has been found residing in pulmonary macrophages and within cardiac valvular vegetations. The pathogenesis of Q fever seems to also involve host factors, since there is granuloma formation in organs of the reticuloendothelial system. Granulomatous liver inflammation occurs [3].

45.3 Aetiology

45.3.1 RMSF

The pathogen responsible is *R. rickettsii* [1, 4].

RMSF may be transmitted by a number of different ticks, which act as vectors. These ticks include the Rocky Mountain wood tick (*Dermacentor andersoni*), which inhabits the west of the USA and Canada, *Dermacentor variabilis* (the American dog tick), found in the east of the US, the Pacific coastal regions, and in central US states, and *Amblyomma americanum* (the Lone Star tick), which inhabits certain parts of the southern US [10].

45.3.2 Rickettsialpox

Rickettsialpox is within the spotted fever biogroup. The pathogen responsible is *R. akari*. The vector is the mouse mite, *Liponyssoides sanguineus*.

The features that are unique to rickettsialpox are the formation of an eschar at the location where the bite occurred, a rash of vesiculopustular type, and the fact that Weil-Felix agglutination does not occur [3].

Liponyssoides sanguineus normally parasitises house mice (*Mus musculus*) within the USA. In other countries, there are associations with different rodents [4].

45.3.3 Boutonneuse Fever

In boutonneuse fever, the pathogen responsible is any of a number of subspecies of *R. conorii*. Mediterranean spotted fever is due to infection by *R. conorii conorii*, whereas Israeli spotted fever is caused by *R. conorii israelensis*. Astrakhan spotted fever results from *R. conorii caspica* and Indian tick typhus is associated with *R. conorii indica*. Two other rickettsial species also cause boutonneuse fever, namely *R. africae* and *R. slovaca*. The former causes African tick-bite fever. Both are obligate intracellular parasitic bacteria which may be transmitted by a variety of tick species, according to geographical location [9].

The risk of a human patient becoming infected rises mainly if the patient has contact with a dog on which an infected tick is feeding [3].

45.3.4 Epidemic (Louse-Borne) Typhus

The pathogen responsible for louse-borne typhus is *R. prowazekii*.

The vector carrying the infection to humans is a louse, *Pediculus humanus*. The primary infective reservoir for the pathogen is *Homo sapiens* [3].

45.3.5 Brill-Zinsser Disease (Louse-Borne Typhus of Relapsing Type)

In these cases, the pathogen is the same, i.e. *R. prowazekii*, but the pathogenesis involves the bacterium being roused from a state of dormancy in the human host,

rather than reinfection from an external source. This dormant state is not well understood [3].

45.3.6 Murine (Endemic or Flea-Borne) Typhus

The main causes of endemic typhus are *R. typhi* (also known as *R. mooseri*) and *R. felis*. These bacterial species have antigenicity resembling *R. prowazekii*.

The vector is the rat flea (*Xenopsylla cheopis*), which transmits the infection from rat to rat. Human cases occur when the patient comes into contact with the faeces from a flea infected by the pathogen [3].

Another vector for this disease is *Ctenocephalides felis*, the cat flea [11].

45.3.7 Scrub Typhus (Tsutsugamushi Disease)

The causative pathogen in scrub typhus is *O. tsutsugamushi*. This bacterium displays a wide range of antigenic characteristics [3].

Transmission of *O. tsutsugamushi* occurs by contact of a human with a trombiculid mite during its larval stage. These larvae are referred to as chiggers. Their habitat and location for breeding are soil and scrub plants. The trombiculid species acts as both the principal reservoir and the vector. Infection occurs through the eggs of the mite. Some rodent species may also act as reservoirs. Humans are only accidental hosts [3].

45.3.8 Q Fever

The origin of this strangely named disease is "Query fever", a term applied in 1935 to a pyrexial illness linked to an Australian slaughterhouse. The pathogen responsible is *Coxiella burnetii*. This strict intracellular bacterial parasite is short and stains gram-negative [3].

The *C. burnetii* organism was formerly classified within the rickettsiales order, but it is now classified, based on the genetic sequencing of the 16SrDNA gene, within the gamma subdivision of the Proteobacteria. Other genera in the same subdivision are *Legionella* and *Francisella* [7].

Q fever differs from the usual rickettsial diseases which afflict humans in its being a zoonosis. It is spread to humans by aerosol or through drinking unpasteurised milk [3].

45.4 Physical Examination and Auditory Impairment

45.4.1 RMSF

- Pyrexia may be as high as 40–41 °C. Fever is typically constant rather than fluctuating in intensity [8, 12].
- The exanthem appears 2–3 days after symptoms begin, beginning on the distal portions of the limbs (wrists and ankles) and spreading towards the extremities and over the trunk. Somewhat infrequently, the exanthem may fade or be confined to a specific location on the skin [13].
- The characteristic size of the red-coloured macules is no more than 1–5 mm across and they blanch on pressure. They may transform into maculopapules and petechiae over time.
- It is unusual for the skin to become necrotic. Up to a fifth of cases of RMSF do not have any associated exanthem (a condition referred to as spotless RMSF). However, the absence of a rash is not an evidence against a diagnosis of RMSF. If the other clinical features and the history suggest the diagnosis, treatment should begin immediately.
- Patients who develop delirium may progress on to meningoencephalitis and enter a coma.
- Signs of meningeal irritation may be present, even where the CSF analysis reveals no or, at most, slight abnormality, such as a raised lymphocyte number. Neurological presenting features include blindness of cortical type, seizures, central deafness, ataxia, paralysis, or abnormalities of the cranial nerves.
- The heart is commonly affected. A full cardiac workup and detailed monitoring are required, to give warning of rhythm disorders or congestive heart failure.
- Lung involvement may present as a collapse of a lobe or entire lung, the presence of an infiltrate or pulmonary oedema.
- Muscular aches are frequently noted, usually affecting the thigh or calf and triggered by touch on these areas of the body.
- It is more usual for the retina to be affected than the uvea or iris. Retinal involvement leads to (papill-)oedema, cotton wool exudates, haemorrhage, or occlusion of the retinal artery.
- Hepatosplenomegaly is an uncommon presenting feature [3].

45.4.2 Rickettsialpox

- Generally, there is lymphadenopathy evident in the nodes draining the region where the primary eschar appears.
- Once pyrexia occurs, a macular exanthem is apparent a few days later. This macular rash then takes on a maculopapular or vesiculopapular form over the course of the ensuing days. The rash is facial, cervical, and covers the trunk, as well as the ends of the limbs. It may cause diagnostic confusion with the lesions of varicella, particularly in adults. This is the reason for the use of “pox” in the name of

the disorder. The skin rash may occur in conjunction with a mucosal eruption, i.e. an enanthem. The rash typically resolves within a fortnight to 3 weeks and does not cause scar formation.
- The mucosal membranes should be examined for the enanthem [3].

45.4.3 Boutonneuse Fever

- There are aches in all the muscles and it may be possible to note myositis.
- The eschars are frequently located on the trunk, upper or lower limb. In young paediatric patients, the scalp area behind the ear is commonly affected.
- The exanthem follows 3–5 days after the beginning of pyrexia. The rash starts at the ends of the limbs, but then spreads to the truncal and cervical regions, as well as the palmar and plantar surfaces of the hands and feet within a day and a half. There is generally facial sparing [9].
- This rash lasts for around 2–3 weeks, changing from a macular to a maculopapular exanthem.
- In isolated cases, other forms of skin abnormality are noted and the exanthem is entirely absent in between 1% and 4% of patients.
- Between one third and three quarters of paediatric cases develop cervical adenopathy.
- The frequency of exanthem is decreased in cases of African tick-bite fever. Where it occurs, the rash is of vesicular type and affects a smaller area than in boutonneuse fever. These cases also present with several eschars and the regional lymph node enlargement is pronounced [14].
- In terms of other clinical features and the potential complications, this disease resembles RMSF [3].

45.4.4 Epidemic Typhus (Louse-Borne) [15]

- An exanthem is noted starting 4–7 days after symptoms begin. This rash is initially truncal, but then extends to the ends of the limbs, without affecting the face or plantar/palmar surfaces. At first, the exanthem may be mostly in the axillary region.
- The exanthem begins as a macular rash, then transforms into maculopapular and petechial.
- The complications include gangrene, inflammation of the pericardium or myocardium, and a pleural effusion or pneumonia. These complications are, however, infrequent.
- If the typhus is of high severity, the patient may become delirious and show features of meningoencephalitis. These cases may end in death secondary to cardiac and renal failure [3].

45.4.5 Brill-Zinsser Disease

Brill-Zinsser disease is the name given to the relapsing form of epidemic typhus. In this form, the exanthem is generally less severe and resolution of the lesion occurs more rapidly [3].

45.4.6 Murine Typhus

Murine typhus is also termed endemic or flea-borne typhus.

- The general features resemble the louse-borne form, but murine typhus is generally less severe and its duration is briefer.
- The associated exanthem covers a smaller area than in louse-borne typhus. The exanthem is usually initially confined to the trunk, but then extends to the extremities, the opposite pattern from RMSF [3].

45.4.7 Tsutsugamushi Disease (Aka Scrub Typhus)

- An unusual feature of scrub typhus, compared to other disorders caused by infections with rickettsiae, is that generalised lymph node involvement is usual, affecting 80% of cases. This lymphadenopathy occurs alongside pyrexia, headache, and an exanthem [15].
- The exanthem appears 1–3 weeks after the rickettsial inoculation occurred, commonly affects the trunk, and lasts briefly. Half of patients develop an eschar at the point where the skin was pierced.
- Enlargement of the liver and spleen, eye pain, and injection of the conjunctivae are frequent presenting features.
- Less frequent presenting features include auditory impairment, ringing in the ears, inflammation of the myocardium, atypical pneumonia, and adult respiratory distress syndrome [3].

45.4.8 Q Fever [16]

- Pneumonitis is found in above 50% of cases. There is generally a dry cough. Physical examination may not reveal any remarkable findings.
- Chest imaging may show a range of different abnormalities, such as multiple opacities in different lung segments, plural effusion, consolidation of a lung lobe, or atelectasis of a linear type.
- Hepatitis is revealed by pyrexia and abnormal liver function tests, especially the transaminases. There are usually no other symptoms of the hepatitis, although the liver and spleen may both be enlarged [7].

- In any patient with multiple foci of osteomyelitis, the differential diagnosis should include chronic Q fever, particularly where the patient has been exposed to livestock [17].

45.5 Rickettsial Diseases and Deafness

Auditory impairment, in particular, central deafness, is found in cases of RMSF. Furthermore, auditory impairment and tinnitus feature in cases of scrub typhus [3].

In a case series authored by Kang et al. [18], one individual with scrub typhus had associated deafness of sensorineural type and three others had complaints of acute onset earache of high severity. In these latter cases, the pain came in waves lasting several seconds, interspersed with absence of severe pain. These symptoms appeared less than a week after an exanthem was seen and pyrexia noted. Resolution of the deafness and ear pain occurred following antibiotic therapy.

Sensorineural deafness is reported in cases of infection due to *R. rickettsii*, *R. typhi,* and *R. coronii* [19–21]. The precise way is which deafness occurs has not yet been fully established, but there are two competing hypotheses available. According to one of these hypotheses, there is direct invasion of the central nervous system by the pathogen, which leads to vasculitis during the acute phase. This vasculitis is then responsible for injury to the cochlear branch of the vestibulocochlear nerve [19, 22, 23]. The alternative theory agrees that vasculitis affects the vasa nervorum of the cochlear nerve, but considers the vasculitis to be a dysfunction of the immune response. Deafness of a sufficient degree of severity as to render television programmes inaudible has been reported, with the explanation that this implies both ears suffered sensorineural auditory impairment. It was also reported that there was only unilateral improvement in the level of hearing, as demonstrated audiometrically, following a course of rifampicin. The reason for the choice of this agent were the findings of Watt et al. [24] These authors found that rifampicin was clinically superior to doxycycline in the treatment of cases of scrub typhus in a trial involving randomisation between treatment arms [24]. According to Premarantna et al., auditory impairment and tinnitus commence a week after scrub typhus first appears [25].

R. felis causes spotted fever. It is found everywhere in the world. The cat flea (*C. felis*) is the principal reservoir of infection in addition to acting as vector in human infections. The involvement of *R. felis* has been proven by PCR of bacterial DNA and serological testing in some 70 cases. The usual clinical features are pyrexia, headache, muscle pains, skin involvement (exanthem and eschar), lymph node enlargement, and signs of central nervous involvement, such as photophobia or deafness [26–29].

45.6 Treatment

45.6.1 Antimicrobial Pharmacotherapy

Treatment involves prescribing antibiotics empirically. The choice of agents should be sufficient to provide cover for all of the potential pathogens which may account for the clinical presentation [3].

45.6.1.1 Doxycycline

The mode of action involves binding to a 30S and sometimes 50S ribosomal subunit, thereby preventing the bacterium from synthesising protein. It thus prevents the pathogen from growing.

45.6.1.2 Chloramphenicol

This agent also achieves the effect of arresting growth of the bacterium. It does this by binding to the 50S subunit of the bacterial ribosome and preventing production of proteins. Chloramphenicol acts on both gram-positive and gram-negative organisms. It has potentially less efficacy against rickettsiae than doxycycline [3].

When chloramphenicol was prescribed to patients outside the hospital, some 30% went on to require hospital admission, whereas when a tetracycline was used, this number fell to 11% [3].

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Scrub Typhus and Hearing Loss: Orientia tsutsugamushi Infection via Leptotrombidium Bites

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46.1 Definition

The cause of scrub typhus is the bacterium *Orientia tsutsugamushi*, which is transmitted to humans via mites. The former name for *O. tsutsugamushi* is *Rickettsia tsutsugamushi*. Although mention of scrub typhus goes back to the third century CE in Chinese sources, the first report listing its characteristics in Western scientific literature only appeared in the late 1800s. The disease became much better understood following WW2, in which many Japanese and Allied servicemen became infected by the disease while serving in the Pacific theatre of war [1].

46.2 Microbiological Aspects

The *O. tsutsugamushi* bacterium stains gram-negative and has a coccobacillary morphology. It has different antigenic characteristics from the other organisms causing typhus in the *Rickettsia* genus. *O. tsutsugamushi* has both similarities to and differences from the rickettsial bacteria.

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A feature in common with the rickettsiae is the impossibility of conventional bacteriological culture. It can only be cultured within cells.

O. tsutsugamushi bears a three-layered outer cell membrane that has a unique structure not found in the rickettsiae.

The method by which this bacterium escapes from the cell cytoplasm and invades another host cell is also unique. The process involves wrapping the bacterium in host membrane and then budding off. Cells located nearby then phagocytose this parcelled bacterium complete with the cell membrane. The rickettsial-type phospholipase A2 plays an apparent role in permitting the pathogen to enter the host cell, escape from the host phagosome, and begin controlling the host metabolism [2].

Once the pathogen has entered into human skin, it is able to spread around the body. According to one study [3], mononucleocytes were found to bear the pathogen in three of seven cases of acute scrub typhus. The method of detection was staining.

The *O. tsutsugamushi* organism has three variant strains, termed Karp, Gilliam, and Kato. After a patient becomes infected with one strain, this does not confer immunity against subsequent infection with another strain [1].

46.3 Pathophysiology

The larvae of the *Leptotrombidium* mite are known as chiggers or harvest mites. These larvae may bite humans, allowing *O. tsutsugamushi* to be transmitted. The mites measure 0.2 mm in length and have six legs. They do not have a preference for a specific host. Their nourishment comes from fluids on the host skin. These organisms persist naturally by parasitising wild rats. Exposure to wild rats is therefore a risk factor for scrub typhus [4]. Interestingly, however, these rats seldom become infected with *O. tsutsugamushi* [5]. The infection occurs when a mite chooses to bite a human being [6].

There is transovarial transmission of the bacterium in mites, which causes more female than male mites to be formed. This imbalance then assists with transmission of the *O. tsutsugamushi* pathogen [5, 7]. The activity of the mites and the resulting frequency of scrub fever depends on the species of trombiculid mite involved, as well as the characteristics of the locality where the interaction occurs. Three species known to act as vectors are *Leptotrombidium akamushi*, *L. deliense,* and *L. pallidum*. As may be expected, there is a positive correlation between the number of mites resident in an area and the rate of human infection [8].

In the tropics, the infections occur throughout the year. However, in Japan, where the temperature is above 25 °C for only 3 months (July, August, and September), the *L. akamushi* mites are only active enough to cause infection during that period. The *L. pallidum* mite, which inhabits a wide area, is, by contrast, active once the temperature reaches around 18–20 °C, which means it acts as a vector for infection from the spring right through to autumn [5, 9].

Human scrub typhus develops after an infected mite feeds on a human, biting the skin and introducing the pathogenic bacterial species, *O. tsutsugamushi*, into the

skin. The pathogen divides at the location where the bite occurred, forming a papule which then forms a necrotic ulcer. This lesion then becomes an eschar. The regional lymph nodes undergo enlargement and then lymphadenopathy may become generalised shortly afterwards. In experimental studies, it has been shown that an acute pyrexial episode occurs 8–10 days after inoculation. The bacteria could be demonstrated in the bloodstream 1–3 days prior to the patient exhibiting pyrexia [10].

There is perivasculitis affecting the small calibre blood vessels, as occurs with rickettsial infections. This inflammation also affects the endothelial cells, although the appearances on histopathology imply that macrophages play a more central role in the pathogenesis [11].

Phagocytes of the immune system engulf the pathogen, which is then able to evade digestion by the phagosome. Following division within the host cytoplasmic compartment, *O. tsutsugamushi* can then escape from the cell by a budding process. The pathogen utilises the microtubules of the host to achieve mobility. Even where the pathogen has already been opsonised through binding of immunoglobulin, it can still evade digestion by the phagosome, but the opsonised bacterium can no longer utilise the microtubular network for mobility and this renders it significantly less capable of transmitting itself to other host cells [5].

The pathogen can invade multiple organs by first entering the endothelium and the macrophages. The involvement of multiple organs may prove fatal [12, 13]. It appears, according to a 2009 study, that higher severity of the disease is associated with raised levels of bacterial load, as determined by PCR amplification of bacterial DNA [14].

46.4 Epidemiological Factors

The principal geographic area where *O. tsutsugamushi* is endemic is the Asian Pacific rim. Scrub typhus has endemic status in Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia, and the tropical parts of Australia (i.e. those in the north of the country) [15, 16]. Between 2015 and 2016, Chile reported three cases of scrub typhus [17, 18]. Another case was reported concerning an individual seemingly exposed to *O. tsutsugamushi* within West Africa [19]. It was also reported that a case of scrub fever occurred in Dubai where the causative pathogen was the newly discovered bacterium, *Orientia chuto*. This pathogen bears close genetic similarity to *O. tsutsugamushi* [20].

There are several reasons for which information on the precise prevalence of scrub fever is usually unavailable: the diagnosis is frequently given without laboratory confirmation; the diagnosis may not be considered; or scrub fever is mistaken for another disease causing pyrexia which may be prevalent in that area. Despite these limitations on surveillance, it has been proposed that as many as one million infections may occur each year in Southeast Asia [21]. A study which examined the epidemiology of some 27,391 Chinese cases between 2006 and 2012, where a scrub typhus diagnosis with laboratory confirmation was made, revealed some key epidemiological factors affecting prevalence in endemic regions [1, 22], namely:

- Around two out of three of the cases occurred in farmers.
- The peak incidence was between the ages of 40 and 60 years. The rate in young children is above that seen in young adults.
- The summer and autumn months (i.e. July to November) were the period when around 80% of cases were presented.
- The cases tended to occur in clusters, with a limited number of provinces in the southeast of China having the majority of cases.

Despite the majority of scrub typhus infections being found in the countryside, cases do also occur in urban areas. The suburbs of Bangkok have a seroprevalence above 20% [23]. There are also cases within the cities themselves, e.g. in Beijing and Seoul [22, 24].

46.5 Clinical Features

In some cases, the disease has an insidious onset, where the presenting features are headache, loss of appetite, and feeling generally unwell. The case may also present with sudden onset chills and pyrexia. As scrub typhus progresses, the majority of cases exhibit characteristic symptomatology, as described here:

- Pyrexia, generally of lengthy duration if treatment is not started (median 14.4 days; range 9–19) [21]
- Severe headache all over the head
- Muscle aches throughout the body

An exanthem, eschar, or other symptoms or signs may be noted. There is a wide range in the severity of the clinical picture. Some patients have a mild illness, whereas others suffer multi-organ failure with a fatal outcome [21, 25, 26]. According to a systematic review which collated data on some 19,644 cases where treatment did not occur, scrub typhus had a fatal outcome in 6% (the median rate; range was between 0% and 70%) [21]. The frequency of death showed a wide variation according to location, with a higher frequency as age increased. There was an association between the occurrence of myocarditis, delirium, and pneumonitis with mortality. The sex of the patient and the presence of an eschar did not predict outcome. There is potentially a correlation between the circulating bacterial DNA level when the patient is admitted to hospital and the likelihood of a fatal outcome [27].

Cases occurring in older adults are more at risk of severe symptoms and the occurrence of complications than in younger individuals. This has been shown in a retrospective case series involving 615 patients who attended one hospital in Korea. All these individuals were over the age of 16 years and had a diagnosis of scrub typhus [28]. The rate of occurrence of at least one complication in the group aged above 65 years was 46%, double that seen in the younger group (i.e. 23%). Acute renal impairment, cognitive disorientation, and shortness of breath occurred more frequently in the older patients. The rate of pyrexia, exanthema, and eschar did not

significantly differ between the groups. Delayed treatment increased the likelihood of the case becoming complicated. There was a slight increase in the time elapsed between first symptoms and appropriate treatment (7 vs. 6 days) in those cases where complications occurred [1].

46.6 Diagnosis

In common with the rickettsial infections generally, laboratory confirmation of infection is unreliable in the initial stages of scrub typhus. The diagnosis is generally made on the basis of appropriate clinical features and history, laboratory results consistent with scrub typhus, and the presence of epidemiological risk factors, such as the patient having recently been in a region where the trombiculid mites are found or expected to be present [1].

The following laboratory abnormalities are all consistent with a diagnosis of scrub typhus [1]:

- In the majority of cases where the disease is of high severity, thrombocyte levels are low.
- The liver enzymes are raised, as are bilirubin and creatinine.
- Although the white cell count may be either raised or low, in the majority of cases, the level is normal.

The laboratory results, while characteristic of scrub fever, are not unique to this disease. There are, however, four methods of definitively confirming the diagnosis of *O. tsutsugamushi* infection, namely serologically, by histopathology, by culture, and by PCR amplification of bacterial DNA.

46.7 Scrub Typhus and Deafness

In an epidemic of scrub typhus in Sri Lanka, which occurred between 2003 and 2004, there were 32 suspected cases. In a number of cases, the patients failed to come to medical attention before the ninth or tenth day of symptoms, by which point several complications had arisen. These complications included pneumonitis, myocardial inflammation, auditory impairment, and encephalitis [29].

However, deafness is an infrequently occurring feature of most cases of scrub typhus [30]. Moreover, acute onset of sensorineural deafness in both ears very seldom presents in scrub fever. More commonly, the patient complains of earache or ringing in the ears. Where the ears are affected, this generally becomes apparent in the second week after the onset of scrub fever [29, 31].

Auditory impairment of sensorineural type has been noted infrequently in cases of infection with Rickettsiae, in particular *R. rickettsii*, *R. typhi,* and *R. conorii* [32]. According to Premaratna et al. [29], the frequency of auditory involvement in a

series of 32 cases of scrub typhus was 6/32, with 3 of these 6 patients experiencing some form of deafness, the exact details of which were not reported.

The precise way is which deafness occurs has not yet been fully established, but there are two competing hypotheses available. According to one of these hypotheses, there is direct invasion of the central nervous system by the pathogen, which leads to vasculitis during the acute phase [33, 34]. This vasculitis is then responsible for injury to the cochlear branch of the vestibulocochlear nerve. The alternative view agrees that vasculitis affects the vasa nervorum of the cochlear nerve, but considers the vasculitis to be a dysfunction of the immune response [35]. One study examined sections of the temporal bone obtained post-mortem from five servicemen in British service during WW2 in the Pacific theatre, whose death occurred secondary to epidemic typhus. Histopathological examination of these sections showed numerous typhus nodules, with interstitial neuritis affecting the vestibulocochlear nerve and loss of myelin. At the same time, mononucleocytes were aggregated at various points within the inner ear. This study was conducted on historical specimens collected by the late C.S. Hallpike [36].

46.8 Treatment

At present, the management of scrub typhus involves prescription of antibiotics. There is a danger of relapse if the duration of treatment is insufficient. Several different antibiotics have been utilised for this indication, as follows [6]:

- Tetracycline antibiotics (these are the usual first line treatment, particularly doxycycline)
- Macrolides (such as azithromycin, roxithromycin, and telithromycin)
- Fluoroquinolones are not routinely advised due to the uneven benefit derived from use of these agents

There are no specific recommendations about the need to rest or stick to a specific diet. In cases of severe disease, admission to hospital may be required. For severely ill patients, a high level of supportive care is essential to prevent disseminated intravascular coagulation and cardiovascular failure from occurring.

Precautions which may prevent infection in areas where the disease is endemic are as follows [6]:

- Wearing protective clothing
- Use of insect repellents
- Cutting back of overgrown vegetation and spraying of insecticides may be employed as short-term measures

Antibiotic prophylaxis may also be used as follows [6]:

- Doxycycline may be administered once a week prior to travel to the endemic area, then continuing for 6 weeks after return [37].
- Chloramphenicol once by mouth or a tetracycline at 5 day intervals, the same to be repeated seven times. Note that Chloramphenicol is rarely employed in US clinical practice.

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Tropheryma whipplei Infection (Whipple's Disease) and Hearing Loss

47

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47.1 Introduction

Tropheryma whipplei, a bacterial organism which stains gram-positive, is the probable cause of Whipple's disease [1, 2]. The organism was previously named "Tropheryma whippelii" (note the different spelling). Whipple's disease was first characterised as a malabsorption syndrome that affected the small bowel; however, it is now recognised to be a multi-system disorder which involves the joints and central nervous and circulatory systems. A large number of cases of culture-negative endocarditis are thought to be caused by *T. whipplei* [3]. However, since there are only 1000 cases which have so far been reported in the literature, the evidence base for Whipple's disease remains rather slender [4, 5].

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47.2 Pathophysiological Features

Whipple's disease is a rarely occurring inflammatory disorder that involves multiple organ systems. The various features of the clinical presentation have been linked to invasion of multiple tissues by the *T. whipplei* pathogen. The immune response to the presence of the pathogen is to phagocytose *T. whipplei*, which then remains within the macrophages [5].

The presence of macrophage infiltrates into the tissues is readily observable in histopathological specimens. The sections used are stained with the periodic acid-Schiff (PAS) stain. Although these stained macrophages are seen in Whipple's disease, they are not unique to the condition, since they also occur in several other types of infection, especially if patients are immunosuppressed due to infection with HIV. Similar histological appearances are therefore seen in cases of *Mycobacterium avium intracellulare*, *Cryptococcus,* or parasitic infections [6, 7]. If these alternative infective causes are suspected, the sections should be stained to reveal fungi or acid-fast bacilli.

The *T. whipplei* bacteria can be demonstrated by electron microscopy, where they appear as coccobacilli. In conjunction with polymerase chain reaction (PCR) amplification of bacterial DNA, electron microscopy provides diagnostic confirmation of organ involvement [8–10].

The pathological mechanism which causes malabsorption from the small intestine is considered to result from abnormal function of the intestinal villi. The villi fail to work as expected due to infiltration of the lamina propria by the Whipple organism. Whipple's disease produces systemic symptoms through involvement of many, but not all, of the body's different organ systems [5].

The pathogen has also been detected within the synovial tissues in cases where there is joint involvement wherein pain was a feature [11]. Furthermore, the pathogen was present in cardiac valvular tissue in cases of Whipple's disease in which there were cardiac features, and in the central nervous system when there were neurological features [12–14]. The pathogen has also been detected, albeit infrequently, in the pulmonary tissues [15].

47.3 Aetiology

The pathogenic bacterium *T. whipplei*, in conjunction with a maladaptive host immune reaction, is thought to be the cause of Whipple's disease [16]. It is interesting to observe that Whipple's disease does not appear to occur in HIV+ individuals [5].

There is evidence to indicate that, even where no symptoms occur, patients may carry *T. whipplei* [16–18]. PCR DNA amplification on saliva in such individuals was positive 35% of the time, in a study involving 40 apparently healthy individuals [19]. This result may point to the conclusion that Whipple's disease only occurs due to a dysfunctional immune response to the presence of the bacterium, with the usual

condition being asymptomatic carriage. This may occur in a way analogous to that seen with *Helicobacter pylori* [5].

At present, researchers have been unable to demonstrate that *T. whipplei* causes Whipple disease in a manner satisfying Koch's postulates, i.e. experimental infection of an animal reproduces the features of the original disease. It has proven feasible to culture *T. whipplei* in cell culture, using human fibroblasts (i.e. HEL culture) [2]. Moreover, the organism has been demonstrated to trigger production of specific immunoglobulins of types G and M. In patients with Whipple's disease, the pathogen could be detected in cerebrospinal fluid and vitreous humour and was then cultured in fibroblasts [5].

47.4 Diagnosis

Tissue biopsy of the affected organ is a vital step in confirming the diagnosis. The tissues liable to be biopsied in this way are the small intestine, central nervous system, endocardium, and synovial joints. Small intestinal biopsies show expansion of the villi and multiple PAS-positive staining histiocytes. When these histological appearances are present, the next step is electron microscopy and PCR DNA amplification, to confirm the presence of *T. whipplei* organisms [5].

In all new cases of Whipple's disease, it is important to perform a lumbar puncture to obtain cerebrospinal fluid for a baseline assessment. This applies even in the absence of any apparent neurological features of the disease [5].

47.5 Clinical Feature

Whipple's disease may present with a wide variety of different manifestations [20]. Classically, the disease involves multiple organ systems and manifests as arthralgia, persistent diarrhoea, malabsorption, and unintentional loss of weight. There may also potentially be involvement of several other organ systems. The manifestation of the various features occurs slowly over time, such that arthralgia may occur many years prior to other features, and thus not every case demonstrates the full classic panoply of symptoms. A single organ system may be affected, especially the cardiac valves or the brain and spinal cord, without other features of Whipple's disease being detectable. In a case series involving 52 individuals with the disorder, joint symptoms occurred in 67%, gastrointestinal in 15%, systemic in 14%, while central nervous system involvement was seen in 4% [21]. On average, joint symptoms were complained of 6 years before the diagnosis of Whipple's disease was finally confirmed [20].

Cases have also been reported in which administration of immunosuppressants has either caused a deterioration in the symptoms of Whipple's disease or revealed the disorder as underlying. In certain patients, this led to grave complications, including sepsis or dissemination of the bacterium into multiple organ systems [22].

The improvements in molecular diagnostic techniques have meant that the involvement of *T. whipplei* in other disorders has been detected. One study involving 241 paediatric patients between the ages of 2 and 4 years, suffering from acute gastroenteritis, found that the bacterium was present in 15% of the cases, whereas it was not detected in any of 47 control cases. A further diarrhoeal pathogenic organism was found to co-exist in a third of cases [23]. A study of cases of non-specific pyrexia in a rural west African setting also discovered an association with *T. whipplei* [24, 25]. *T. whipplei* was detected by PCR in the blood of 6.4% of cases ($n = 13$) in a study in Senegal where the patients had pyrexia, but testing for malaria was negative. In the majority of the cases involved, the patient was a child and the symptomatic presentation was of coughing and insomnia [20].

There are also reports concerning asymptomatic carriage of the bacterium in apparently healthy individuals. The presence of the bacterium was confirmed by PCR testing of stool or saliva [17, 19, 26–29]. The frequency of carriage is related to geographical location. European samples taken from the faeces of healthy adults show a prevalence of between 1% and 11% [30]. However, when the prevalence was assessed in a rural setting in Gabon, using the same method of detection, it appeared that 20% of individuals exhibited asymptomatic carriage. The rate in children in this group was even higher [31].

47.5.1 Classical Presentation of Whipple's Disease

The key features of late-presenting Whipple's disease are as follows [21]:

- Joint pain
- Unintentional loss of weight
- Diarrhoeal illness
- Abdominal colicky pain

47.5.2 Involvement of the Central Nervous System

Evidence of central nervous system involvement may be found either in classic Whipple's disease or may indicate that infection has relapsed following initial treatment. The rate of nervous system involvement in cases with the classical manifestation of Whipple's disease is between 10% and 40%. Whipple's disease which only affects the nervous system does occur, but infrequently. The longer the infection continues, the higher the probability that it will involve the central nervous system [32].

The involvement of the central nervous system only rarely results in symptoms. It becomes apparent when PCR for bacterial DNA is performed on CSF. Where symptoms are noted, they generally affect cognition, including irreversible, progressive cognitive decline, and disorientation [33]. There are two signs which are pathognomonic for Whipple's disease, namely oculomasticatory and

oculo-facio-skeletal myorhythmia [21, 33, 34]. The former sign consists of continuous rhythmic action of the ocular convergence reflex and simultaneous action off the muscles of mastication. In both cases there is virtually invariably a concomitant supranuclear vertical gaze palsy [20]. One or both of these signs is/are present in around a fifth of cases.

The frequency of cerebellar ataxia is likely to be higher than was initially claimed in the literature. A study with a retrospective design which reviewed 11 cases of Whipple's disease noted cerebellar ataxia as a presenting feature in 5 patients [35]. In published case series, there have been descriptions of several possible neurological abnormalities, such as myoclonus, hemiparesis, peripheral neuropathy, seizures, and disorders of upper motoneuron type [14]. The bacterium may interfere with the proper functioning of the hypothalamus. In cases where neurological abnormalities present clinically, neuroimaging with CT (computed tomography) or MRI (magnetic resonance imaging) sometimes demonstrates foci of disease of a non-specific type. These foci usually disappear once adequate treatment has been administered [21].

Whipple's disease confined to the nervous system seldom occurs and is challenging to correctly identify. An article which reviewed all the published evidence found 20 cases where Whipple's disease was confined to the central nervous system. Two distinct syndromes were noted to occur in such cases [20, 36]:

- In 72% of the reported cases (i.e. 13 out of 18), there were multiple, varied presenting features of neurological type, such as generalised seizures, ataxia, oculomotor dysfunction, amnesia, SIADH (syndrome of inappropriate anti-diuretic hormone secretion), obstructive sleep apnoea, difficulty sleeping, meningoencephalitis, hemiplegia, irreversible, progressive cognitive decline, etc. Imaging in these patients revealed numerous lesions exhibiting enhancement.
- In 28% of cases (i.e. 5 out of 18), there was an identifiable focus for the abnormality and imaging revealed a single mass lesion.

For cases which do present with neurological signs within Whipple's disease, it is essential to send CSF for analysis. If neurological signs and symptoms are absent, the CSF is generally also reported as normal. Cases where symptoms are present feature abnormalities of the CSF, such as a slight or moderate increase in cell count (between 5 and 100 cells per microlitre). The cells present are typically lymphocytes or monocytes/macrophages. Cytology specimens of CSF stained with PAS may reveal multiple stained macrophages. Furthermore, the protein content may be abnormally high and oligoclonal bands may be detected. In patients prior to treatment, PCR in CSF of *T. whipplei*-affected patients gives a positive result when neurological features are present clinically [20].

47.6 Deafness/Auditory Impairment

The onset of auditory impairment has been stated to be a possible initial presenting feature of Whipple's disease [37]. However, deafness affecting both ears, associated retinal vasculitis and intestinal features, is not an initial presenting feature. Auditory impairment as a presenting feature is of sensorineural type and affects both ears [38]. A case report by Scheurer et al. [39] describes deafness in both ears affecting the high and mid-frequencies in a patient whose diagnosis of Whipple disease had been confirmed by electronic microscopic examination of the duodenum.

47.7 Management

47.7.1 Susceptibility to Antibiotics

It has been shown in vitro that the *T. whipplei* organisms are sensitive to the following antibiotic agents: doxycycline, macrolides, ketolides, aminoglycosides, penicillin, rifampicin, teicoplanin, chloramphenicol, and the combination of trimethoprim and sulfamethoxazole. The minimum inhibitory concentrations are between 0.25 and 2 μg/mL. This was shown on organisms grown in cell culture and utilised real-time PCR DNA amplification [40–42]. A bactericidal effect has been shown for doxycycline and hydroxychloroquine used concomitantly [41]. For *T. whipplei* organisms within host cells, the cephalosporins, polymyxin, and aztreonam exhibit less efficacy.

T. whipplei is not susceptible to fluoroquinolones. The gyrA and parC genes have been sequenced and shown to possess mutations that have the effect of rendering *Escherichia coli* resistant to fluoroquinolones. It is probable that the same mutations in these genes are what render *T. whipplei* similarly resistant [40].

Furthermore, there is no gene coding section within the *T. whipplei* genome that corresponds to a dihydrofolate reductase. This is the enzyme which trimethoprim inhibits. The fact that *T. whipplei* is susceptible to combined trimethoprim and sulfamethoxazole is thus entirely the result of sulfamethoxazole [20, 42].

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Part V

Viral Infections

Viral Infections in Children and Hearing Loss: An Overview

48

Benhur Şirvan Çetin, Emin Sami Arısoy, and Gail J. Demmler-Harrison

48.1 Introduction

An estimated 1.3 billion individuals worldwide have some hearing loss (HL) [1]. By 2050, over 2.5 billion people—or one in every four people—will have some degree of HL, according to the first World report on HL of the World Health Organization (WHO) [2]. Hearing loss is a common disability among children. In the United States of America (USA), 1.1–1.7/1000 neonates are born with bilateral HL ranging from severe to profound, and 1–2/1000 are born with mild to moderate unilateral or bilateral HL [3, 4]. Improved maternal and neonatal care, immunization, and screening for and early management of the middle ear's inflammatory illnesses can prevent about 60% of HL in children [2].

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Sensorineural HL (SNHL) is responsible for around 45% of unilateral and 70% of bilateral HL in children with HL, while conductive HL (CHL) accounts for 30% of unilateral and 7% of bilateral HL. Sensorineural HL has a variety of etiologies, including genetic, anatomic, autoimmune, infectious, ototoxic, and traumatic, whereas CHL frequently has an underlying anatomic origin [5].

Infectious diseases can have a negative impact on the development of the auditory system if a fetus is exposed to the infection during pregnancy, delivery, or shortly after birth. Viral infections are one of the most common etiologies of SNHL among the other causes of HL [6].

Viruses typically cause damage to the cochlea that results in SNHL. Certain viruses like CMV, measles virus, and HIV can cause CHL and mixed HL, as well [7]. Hearing loss induced by viruses can range from mild to severe, unilateral or bilateral. In some cases, effective antiviral medication can reverse or halt the progression of HL.

Various viral infections can cause HL, including cytomegalovirus (CMV), hepatitis B and C viruses, herpes simplex virus (HSV) types 1 and 2, human immunodeficiency virus (HIV), lymphocytic choriomeningitis virus (LCMV), measles, mumps, rubella, varicella-zoster virus (VZV), West Nile virus (WNV), and ZV infections [7–9]. A recent 13-year nationwide population-based cohort study in Taiwan found that human papillomavirus (HPV) infection was also associated with a higher risk of HL [10]. Baseline knowledge of HL's various viral origins and treatments is required to recognize these entities and manage them appropriately.

48.2 The Pathophysiology of Hearing Loss in Viral Infections

Viruses can cause HL in three manners: Congenital, in which HL is generally present at birth; acquired, in which HL occurs over time after the onset of infection; or a combination of the two. In general, very young children are the most at-risk group.

Viral infections can cause HL in three different ways [6]:

- Invasion of the cochlear nerve or the cochlea's fluid spaces and/or soft tissues.
- Under certain conditions, the latent virus activation within the inner ear.
- Indirectly over-activating stress pathways in the cochlea by an antibody response triggered by a viral infection that responds with an inner ear antigen or a circulating ligand.

48.2.1 Direct Invasion

Mumps infection can cause damage to the inner ear, which may be a direct result of the illness. In mice, HSV-1 and HSV-2 infections destroy the Corti organ and its supporting structures and cause deafness [11]. In an animal model, the Lassa virus caused direct damage to the hair cells, spiral ganglion neurons, and vascular rich cells within the cochlea [12].

48.2.2 Viral Reactivation

Herpesviridae, the family of human herpesviruses, is the most likely viral etiology of sudden SNHL [6]. Varicella-zoster virus, a member of Herpesviridae, often remains dormant in the body after the primary infection, namely chickenpox. Reactivation of the VZV causes the "zoster" or "herpes zoster" phenomenon. Ramsay Hunt syndrome, also known as herpes zoster oticus (HZO) or geniculate ganglion herpes zoster, is a late manifestation of VZV infection that causes inflammation of the geniculate ganglion of the seventh cranial nerve [13]. It is distinguished by a characteristic triad of ipsilateral facial paralysis, otalgia, and vesicles in or on the auricle. The closeness of the facial nerve to the vestibulocochlear nerve can also cause HL, vertigo, and tinnitus. In a case series, SNHL was observed in up to 43% of HZO patients [14].

48.2.3 Immune-Mediated Reactions and Stress-Response

Many factors, including physical, mental, and metabolic stresses, systemic inflammatory diseases, or viral infections, can trigger the innate immune system in the cochlea, resulting in the production of antigens in the inner ear and the activation of robust adaptive immunological reactions which can lead to immune-mediated HL [15, 16]. Sudden SNHL has been linked to numerous stressful experiences that promote subclinical infection or immunological dysregulation [6].

There are many obstacles to explaining the etiopathogenesis of viral infections in HL. Medical imaging and serological and immunologic testing cannot consistently demonstrate the direct etiology of SNHL. Moreover, in most studies, the acquired data from patients are insufficient, or the study has methodological limitations.

48.3 Viral Infections Causing Hearing Loss

While viral infections can cause HL with different physiopathological processes, the time of infection and HL is essential in clinical presentation. Viral infections can result in HL in three ways; congenital (taking place at birth) HL, HL occurring over time after the onset of a viral infection, or a combination of the two (Table 48.1).

48.3.1 Viral Infections: Congenital Hearing Loss

Development of the inner ear occurs during the first trimester of pregnancy; abnormalities at this time, whether caused by genetic mutations or environmental factors, can lead to HL [20]. Identifying variables that may act intrauterine and contribute to congenital HL is critical. Early detection and treatment of congenital HL can help prevent later difficulties, such as delays in speech and language development, cognitive impairment, lower school achievement, and socializing.

Table 48.1 Viral causes of hearing loss

Virus	Type of HL	Notes for clinicians	Prevention	Treatment
Congenital infections				
CMV	Progressive SNHL	• Congenital disabilities may accompany but may also be seen in asymptomatic infection • Progressive SNHL can occur later in life • Incidence is 10–15% in congenital CMV infection [17]	None	Ganciclovir, valganciclovir, cidofovir, foscarnet
Rubella	SNHL	• Congenital disabilities may accompany. • SNHL is the most common sequela of congenital rubella infection (58%) [18]	Vaccine (MMR)	None
Zika virus	SNHL	• Congenital disabilities may accompany • Travel to endemic regions in history	Avoidance of exposure	None
LCMV	SNHL	• Lack of hepatosplenomegaly	Avoidance of exposure	Ribavirin, favipiravir
Congenital and acquired infections				
HSV	SNHL	• Following primary infection or reactivation of latent infection	None	Acyclovir
HIV	SNHL, CHL, mixed	• The prevalence of auditory symptoms in patients with HIV is 14–49% [7]	Avoidance of exposure and postexposure antiretroviral treatment	HAART
Acquired infections				
Rubeola (measles)	SNHL, CHL	• Measles infection has been hypothesized to cause otosclerosis	Vaccine (MMR)	None
VZV	SNHL	• Reactivation of the virus (Ramsey Hunt syndrome [HZO]) • Symptoms of VZV reactivation	Vaccines (for chickenpox and zoster)	Acyclovir, prednisone
Mumps	SNHL	• The risk of SNHL is not correlated with the severity of the infection or the presence of parotitis	Vaccine (MMR)	None
WNV	SNHL	• HL is extremely rare • More frequently in immunocompromised patients	Avoidance of exposure	None

Table 48.1 (continued)

Virus	Type of HL	Notes for clinicians	Prevention	Treatment
SARS-CoV-2	SNHL	• The pathophysiology of HL is not clear • The event rate was 3.1% in a meta-analysis [19]	Vaccine	None

CHL conductive hearing loss; *CMV* cytomegalovirus; *HAART* highly active antiretroviral therapy; *HL* hearing loss; *HSV* herpes simplex virus; *HZO* herpes zoster oticus; *LCMV* lymphocytic choriomeningitis virus; *MMR* measles, mumps, rubella; *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2; *SNHL* sensorineural hearing loss; *VZV* varicella zoster virus; *WNV* West Nile virus

All the members of TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and syphilis, respectively), an acronym for infectious teratogens seen frequently, can cause similar congenital abnormalities. In general, the congenital infections contained by the TORCHS group are among the leading causes of HL that result in pediatric cochlear implantation [21]. Severe central nervous system involvement occurs in 50–90% of these infants with microcephaly, intracerebral periventricular calcifications, and HL.

48.3.1.1 Congenital Cytomegalovirus Infection

Cytomegalovirus is the leading cause of nonhereditary SNHL, occurring in 0.2–2% of live births worldwide [22, 23]. Congenital CMV (cCMV) infection is a significant cause of both congenital and delayed-onset SNHL. Early detection of cCMV infection is critical to diagnosing and treating children with HL. The leading manifestations of cCMV disease include intrauterine growth restriction (IUGR), hepatosplenomegaly, jaundice, pneumonitis, rash, and HL.

Sensorineural HL caused by cCMV infection has a wide range of symptoms, findings, progression, and severity. Hearing loss, unilateral or bilateral, caused by cCMV infection can be present in early childhood. Congenital CMV-infected children may have normal hearing at birth, but a progressive SNHL can occur later in life and affect speech development [24]. In general, cCMV causes unilateral and progressive HL [25]. According to the 2019 Joint Committee on Infant Hearing (JCIH) guidelines, cCMV plays a more prominent role in childhood HL than previously expected, with 10–15% of babies with cCMV suffering SNHL [17].

Typical intracranial findings on computed tomography (CT) or magnetic resonance (MR) imaging may support the diagnosis of cCMV infection. An early diagnosis may be obtained by examining neonatal dried blood spots collected for neonatal screening [5]. In initially asymptomatic newborns without predisposing factors for SNHL, periodically repeated screening of cCMV-infected neonates is essential for the prognosis and treatment [22]. Because of the frequent progression of SNHL in children with cCMV infection, ongoing audiometric surveillance is also required.

48.3.1.2 Congenital Rubella Infection

Congenital rubella infection can present at birth with manifestations including microcephaly, microphthalmia, cataracts, cardiac anomalies, thrombocytopenia, rash, and HL. Congenital rubella is still one of the leading causes of severe bilateral SNHL in places where rubella vaccination rates are low [26]. Sensorineural HL is the most prevalent (58%) complication of congenital rubella syndrome and occurs most frequently when the mother is infected during the first trimester of pregnancy. Typically, the vestibular function is preserved [18]. Hearing loss typically develops within the first 6–12 months of life. Although the rubella infection directly causes cochlear damage and cell death, the mechanism of rubella-induced HL has not been fully elucidated [27]. Vaccination of women before or throughout their reproductive years is highly efficient in preventing congenital rubella infection in children.

48.3.1.3 Congenital Lymphocytic Choriomeningitis Virus Infection

The LCMV has been identified as an emerging teratogen. The ordinary house mouse and other rodents are the primary hosts and reservoirs of LCMV. The virus is transmitted through contact with rodent saliva, urine, or feces. The LCMV infections are usually asymptomatic or characterized by upper respiratory tract infection symptoms. The fetus can be affected by LCMV infection, mainly if maternal infection occurs during pregnancy's first or second trimester. The congenital LCMV infection is associated with microcephaly (or macrocephaly), hydrocephalus, seizures, ventriculomegaly, cerebellar hypoplasia, pachygyria, periventricular calcification, chorioretinitis, neurodevelopmental sequelae including intellectual disability, HL, and even death [28, 29]. Microcephaly and visual impairment are more common than HL in congenital LCMV infection [30].

48.3.1.4 Congenital Zika Virus Infection

Zika virus was first isolated in 1947 in a rhesus macaque monkey in the Zika Forest of Uganda. The majority of infected persons have no symptoms. The most common symptoms and signs of ZV infection are fever, headache, retrobulbar pain, vomiting, conjunctivitis, skin rashes, edema, muscle pain, and arthritis or joint pain. The ZV is a mosquito-borne infection that can be passed from pregnant women to fetuses.

Congenital Zika syndrome (CZS) causes birth defects, such as microcephaly, decreased brain tissue, and vision and hearing impairment. In a systematic literature review, a large percentage of children exposed to ZV intrauterine presented with failed outcomes in the hearing examination, with otoacoustic emissions (OAEs) or auditory nerve brainstem response (ABR) up to 30.2% and 19.9%, respectively [31]. Around 7% of newborns with CZS suffer from persistent SNHL [32]. As a result, there appears to be a link between ZV exposure of the fetus during pregnancy and SNHL [31]. While the primary concern for ZV infections is CZS, children infected with Zika beyond the neonatal period are at risk for transient SNHL and Guillain-Barre syndrome [33].

48.3.2 Viral Infections: Congenital and Acquired Hearing Loss

48.3.2.1 Human Immunodeficiency Virus Infection

Different factors can contribute to hearing impairment in HIV-infected individuals, including the direct effects of the virus, increased vulnerability to infections in the ear and brain, and adverse effects of the ototoxic drugs used in the treatment. Several investigations have shown that HIV has central and peripheral effects on the auditory system, although the processes by which this occurs remain largely unknown. The prevalence of auditory complaints in HIV-infected patients ranges from 14% to 49% [7]. Common auditory symptoms include HL, tinnitus, facial nerve palsy, and chronic otitis media. The risk of developing HL in HIV-infected individuals is more frequent later in life, although infants can present with HL following infection at postpartum or in utero [34]. In a study from Uganda, of 370 HIV-positive children aged 6 months to 5 years old, 33% suffered from HL [35].

Human immunodeficiency virus-associated HL may present with different clinical presentations. It can be unilateral or bilateral, progressive or sudden, sensorineural, conductive, or mixed. Antiretroviral therapy does not significantly reverse HL. While HL and speech developmental delays are not the most critical problems for the HIV-infected population, they are essential components of a child's quality of life that should be considered. For HIV-infected patients with mild to moderate SNHL, hearing aids can be used. Cochlear implantation can be successful for patients with severe SNHL.

48.3.2.2 Herpes Simplex Virus Infection

The consequences of neonatal HSV infection range from infection of the eyes and mucous membranes to encephalitis, motor-mental retardation, HL, and death. Hearing loss has been linked to HSV types 1 and 2. Many infants infected with HSV do not present with a vesicular rash; therefore, they may not be tested for HSV infection. Compared to HSV-2, encephalitis and HL in newborns are far more commonly associated with HSV-1 infection and severe neurological complications. After the HSV infection in newborns, HL can be unilateral or bilateral, and mild to severe SNHL. Hearing loss has also been linked to the primary or reactivation of latent HSV infection beyond childhood [36].

In animals, HSV infections were linked to hearing impairment and vestibular symptoms. After the infection with HSV-1 or HSV-2 in animal models, loss of outer hair cells, fibrosis of the scala tympani and vestibule, and atrophy of the stria vascularis and the tectorial membrane were reported [6].

Antiherpetic drugs and corticosteroids are used to treat HL caused by HSV-1 or HSV-2 infections. Hearing loss not responding to steroid and antiherpetic therapy can be treated with hearing aids or cochlear implants, depending on the severity of the HL.

48.3.3 Viral Infections: Acquired Hearing Loss

48.3.3.1 Measles (Rubeola)

In the USA, before nationwide vaccination, measles accounted for 5–10% of cases of severe HL [37]. Unfortunately, measles remains a leading cause of HL in countries with low vaccination rates. Otitis media is common in patients infected with measles, up to 8.5–25% of infected people, more significant in low-income countries [7]. Measles infection is associated with otosclerosis, which causes CHL and SNHL by forming foci of abnormal bone remodeling in the middle and inner ear [38]. Measles-related HL is usually bilateral, moderate to profound SNHL, and may occur after encephalitis [37]. Sequelae of bacterial superinfection may account for some cases of HL associated with measles infection [39].

48.3.3.2 Varicella-Zoster Virus Infections: Chickenpox and Zoster

Varicella-zoster virus, a member of the Herpesviridae family, causes a primary chickenpox infection with an erythematous papulovesicular rash when symptoms are present. In some people, the primary infection may be asymptomatic. Varicella-zoster virus is highly infectious and spreads by droplets from infected people or by direct contact with fluid from vesicles.

Varicella-zoster virus can remain latent in neurons in various body parts and reactivate years later. The reactivation infection (zoster or shingles) can include systemic (fever and malaise) and local (severe pain and a vesicular rash) symptoms. The local symptoms are typically limited to the area innervated by the neurons in which the virus reactivated.

Ramsay Hunt syndrome, or HZO, is caused by the reactivation of latent VZV within the geniculate ganglion, which results in inflammation in the geniculate ganglion and facial nerve. Involvement of the eighth cranial nerve is caused by virus transfer from a neighboring geniculate ganglion or directly from the facial nerve within the internal auditory canal. The main symptoms and signs are facial nerve paralysis, herpetic vesicles, acute otalgia, tinnitus, vertigo, and SNHL. Sensorineural HL is usually mild to moderate and typically unilateral. Occasionally, SNHL might appear unexpectedly as the first symptom, so HZO must be considered in the differential diagnosis of sudden SNHL.

In about 5% of cases of HZO, permanent HL occurs [7]. The current treatment for HZO consists of antiherpetic agents and corticosteroids. Hearing loss caused by HZO may improve with treatment, although facial nerve recovery is reported less frequently [40]. Hearing aids are the backbone of nonpharmacological treatment for mild to moderately severe SNHL.

The direct effect of varicella vaccination on HZO has not been assessed widely, but the incidence of these cases is expected to decrease. On the other hand, immunization with Zostavax©, a live attenuated varicella-zoster virus vaccine for the prevention of VZV reactivation, is currently recommended in the USA for people aged 50 years and older [7].

48.3.3.3 Mumps

The mumps virus is highly contagious and spreads through infected respiratory secretions. Mumps begins with flu-like symptoms and progresses to bilateral enlargement of the parotid glands. Pancreatitis, oophoritis, orchitis, infertility, and SNHL are possible mumps complications [37]. Sensorineural HL usually develops 4–5 days following the onset of influenza-like symptoms and parotitis. Hearing loss is generally unilateral and reversible, but can also be severe and permanent. The likelihood of developing SNHL after mumps is unrelated to the severity of the infection or the presence of parotitis [7]. Aseptic meningitis and encephalitis are rare complications of mumps infection, but their presence increases the risk of SNHL. Mumps can also cause sudden SNHL, as evidenced by positive IgM antibodies in asymptomatic patients [8].

Hearing loss due to mumps infection is estimated to occur in 1 in 1000 to 1 in 30,000 people. During the 1984 Israeli epidemic, the rate was 3 in 100 people [7]. Immunization with the measles, mumps, and rubella (MMR) vaccine has significantly decreased the number of cases of mumps and its complications. Hearing aids can treat SNHL associated with mumps in mild to severe cases. Cochlear implantation is effective in patients with severe bilateral SNHL.

48.3.3.4 West Nile Virus Infection

West Nile virus, typically transmitted by mosquito bites, belongs to the Flaviviridae family, including dengue and yellow fever viruses. Congenital WNV infections and transmission by breastfeeding and blood transfusions were reported as case-based. Only 20% of WNV infections present with clinical manifestations, and the symptoms and signs of a flu-like sickness are the most frequent. Meningitis, encephalitis, and acute flaccid paralysis are neurological sequelae that occur in less than 1% of cases with WNV infection [41]. Hearing loss resulting from WNV infection is rare and often recovers spontaneously [7]. There is no specific treatment approved for WNV-infected patients.

48.3.3.5 Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that causes coronavirus disease 2019 (COVID-19), generally presents with nonspecific flu-like symptoms. The clinical severity of COVID-19 ranges from no symptoms to severe pneumonia and death. Despite the pulmonary, cardiovascular, and neurological complications, several studies have found that vestibulocochlear symptoms such as dizziness, vertigo, vestibular neuritis, sudden SNHL, and tinnitus are common [42]. A systematic review and meta-analysis showed that the event rate is 3.1% for HL in confirmed cases of COVID-19 [19].

Regarding the potential type of HL, case series and case reports have predominantly reported SNHL. Neuronal death in the brainstem region, disruption of the blood-brain barrier and hyper-inflammation, hypoxia caused by hyperfusion-mediated ischemia in the inner ear structures, and involvement of direct viral

infections in the inner ear tissues are some hypotheses of HL and vestibular complications [42]. Available data on COVID-19 and inner ear complications like HL are insufficient to assess clearly.

48.4 Conclusion

Hearing loss in children commonly results from prenatal infections, such as TORCHS, or postnatal infections by various organisms. Viral infections generally play a crucial role in pediatric HL. Some viral infections and the HL they cause can be treated with specific treatments. Therefore, knowing the characteristics of the viral infections that may be complicated with HL becomes essential in evaluating and managing patients.

A comprehensive medical evaluation should be done once the HL is confirmed in a child, including detailed perinatal history and prenatal exposure to maternal infections. Globally, infectious causes of HL have decreased as a result of extensive vaccination programs. Childhood immunization history can reveal who is at risk for mumps and measles, and travel exposures can reveal who is at risk for some infections, such as ZV infection, among other diseases.

Evaluation for sudden HL is a unique situation in which prompt diagnosis and treatment can determine whether the HL is reversible or permanent. The patient's medical history and physical examination are essential in deciding which diagnostic tests should be considered and performed. Other infectious agents should also be considered in the differential diagnosis, along with acute viral infections. For example, unilateral or bilateral sudden HL may be caused by mumps, syphilis, and delayed-onset congenital CMV infection.

Several viral diseases covered in this chapter can be prevented with standard pediatric immunizations, which should be suggested to patients and parents. In contrast to adults, pediatric HL often occurs before speech and language development, adversely affecting a child's academic success and quality of life. The primary motivation for early detection and treatment of HL should be to prevent speech-language delay and subsequent consequences.

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Measles Infection in Children and Hearing Loss

49

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49.1 Introduction

Measles is an acute, highly contagious childhood viral disease that often causes fever, cough, malaise, runny nose, rash, and conjunctivitis. Measles was a common disease before the live measles vaccine was approved in the United States of America (USA) in 1963 [1, 2]. The incidence has decreased by that time. Although measles control has been achieved globally, epidemics continue from time to time in the world due to low vaccination rates [3].

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49.2 Etiology

The measles virus is an enveloped ribonucleic acid (RNA) virus classified in the Paramyxoviridae family. The measles virus genome encodes eight structural proteins, including C, fusion (F), hemagglutinin (H), large (L), matrix (M), nucleoprotein (N), phosphopolymerase (P), and V proteins. The M protein, a nonglycosylated protein, is essential in virus assembly, and the two glycoproteins, H and F, are related to the envelope. The H glycoprotein is responsible for the attachment to the host cells, while the F glycoprotein plays a role in spreading the virus between cells. The two nonstructural proteins, C and V, regulate transcription and replication. The genotypes are grouped by clades, with 8 clades (A–H) and 23 genotypes. The measles' endemic and epidemic spread are assessed based on this grouping [4].

49.3 Epidemiology

The prevalence of measles has varied throughout time, and after the introduction of the measles vaccine in 1963, the measles' incidence and attack rate declined dramatically [5]. With the widespread implementation of this vaccine and aggressive elimination programs, the incidence of measles declined over the next 20 years from 300 per 100,000 population in the pre-vaccine period to 1.3 cases from 1982 to 1988 [6]. Between 1989 and 1992, measles resurfaced in many countries, including the USA, related to inadequate vaccination coverage among preschool children and vaccine failure after a single measles vaccine dose. A third elimination effort was the introduction of the second measles vaccine dose in the 1990s. As a result, endemic measles was eradicated successfully in 2000. The measles incidence reduced to less than one case per million in 1997–1999 [7, 8], with nearly 90% of all cases reported outside of the USA [9]. However, in 2014, 383 patients were reported during an outbreak in Ohio. This outbreak was attributed to undervaccination in the Amish population following the return of Amish missionaries from the Philippines, which had been experiencing a significant measles epidemic [10]. Another outbreak followed in short order at Disneyland in California, where 125 measles cases were reported between December 2014 and February 2015, again attributed to undervaccination [11].

The World Health Organization (WHO) had planned to eradicate measles in Europe by 2015; however, these efforts were not realized as Europe saw nearly 25,500 cases in 2017 [7, 8]. That year, more than 5000 cases were reported in Italy alone, with the highest incidence among infants and preschool children [12, 13]. A year later, the number of cases in Europe had tripled to 83,000, with over 54,000 reported in Ukraine. Worldwide, measles has continued to rise throughout the end of the last decade, with data showing a 300% increase in 2019 across the same period the year prior [14]. This increase manifested as outbreaks, primarily among young children, in many countries: Brazil, the Democratic Republic of the Congo, Ethiopia, Georgia, Kazakhstan, Kyrgyzstan, Madagascar, Myanmar, the Philippines, Sudan, Thailand, and Ukraine [6, 14].

Before widespread global vaccination began in the 1980s, approximately 2.6 million measles-related deaths were reported worldwide yearly. According to the WHO, 15.6 million deaths were prevented by immunization between 2000 and 2013 [7, 8]. Despite these successes, there were still approximately 145,000 deaths from measles worldwide in 2013 [7, 8]. Differences in the total number of deaths attributed to this infection reflect varied case fatality rates between 0.2% and 0.3% in high-income countries and 2% and 15% in low and middle-income countries [6, 9, 12].

49.4 Transmission

Measles is highly contagious, with person-to-person contact and airborne spread being the essential means for transmission. Alarmingly, in what is consistent with its high basic infection-reproduction rate, infectious patient droplets can remain in air for about 2 h [15]. As individuals are most infectious during the prodromal period [4], measles can spread quickly in the population before signs or symptoms of the infection are present. The basic reproduction ratio (R_0) is 12–18, and infection occurs in 90% of susceptible individuals [16].

49.5 Pathogenesis

Nonhuman primate studies showed that the measles virus initially infects CD150+ alveolar macrophages and dendritic cells [17], migrating to the regional lymph nodes. The prodromal period begins with secondary viremia between the fifth and seventh days of infection. The viral load of blood and other tissues increases between the 11th and 14th days and decreases rapidly over 3 days. Giant cells may be observed in the nasopharynx, tonsils, and bronchial mucosa in the early phase of the disease [18].

49.6 Immune Response

Adaptive immunity is important in establishing and maintaining lifelong immunity against measles. Clearance of the virus begins rapidly; however, measles virus RNA might persist in mononuclear cells for several months [19].

Cellular immunity is essential for aborting symptoms in the acute phase of infection, and humoral immunity is vital in preventing measles. Cytotoxic CD8+ T lymphocytes mediate the initial cellular immune response. Interferon-gamma (γ) and interleukin-2 (IL-2) generate a helper T lymphocyte subtype 1 (Th-1) response, then IL-4 and IL-10 contribute to switching in the T2 response, and antibodies for measles virus are produced in the recovery phase [20].

49.7 Clinical Manifestations

Measles disease has incubation, prodromal, rash, and recovery stages. The incubation period is usually 8–12 days from exposure to the beginning of the symptoms. The contagious period starts 4 days before the rash and continues until 4 days after the rash onset [21]. Generally, the patients have no accurate sign of illness in this period, but some may have a transient mild fever and respiratory symptoms after the virus acquisition [22].

The prodrome period lasts approximately 3 days (2–4 days). It begins with fever, coryza, cough, conjunctivitis, and malaise. Fever increases gradually up to 39.5 °C ± 1.1 °C throughout a 4-day. The nasal symptoms are sneezing, rhinitis, and congestion, like in other viral respiratory tract infections. The cough in the prodromal period worsens and often has a brassy quality. Photophobia and lacrimation may accompany conjunctivitis [21, 22].

Koplik spots are the pathognomonic enanthem of measles, usually appearing 48 h before the onset of the exanthem reported in 50–70% of cases. The lesions are 1–3 mm gray-white specks on a red mucosal base located in the buccal mucosa at the level of the second molars. Still, in some cases, involvement of gingiva, mucosal surface of lips, hard palate, conjunctival folds, and the vaginal mucosa may be observed. Koplik spots may persist for 1–3 days; they start to disappear as the exanthem appears [23].

The rash appears 2–4 days after the beginning of the fever. It is erythematous, maculopapular, and tends to coalesce. Exanthem classically starts behind the ears and at the forehead's hairline, then spreads cephalocaudally to the neck, trunk, and extremities. It lasts about 6–7 days and starts to fade in the same manner as it appeared. As the rash progresses, a coppery brown discoloration is seen, and desquamation may occur in the areas involved in the healing phase, except palms and soles. The total duration of the exanthem is 6–7 days [23].

Other characteristic findings of the exanthematous phase are high fever, lymphadenopathy, respiratory signs including pharyngitis, and nonpurulent conjunctivitis. The fever generally peaks 2–3 days after the rash and rapidly resolves in uncomplicated measles. Complications should be considered in persisting fever on the fourth day of the exanthem. Continued nasal discharge may suggest secondary bacterial infection. With the onset of the rash, the cough subsides and may last 10 days or more [22].

49.8 Special Clinical Variants

49.8.1 Modified Measles

Infection in individuals with partial immunity to measles is typically mild and can be mistaken for other etiologies. While partial immunity is typically attributed to incomplete vaccination, it can also be the result of transplacental antibody transfer, receiving immune globulin (Ig) after exposure to measles, or secondary vaccine

failure. The clinical course is milder than a typical infection, and the classic symptoms may be absent with a slightly prolonged incubation period of 14–20 days [4, 24].

49.8.2 Atypical Measles

Atypical measles, now rare, is the result of infection among the individuals who received the inactivated measles vaccine used in the USA before 1963 [25]. The fever is typically higher and more prolonged in atypical measles. The maculopapular rash starts on the arms and legs and extends to the trunk. Vesicle, petechiae, purpura, or urticaria may be observed. Severe illness is usually seen, and many patients develop chest pain, dry cough, pneumonia, and respiratory distress [4].

49.9 Complications

Complications occur in approximately 30% of patients, and mortality is reported in about 0.2% [22]. Morbidity and mortality related to measles are most significant in individuals younger than 5 and older than 20 years of age [22, 23]. Immunocompromised persons, pregnant women, and individuals with vitamin A deficiency or poor nutritional status have an increased risk for measles complications [22].

Acute otitis media (AOM) is the most frequent complication of measles (7–9%), and it is more common in younger children. Other respiratory complications are pneumonia, bronchopneumonia, bronchiolitis, and laryngotracheobronchitis [4]. Pneumonia is a common fatal complication of measles. Viral invasion of the lungs or secondary bacterial infection may cause pneumonia. *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b (Hib), *Staphylococcus aureus*, and *Streptococcus pyogenes* (group A streptococcus; GAS) are prevalent pathogens that cause secondary bacterial pneumonia. Bronchiolitis obliterans is the fatal complication of severe measles [22]. Myocarditis and pericarditis may occur in measles, but clinical consequences from such involvement are rare [22]. Diarrhea and vomiting are prevalent symptoms in the acute course of measles. Dehydration may be seen, especially in young infants and children. Due to lymphoid hyperplasia and mesenteric adenitis, appendicitis or abdominal pain may occur [23].

Neurologic measles-related complications include encephalitis, acute disseminated encephalomyelitis (ADEM), and subacute sclerosing panencephalitis (SSPE). Encephalitis was reported in up to 1–3 per 1000 cases of measles that generally occur in adolescents and adults. Acute encephalitis symptoms develop during the measles exanthema period within 8 days (range 1–14 days) of the beginning of the illness with fever, seizures, headache, vomiting, and neck stiffness [26]. Cerebrospinal fluid (CSF) includes lymphocyte-predominant pleocytosis, elevated protein, and normal glucose levels. Mortality in measles encephalitis is about 15%, and 20–40% of patients have long-term neurological sequelae [23].

Subacute sclerosing panencephalitis is a rare, mortal, progressive, and degenerative disease of the central nervous system (CNS) that occurs in approximately 4–11 per 100,000 measles cases. Its pathogenesis is not well understood, but may involve persistent infection with wild-type measles virus within the CNS [27, 28] and less so with vaccine strain [29]. Intellectual deterioration, seizures, and behavioral changes are characteristic findings that begin 7–11 years after wild-type measles virus infection [21]. Myoclonic seizures, motor disturbances, and ocular disease are late-stage findings. The disease progresses, and death usually occurs 1–3 years after the first symptoms [30].

49.10 Measles and Hearing Loss

Congenital and acquired hearing loss (HL) have been attributed to viral infections. The pathophysiology of this process varies; some viruses can directly damage inner ear cells, and others can cause an inflammatory process, damaging or increasing susceptibility to secondary bacterial or fungal infection resulting in HL. In general, viral-mediated HL is of the sensorineural type HL (SNHL); however, conductive or mixed type HL can also be seen after some viral infections owing to disturbances in the mechanistic function of the ear [31].

In the pre-vaccine era, measles was a significant cause of profound bilateral SNHL, with 5–10% of these cases being attributed to this infection [32]. Despite having a safe and effective vaccine, measles remains a common cause of profound HL in the twenty-first century in countries where vaccination rates are low [33].

Measles-induced HL is typically bilateral, and its severity ranges from moderate to profound SNHL [32]. The histopathologic effects of measles on the inner ear have been studied in the temporal bones of infected human and animals, which found similarities to the sequela of suppurative bacterial labyrinthitis [34]. In 1954, Lindsay and Hemenway [35] reported a 7-month-old infant who died 4 months after the measles infection. On autopsy, the marked degeneration of the organ of Corti was found, with changes similar to those in the lymphoid tissue during measles infection. From this observation, the authors concluded that the measles virus reached the inner ear through the stria vascularis, causing toxic changes and inflammation.

In an animal study by Fukuda et al. [36], cochlear pathology with destruction/degeneration of the organ of Corti, stria vascularis, and cochlear neurons was also noted. However, they observed more significant variability in damage to the basal turn. In some cases, endolymphatic hydrops was detected, but it was not a typical feature of measles infection. The authors speculated that the fibrous tissue in the basal turns was related to the inflammatory process and that new bone growth in the vestibular labyrinth in some specimens was also consistent with inflammation [32, 36].

Acute otitis media, a secondary bacterial infection resulting from measles infection, is often implicated in the pathogenesis of HL attributed to measles infection [2]. In the acute phase, otitis media generally causes conductive HL due to fluid in the middle ear. However, recent studies have shown varying degrees of SNHL in AOM due to inflammation extending from the middle ear to the inner ear [37, 38].

Hearing loss can also be seen in primary encephalitis due to measles, an unfortunate consequence of this infection that can present within a few days of rash onset [39]. While encephalitis occurs in less than 1% of all measles cases [40], approximately 25% of these children have neurodevelopmental sequelae, which often include or are associated with SNHL [22, 31, 32]. In a study from Nigeria, 46% of the cases of profound bilateral SNHL identified in children in the Ekiti State of Nigeria were attributed to measles infection, particularly in those with neurologic sequelae of their infection [41]. While the authors noted that this association might be coincidental, the observation that neurologic sequelae were associated with a higher risk of HL suggests that these findings may be the sentinel of future otologic complications.

Measles and/or mumps virus-containing vaccines (MMCVs) contain live attenuated viral strains, and some reports have suggested HL as a complication of vaccination against this virus [42]. A study by the USA Vaccine Adverse Events Reporting System (VAERS) for the period 1990–2003 reported 59 cases of HL following MMCV [43]; despite relying on a system without confirmatory testing, HL after MMCV was approximated at one case per six to eight million doses. Given the considerable variation in the onset of HL reported in the literature as opposed to VAERS, it was concluded that definite evidence for or against MMCV causing HL has limited and inadequate quality.

49.10.1 Measles and Otosclerosis

Otosclerosis is a well-known cause of conductive HL, and these deficits result from the abnormal bone remodeling of the otic capsule. Many factors (e.g., genetics, inflammation, autoimmunity, hormonal and environmental factors, and bone metabolism) have been implicated in the development of otosclerosis, including infection. In the case of measles, viral RNA has been detected by reverse transcription-polymerase chain reaction (RT-PCR) in otosclerotic stapes footplates. These observational studies by Karosi et al. [44–47] detected the measles virus in most of these samples, suggesting that the persistence of the measles virus in the ear may be the cause of otosclerosis. These findings were supported by Niedermeyer et al. [48–50] and McKenna et al. [51], who also detected measles virus mRNA in most of the otosclerotic stapes samples they examined. The exact role that measles infection plays in triggering otosclerosis remains debatable, as some studies have found an association with transforming growth factor-beta-1-mediated otosclerosis [52], while others have found no association [53].

49.10.2 Hearing Loss Management

A recent study of 112 children with measles-related HL reported that auditory complications were most common between 0.5 and 5 years of age (92.8%) [41]. This age range, known as the prelingual period, is developmentally crucial as it is during

this time that childhood speech development occurs. As such, due to measles infection during this critical period, HL is likely to affect language and subsequent age-appropriate childhood development profoundly. Furthermore, patients who contract measles and are not serially screened for HL are at risk for delayed diagnosis and may not benefit from early intervention services.

Treatment of measles-related HL depends on the degree and type of HL. Hearing aids may be helpful in patients with mild to moderate SNHL, while cochlear implantation is effective for patients with severe to profound SNHL [32].

49.11 Laboratory Findings

Leukopenia, lymphopenia, and thrombocytopenia may be observed during measles infection. The acute phase reactants are usually normal if not complicated by bacterial infection [22].

49.12 Diagnosis

The clinical diagnosis of measles should be considered in a febrile child with a maculopapular rash and compatible symptoms such as cough, coryza, and conjunctivitis. Furthermore, epidemiologic risk factors should be assessed when risk is stratified for patients, as measles has not been eradicated globally, and these physical exam findings are non-specific [54].

Serological confirmation is a widely used diagnostic method for measles. The enzyme-linked immunosorbent assay (ELISA) is sensitive and easy to perform. Immunoglobulin (Ig) M antibody in serum appears 1–2 days after the rash and persists for 1 month in unimmunized people [4]. Serum IgM antibodies might be low or undetectable during the first 72 h of rash, and second serum obtaining is recommended [21]. Anti-measles IgG generally begins to be detected on the seventh day and peaks about 14 days after the rash appears. Acute and convalescent sera collected 2–4 weeks apart could be used for serologic confirmation. A fourfold or more remarkable increase in IgG antibodies indicates a recent infection [21]. Additionally, measles virus infection can be confirmed by detecting viral RNA by RT-PCR or isolation of measles virus in cell culture from throat, nasal, nasopharyngeal, and urine samples [23].

49.13 Differential Diagnosis

Infections of common respiratory viruses such as adenovirus, rhinoviruses, parainfluenza viruses, influenza, and respiratory syncytial virus are included in the differential diagnosis during the prodromal phase of measles [22]. The typical measles rash may be challenging to differentiate from rashes in other diseases, especially in the absence of Koplik spots. The rashes of *Mycoplasma pneumoniae* and

Streptococcus pyogenes can often mimic that of measles [22]. In the late stages, modified or atypical measles infections may be confused by other exanthems such as rubella, erythema infectiosum, roseola infantum, adenovirus, enterovirus, and Epstein-Barr virus (EBV) infections. Additionally, many other noninfectious processes, like drug allergies and Kawasaki disease, have similar findings, including mucocutaneous involvement, conjunctivitis, and rash, and can mimic measles infection [23].

49.14 Treatment

Currently, no specific antiviral drug exists for the treatment of measles. Treatment is supportive and includes antipyretics, fluids, and antibiotics when bacterial superinfection develops.

Vitamin A is recommended for all children with acute measles [55]. Vitamin A is administered once daily for 2 days, 200,000 IU for children >12 months or older, 100,000 IU for infants 6–11 months, and 50,000 IU for infants <6 months of age. The third dose may be required for children with vitamin A deficiency after 2–4 weeks from the initial dose [21].

49.15 Prevention

Airborne precautions are essential for 4 days after the beginning of the rash. Immunosuppressed patients shed the measles virus during the illness, so they should maintain isolation throughout the disease. Inpatients with measles exposure should undergo airborne isolation between 5 and 21 days after exposure [21].

49.15.1 Passive Immunization

Human immune globulin (Ig) is effective when given intramuscularly (IM) or intravenously (IV) within 7 days of exposure. In children who had exposure and were too young to have been vaccinated or had a contraindication to vaccination, an intramuscular dose of 0.25 mL/kg (15 mL maximum) is recommended. In those kids who continue to have a contraindication to measles vaccination during an epidemic, an intramuscular dose of 0.50 mL/kg is recommended every 4 weeks while at risk for exposure. Alternatively, intravenous Ig (IVIG) may be administered at 400 mg/kg to specific at-risk individuals who lack evidence of immunity to measles, including pregnant women, critically immunocompromised patients, acute lymphoblastic leukemia (ALL) patients at least 6 months after finishing chemotherapy, solid organ transplant patients, people who have severe immunosuppression with human immunodeficiency virus (HIV) infection, and infants (<12 months) born from mothers who used biologic response modifiers during pregnancy [21].

49.15.2 Active Immunization

Immunization with a measles-containing vaccine is the most effective and safe prevention method. Two doses of the measles, mumps, and rubella (MMR) vaccine are recommended beginning with the first dose at 12 through 15 months of age and the second dose at 4 through 6 years of age [56]. Vaccination is not usually recommended for infants <12 months because residual transplacentally acquired antibodies may suppress the induction of immunity. Infants aged 6–11 months should receive one dose of MMR vaccine in the following scenarios: during epidemics, before traveling to countries where measles is endemic or epidemic, or within 72 h of a documented exposure. Afterward, these infants should be given two doses following the vaccination schedule after the 12th month, as doses before 12 months are not considered in the vaccination schedule [57].

Live vaccines are contraindicated in immunocompromised patients and pregnant women; however, people with HIV infection not severely immunocompromised may be immunized. Measles vaccination should also be delayed for 3–11 months in patients who have received whole blood, packed red blood cells, plasma or platelet products, IVIG replacement, or therapy [23]. The measles vaccine may suppress the cutaneous response to the tuberculin skin test (TST), so if indicated, the TST may be performed before or simultaneously with the vaccine. Patients with tuberculosis disease should receive appropriate antituberculous therapy at the time of the measles vaccine [21].

49.16 Conclusion

Measles is a highly contagious viral disease. Although there is a safe and effective vaccine, many countries still have outbreaks. Children with measles may experience short- and long-term complications from this infection. One of the long-term sequelae of measles is HL, which accounted for 5–10% of cases of profound HL in the pre-vaccine era. Hearing loss following measles infection is often sensorineural, bilateral, and moderate to profound, but may also be mixed or conductive. Whether a greater proportion of HL is a sequela of encephalitis and profound SNHL or a result of conductive HL due to AOM associated with measles is unclear. However, what is known is that HL attributable to measles infection is clinically relevant and should be followed closely in these patients.

The age at which most children learn to speak coincides with the age at which most individuals get measles; measles-induced HL during this critical period can affect speech and language development leading to delayed developmental milestones in early childhood and adolescence. Prompt diagnosis of HL is a challenge in these children because these deficits are often noted only when children fail to acquire speech. Routine hearing assessment after measles infection may be helpful and should be recommended for timely diagnosis and prompt treatment initiation in patients with a history of measles infection. Continued global vaccination efforts will be necessary to eradicate this virus from all corners of the world.

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Mumps Infection in Children and Hearing Loss

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50.1 Introduction

Mumps is an acute, contagious viral illness. Parotid gland swelling is the typical clinical manifestation, but many organ systems may be affected. Hearing loss (HL) is rare but a significant complication of the disease. Since it is vaccine-preventable, childhood mumps has become an uncommon disease in countries where measles-mumps-rubella (MMR) vaccination is implemented widely [1, 2]. However, recent outbreaks have been reported in vaccinated communities [1–3]. Because of populations that remain unvaccinated and breakthrough infections in vaccinated individuals, mumps remains an important epidemic problem worldwide.

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50.2 Etiology and Epidemiology

Mumps virus belongs to the *Rubulavirus* genus of the family Paramyxoviridae. It has a single-stranded, nonsegmented, negative-sense ribonucleic acid (RNA) genome with a length of 15,384 nucleotides. The viral genome encodes two nonstructural proteins and seven structural proteins: nucleocapsid-associated protein (NP), phosphoprotein (P), membrane or matrix protein (M), fusion protein (F), hydrophobic membrane-associated protein (SH), hemagglutinin-neuraminidase (HN), and polymerase protein (L). Mumps RNA is surrounded by a helical capsid in a high-lipid structured envelope [4]. The envelope contains the M protein and two surface glycoproteins, which have hemagglutinin and neuraminidase (HN protein) and cell fusion (F protein) activities [2, 4]. These two glycoproteins and the nucleocapsid protein, also referred to as S antigen, constitute the significant antigenic components of the virus. Host antibodies protective against mumps are specific to surface HN and F glycoproteins [2]. The hydrophobic protein (SH) gene is the most variable part of the mumps genome; 12 genotypes of mumps strains were described based on the nucleotide sequence of this gene [5]. Geographic distribution and outbreak relationships vary among mumps strains [5–7]. Besides, in vitro and in vivo findings suggest that cross-neutralization between strains from different genotypes might be reduced compared with strains from the same genotype. Although there is one serotype of the virus, the significance of these genomic types on outbreaks and the effect of vaccination is still a matter of investigation [8, 9].

Various human and monkey tissues and embryonated eggs are used to isolate or propagate the mumps virus. Cytopathic effects caused by the mumps virus in cell cultures include rounding and fusion of cells, causing multinucleated syncytia and intracytoplasmic inclusion formation [1, 2]. The addition of erythrocytes onto cell culture indirectly identifies viral growth through hemadsorption. Viral particles can cause hemagglutination, and partial hemolysis may occur when the virus is attached to cell surface receptors [2]. The mumps virus can be isolated from samples kept at 4 °C for a few days. Keeping viruses viable at −70 °C for an unlimited time is possible when placed in a buffered salt solution with 1–2% inactivated fetal calf serum [2, 9]. Heat (20 min at 56 °C) can destroy the infectivity of mumps. In addition, mumps infectivity is reduced by formalin, ether, Tween 80, and ultraviolet light [2].

Mumps is seen worldwide, and humans are the only hosts. Mumps' incidence is highest in the winter and spring months, but infections by this virus are present throughout the year in warm climates [8]. In the prevaccine era, mumps was a disease affecting predominantly children younger than 10 years old and causing yearly epidemics with high incidence rates [2]. In the postvaccine era, reported cases occur mainly in persons older than 10 years. After implementing routine mumps vaccination in the United States of America, a 99% decline in mumps cases has been observed [10]. However, recent outbreaks have occurred, even in vaccinated populations worldwide [11–13]. Hence, early detection and timely reporting of cases are of great importance. The possible causes of these outbreaks, such as waning immunity or strain change, are under investigation [14, 15].

The mumps virus is moderate to highly contagious. Person-to-person transmission occurs via respiratory droplets through direct contact with saliva or respiratory secretions, although transmission through fomites can also occur [8, 9]. The virus can be isolated from patients' saliva as early as 7 days before and up to 9 days after parotitis onset [9]. Besides, it has been isolated from urine and seminal fluids up to 14 days after the onset of parotitis [16]. Transmission is highest 2 days before and 5 days after the onset of symptoms, and the risk of acquiring the infection is highest among persons in close contact with infected patients, such as those living in the same household or dormitory [1, 8]. People who have an asymptomatic infection can also transmit the virus [1]. The average incubation period for mumps is 16–18 days, but it can range from 12 to 25 days [2].

50.3 Pathogenesis and Immune Response

After contact with infected secretions, the mumps virus replicates in the upper respiratory mucosa of the host and spreads to regional lymph nodes. Subsequently, primary viremia occurs, and the infection spreads to multiple organs [4]. The most prominent infection site is the salivary glands (mainly the parotids); however, the nervous system (meninges and brain), inner ear (cochlea), gonads, pancreas, heart, joints, thyroid, liver, and kidneys may also become secondary infection sites [2].

The virus replicates in the ductal epithelium in the salivary glands, leading to a local inflammation with lymphocytes and macrophages and periductal interstitial edema [4, 9]. Subsequently, tissue damage with necrosis occurs due to the accumulation of lymphocytes and debris in the ductal epithelium [2]. Orchitis can be a direct or indirect consequence of mumps virus propagation [4, 9]. The mumps virus was isolated from semen in a patient with orchitis [17]. While the mumps virus is known to have tropism for testicular tissue, the specific receptors responsible for viral affinity for the testis have not been clearly defined [18]. The infection results in interstitial edema and lymphocytic infiltration. Due to these pathological changes, necrosis and hyalinization of the seminiferous tubules can occur, with subsequent fibrosis and atrophy within the testes [1, 2, 9].

Infected mononuclear cells provide entry of the mumps virus into the central nervous system through the choroid plexus [4]. As the virus propagates in the choroidal epithelium and ependymal cells lining the ventricles, infected cells' desquamation and accumulation into the cerebrospinal fluid (CSF) lead to meningitis and hydrocephalus [2, 4]. Encephalitis may occur with perivascular infiltration by mononuclear cells, scattered foci of neuronophagia, and microglial rod-cell proliferation. Demyelination of the periventricular area also can be observed [2].

In response to mumps infection, specific immunoglobulin M (IgM), immunoglobulin A (IgA), and immunoglobulin G (IgG) antibodies are produced [1]. IgM may appear on the second day, peak within the first week, and become undetectable after 3 months; however, in some instances, it may persist for 5–6 months. Mumps-specific IgG becomes detectable at the end of the first week, peaks after 3 weeks, and lasts throughout life. Salivary IgA appears simultaneously with the cessation of

viral shedding in saliva [2]. A specific cell-mediated immune response to the mumps virus also develops [19]. In addition, increased levels of interleukin (IL)–6, IL-8, IL-10, IL-12, IL-13, and interferon-gamma (IFN-γ) were found in the sera of the patients with mumps meningitis and encephalitis [20, 21]. In general, lifelong immunity against mumps persists after the infection's resolution; however, studies show possible reinfection [22].

50.4 Clinical Manifestations

Mumps causes subclinical or mild respiratory tract illness in one third of patients. In symptomatic patients, the initial clinical manifestations include fever, headache, anorexia, vomiting, and generalized aches and pains, constituting the prodromal phase of the illness, which lasts 1 or 2 days [8, 9]. After the prodromal period, painful parotid swelling occurs; this is usually unilateral in the beginning and later becomes bilateral in 70% of cases. Parotitis is the most common manifestation, with an incidence rate of 95% in symptomatic patients [9]. It may be accompanied by earache and discomfort while eating and drinking sour liquids. Pain and difficulty while opening the jaw may be seen [2]. Parotid swelling does not have discrete borders; it shifts the earlobe out and upward and obscures the angle of the mandible [9]. Other salivary glands may be affected separately or in combination with parotids in up to 10% of cases [9]. Salivary production and flow can change during the illness, leading to dry mouth or extreme salivation [2]. Redness of the orifices of the Stensen or Wharton ducts can be seen at the onset of the illness and may be a helpful finding to guide the diagnosis [2, 9]. Presternal and supraglottic edema have been described in a few cases due to probable obstruction of lymphatic drainage by bilateral glandular swelling [9, 23]. Although systemic symptoms resolve in 3–5 days, parotitis may last up to 10 days. Adults and adolescents are more prone to severe disease and complications [1]. Laboratory tests usually show low white blood cell (WBC) count, slight relative lymphocytosis, and elevated serum amylase in uncomplicated mumps [2].

50.5 Complications

50.5.1 Central Nervous System Infection

Central nervous system infection is the most frequent complication of mumps in children [2, 9]. Meningeal inflammation accompanies parotitis in about 50% of patients (evidenced by CSF pleocytosis), but less than 10% show symptoms of meningitis [1, 9]. Mumps meningitis is usually a benign entity, and severe cases or deaths are unusual. Headache, fever, vomiting, neck stiffness, and lethargy are typical symptoms that resolve within 7–10 days [9]. Seizures can be seen in 20% of hospitalized patients [1]. Meningeal signs are more prominent in older children and adolescents [2]. Physicochemical analysis of the CSF shows normal or slightly

decreased glucose and normal or elevated protein concentration; the WBC count is usually lower than 1000 cells/mm^3, with lymphocytes predominating over polymorphonuclear leukocytes [1]. Mumps encephalitis is rare (0.1%) and may manifest with changes in the level of consciousness, seizures, focal neurological signs, ataxia, behavioral changes, and abnormal electroencephalography [9]. Mumps encephalitis's outcome is generally good; however, complications, long-term morbidities, and deaths may rarely occur (1.4%) [1, 2]. Ependymitis, acquired aqueductal stenosis, hydrocephalus, cerebellitis, transverse myelitis, progressive encephalitis, paralysis, neuroretinitis, and sensorineural HL (SNHL) due to mumps have been described [1]. Adults are more prone to unfavorable outcomes than children [9].

50.5.2 Epididymo-Orchitis and Oophoritis

Epididymo-orchitis and oophoritis with mumps infection are rarely seen before puberty [9]. However, the orchitis rate is between 14% and 35% in postpubertal males with mumps [24]. The highest risk is observed in males aged 15–29 years [1, 2]. Symptoms usually manifest 4–8 days after parotitis, but may appear up to 6 weeks later [9]. Generally, unilateral testicular involvement occurs, and epididymitis accompanies orchitis [1]. Malaise, fever, lower abdominal pain, testicular pain, and vomiting are the most common symptoms in the clinical onset. Physical examination usually reveals swelling, warmth, tenderness of the affected testicle, and inflammation of the scrotum. Symptoms typically progress for 2–3 days and resolve within 1–2 weeks, but testicular tenderness may persist longer [9]. The C-reactive protein level usually is elevated [1]. Mumps virus can be isolated in seminal fluid, and viral RNA may remain detectable for several weeks [17]. Half of the patients recover completely, but testicular atrophy occurs in the other half at varying degrees [16]. Infertility in patients with bilateral orchitis is rare. However, sperm count and motility decrease can be seen in up to 25% of patients [9]. In addition, there are reports about cancer development in affected testes [2]. Oophoritis occurs in 5–7% of postpubertal women with mumps infection. Symptoms include fever, lower abdominal pain, and vomiting [9]. Pelvic pain and tenderness are noted in physical examination [2]. Rarely, premature menopause and infertility have been reported following oophoritis due to mumps [9].

50.5.3 Other Manifestations

Pancreatitis develops in about 4% of mumps infections. It generally occurs subclinically or follows a mild course with epigastric pain. However, severe hemorrhagic pancreatitis was reported in some patients [1]. Although insulin-dependent diabetes mellitus cases were identified after mumps outbreaks, the relationship between the mumps virus and this disorder remains controversial [1]. Hematuria, proteinuria, and abnormal renal function can frequently occur in children during mumps, but severe glomerulonephritis is rare [9]. Mumps can cause arthralgia and arthritis,

especially in young males. The clinical course mainly includes single-joint arthritis or migratory polyarthritis of large joints [1, 9]. Joint symptoms usually appear 1–3 weeks after the onset of parotitis, and they can last 2 days to 6 months. Full recovery is usually observed without recurrence or joint damage [9]. Electrocardiographic abnormalities indicating myocarditis are observed in up to 15% of patients with mumps infection. Although clinically apparent myocarditis is rare, sequelae and mortality have been reported [1, 9]. Mastitis, thyroiditis, thrombocytopenic purpura, hepatitis, acalculous cholecystitis, hemophagocytic syndrome, and kerato-uveitis are other rare manifestations of mumps disease [1, 9]. Hearing loss is a well-known and important complication of mumps virus infection [9].

50.6 Mumps and Hearing Loss

Permanent HL is an important long-term sequela of mumps. The precise frequency of HL as a result of mumps virus infection has not been established due to the limited number of studies in which this complication has been systematically analyzed. The estimated incidence of HL has been reported to be 0.5–5.0 per 100,000 cases of mumps [2, 9]. However, the incidence of HL may be higher when non-severe cases are included [2]. The patients or their guardians may not recognize unilateral HL when it is mild or even profound [25, 26]. There was transient high-frequency HL in 4.1% of adult males (military) with mumps infection [27]. In a prospective study of children with the clinical diagnosis of mumps, the incidence of SNHL was approximately 1 in 1000 cases [28].

The precise mechanism leading to HL associated with mumps infection has not been defined; alterations in the stria vascularis, organ of Corti, and vestibulocochlear nerve have been considered [29]. Mumps virus may enter the inner ear through viremia or the CSF, reaching the perilymphatic space through the cochlear aqueduct. Mumps virus has been isolated from perilymphatic fluid in a patient with sudden deafness occurring within 2 days of mumps [30]. The vestibular system is also affected due to labyrinthine lesions with possible eighth cranial nerve involvement following mumps infection [31–33].

Hearing loss may be the sole clinical manifestation in patients with mumps virus infection or might develop in patients with parotitis with or without associated meningoencephalitis [34, 35]; however, mumps patients with clinical meningoencephalitis can suffer from HL more frequently than those without central nervous system involvement [35]. Mumps-associated deafness usually is unilateral and often permanent; bilateral, severe HL is rare [9]. Hearing loss may occur in an acute onset or gradually and is frequently accompanied by vertigo [2, 9]. Vestibular symptoms may go unnoticed in pediatric patients, as they can be confused with the malaise associated with the disease, and infants may have difficulty expressing the presence of this symptom [32].

Hearing loss due to mumps is a diagnostic and therapeutic emergency since it may result in permanent HL [36]. Thus, the suspicion threshold for HL should be

kept low in patients with mumps, and audiological evaluation should be performed readily when HL is suspected [25]. Different treatments, including steroids, vasodilators, vitamin B12, and hyperbaric oxygen therapy, are used; however, there is no definite treatment protocol for HL due to mumps infection. Among these options, systemic steroids have become the standard therapy for children and adults [37]. Steroids show therapeutic properties via their anti-inflammatory effects by reducing cytotoxic immune responses, activating ion transport in the stria vascularis and spiral ligament in the cochlear canal, controlling endolymph homeostasis, and increasing blood circulation in the cochlea [37]. However, the effectiveness of steroid therapy in reducing the degree of HL or attaining full recovery remains unclear [38]. While the time of treatment initiation from the onset of HL may affect the prognosis, this might depend on other factors, including the etiology of HL [39].

Profound and bilateral HL due to mumps generally has a poor prognosis [25, 36]. Accompanying vestibular symptoms are also considered poor prognostic factors [38]. In patients with profound HL without improvement after medical therapy, cochlear implant (CI) installation and audiologic rehabilitation should be considered [33, 36]. The optimal time of CI implantation must be determined on an individual basis. Since the need to carry out this intervention is not an emergency, it is reasonable to wait for some time to assess the response to medical therapy and to allow for the family's or patient's acceptance of the permanent HL and the need for CI [33, 37]. An essential factor to take into consideration regarding the optimal time for CI is the patient's age. Young children with deafness can rapidly show a delay in language development and dysarthria [33, 37]. In addition, sudden HL at school age can lead to language and understanding impairments and disruptions in education [33]. In patients with bilateral HL, CI installation showed promising results for speech perception [26, 40]. Early installation of CI may be associated with better outcomes; therefore, it should be considered after 2–3 months of the onset of HL [33, 37]. However, patients may not benefit from a CI when the HL is due to central nervous damage associated with meningitis and encephalitis [40].

50.7 Mumps in Pregnancy

Mumps has a benign course in pregnant women, similar to nonpregnant women. Although case reports suggest the potential effects of mumps infection on the developing infant, there is no evidence of an increased risk of fetal malformations related to gestational mumps disease in prospective and retrospective studies [41]. Several studies reported that spontaneous abortion could occur due to mumps infection in the first trimester, but comparative studies controlled with the normal population are needed to confirm these observations [9, 41]. The relationship between maternal mumps infection and fetal endocardial fibroelastosis was investigated, and the results were inconclusive [41]. Perinatal mumps generally results in a mild course of illness; however, parotid swelling, pneumonia, and pulmonary hypertension have been reported [41, 42].

50.8 Differential Diagnosis

Parotitis or parotid swelling can also be caused by viruses other than mumps virus, such as influenza, echovirus, coxsackievirus A, parainfluenza virus types 1 and 3, cytomegalovirus, Epstein-Barr virus, human herpesvirus-6, lymphocytic choriomeningitis virus, adenovirus, parvovirus B19, and human immunodeficiency virus (HIV) [43, 44]. These viral agents can be distinguished by epidemiological and clinical characteristics, serologic studies, and culture [2]. Purulent parotitis may occur due to bacterial agents; the clinical course is characterized by parotid tenderness, increased WBC count, and pus coming out of the Stensen duct [2, 9]. Drugs (e.g., iodides, phenylbutazone, phenothiazines, and thiouracil), tumors, malnutrition, salivary gland stones, cysts, metabolic disorders, and miscellaneous syndromes (e.g., Parinaud's, Mikulicz's, and Sjogren's syndromes) may be other causes of parotid swelling [9]. Since mumps can occur without parotitis, it should be kept in mind in all children with aseptic meningitis, meningoencephalitis, and encephalitis [2].

50.9 Diagnosis

All children with acute parotitis, orchitis, and oophoritis lasting for 2 or more days should be tested for the mumps virus when no other cause is detected [1, 9, 16]. The main laboratory finding is elevated serum amylase levels, and low or normal WBC count with a relative lymphocytosis can be observed [1, 9]. Isolation of mumps virus in cell culture, detection of the viral genome by reverse transcriptase-polymerase chain reaction (RT-PCR), positive serum mumps-specific IgM antibody test result for a single serum sample, or demonstration of a fourfold or greater rise in mumps-specific IgG antibody titers between acute and convalescent serum samples can confirm mumps infection [8]. Throat swabs, Stensen duct exudates, saliva, CSF, and urine specimens are suitable for mumps virus isolation [1, 8]. Since vaccinated individuals may shed the virus for a shorter time or in a lower concentration, samples should be obtained as soon as possible after the onset of symptoms to increase the likelihood of detecting the virus [1]. In cell culture, the typical cytopathic effect of cellular degeneration and syncytium formation can be seen, and the virus is confirmed by hemagglutination inhibition assays or immunofluorescent antigen detection [1]. Recently, RT-PCR has replaced viral culture as it is more rapid and sensitive [1, 16]. However, a negative RT-PCR test result does not exclude infection with this virus when clinically compatible symptoms are observed [16].

Quantitative and semiquantitative serologic tests can measure mumps-specific IgM and IgG antibodies [1]. Although these serologic assays can help to diagnose mumps, there may be false-positive results due to cross-reaction between mumps and parainfluenza viruses [2]. Usually, enzyme-linked immunoassay (ELISA) is used to determine mumps IgM; positivity shows a current or recent infection [1, 2]. The optimal serum collection time for IgM testing is 7–10 days after the beginning of symptoms [1]. Mumps-specific IgM antibodies can also be determined by ELISA

in oral fluid [45] and detected in CSF samples of patients with mumps meningitis [1]. A positive IgG result indicates recent or past wild-type mumps virus or vaccine exposure. A second serum sample should be obtained 2–3 weeks after symptom onset to assess if there is a significant increase in IgG titers, indicating a recent infection [46].

Serologic confirmation of mumps can be difficult in vaccinated people. In previously vaccinated patients, mumps IgM response is less likely to be positive and may be transient or delayed [1, 16]. Besides, detection of a fourfold increase in mumps IgG titer may not be possible in vaccinated individuals since IgG titers may already have been elevated in the acute phase of the illness [1, 16]. Serologic tests cannot differentiate wild-type mumps virus exposure from vaccine effect, but RT-PCR can detect viral RNA in previously vaccinated children who develop mumps [1, 16]. A buccal or oral swab sample is required for genotyping to distinguish wild-type mumps virus from vaccine virus [16].

50.10 Treatment and Prognosis

There is no specific antiviral drug for the mumps virus. According to the symptoms, treatment is supportive since the clinical course is usually benign and self-resolving [9, 16]. Analgesics may be used for the pain occurring due to parotitis or orchitis. A lumbar puncture may relieve the headache related to meningitis. Adequate hydration and alimentation should be provided [1, 9].

The prognosis of uncomplicated mumps is good. The outcome of mumps meningoencephalitis is primarily good, but neurologic damage and even death may occur. Sterility and HL are rare complications [2].

50.11 Prevention

50.11.1 Vaccination

There are numerous mumps vaccines in use worldwide. All mumps vaccines are live-attenuated virus vaccines [47, 48]. Mumps vaccines may be administered as monovalent or combined vaccines. The most common combination vaccines include measles and rubella in addition to mumps (MMR vaccine); recently, formulations that include varicella in addition to measles, mumps, and rubella are also in use (MMRV vaccine) [9]. More than 80–85% of vaccine recipients develop neutralizing antibodies after a single dose [49]. According to post-licensure data, the protective efficacy of one dose is about 78%, ranging from 49% to 92%, and after two doses, it increases to approximately 88%, ranging from 66% to 95% [50, 51]. It is estimated that a 90–92% rate of population immunity is needed for herd immunity [2]. The mumps vaccine should be applied to all susceptible children, adolescents, and adults [52]. Individuals who document previous mumps diagnoses, two doses of live mumps virus vaccine, or laboratory evidence of immunity should be considered immune [2].

50.11.1.1 Vaccine Recommendation

The mumps vaccine is administered in two doses, separated by at least 1 month by subcutaneous injection of MMR or MMRV vaccine at any age on or after the first birthday. Both vaccines can be administered during the same visit with other vaccines [48, 49]. If the MMR vaccine is received before 12 months of age, the vaccine dose is not taken into account to assess the completeness of the immunization schedule, and two additional doses are recommended beginning at 12–15 months of age, separated for at least 28 days [48, 49].

During an outbreak, people with evidence of immunity to mumps or documentation of two doses of mumps vaccination should receive a third dose if they are in a high-risk group for acquiring mumps infection. No additional mumps vaccination is recommended for individuals previously vaccinated with three doses [16]. Routine administration of the mumps vaccine is not recommended for people born before 1957; this recommendation excludes healthcare personnel with no laboratory evidence of immunity or history of having had the disease [16]. Before mumps vaccination, testing for susceptibility is unnecessary, especially in adolescents and young adults [2]. There is no evidence of a harmful effect of MMR or MMRV on people who already have immunity from previous infection or immunization [48].

50.11.1.2 Adverse Reactions

Adverse reactions associated with the mumps component of the vaccines, including parotitis, fever, febrile seizures, encephalitis, aseptic meningitis, and orchitis, are rare [1, 2, 16]. Allergic reactions such as pruritus, rash, and purpura associated temporally with mumps vaccination are uncommon, usually mild, and of short duration. Severe allergic reactions, including anaphylaxis, are rare [1]. No causality has been identified for temporally related reactions such as pruritus, rash, purpura, SNHL, encephalitis, and aseptic meningitis [2, 16]. Other reactions following MMR or MMRV vaccine administration may be related to other vaccine components [49].

50.11.1.3 Precautions and Contraindications

Fever is not a contraindication of mumps vaccination. Children with minor febrile illnesses should be immunized. However, in patients with severe diseases, with or without fever, vaccination should be deferred until recovery [16, 48].

Hypersensitivity reactions are rare and usually minor, presenting mainly as wheal-and-flare reactions or urticaria at the injection site [16]. Anaphylaxis rarely occurs. Since mumps vaccines produced in chicken embryo cell culture have minimal amounts of ovalbumin cross-reacting proteins, individuals with egg allergy but no anaphylaxis history are at low risk for anaphylactic reactions and can be vaccinated routinely. However, according to published protocols, persons with egg allergy and anaphylactic reactions should only be vaccinated with caution [2]. No proven increased risk exists for allergic reactions to the mumps vaccine in people allergic to chickens or feathers [16]. People with a history of anaphylactic reactions to gelatin or neomycin should be assessed by an allergist or immunologist and receive mumps vaccine in hospital settings where adverse reactions, if present, can

be managed [16]. Contact dermatitis is the most common finding of neomycin allergy and is not a contraindication to the mumps vaccine [2, 16].

Although mumps vaccination during pregnancy has not been shown to be related to congenital malformations, pregnant women should not be vaccinated due to the theoretical risk of fetal damage. Conception should be avoided for 4 weeks after receiving the mumps vaccine. In the case of vaccination during pregnancy, the termination decision should be made individually since MMR vaccination is not a definite indication [49].

Blood products, such as immunoglobulin administration, may interfere with the immune response to MMR or MMRV vaccines; therefore, in individuals who have received such products, vaccination should be deferred for at least 3 months if possible [48]. Mumps vaccine should be administered at least 2 weeks before the planned immunoglobulin administration, or it should be deferred for 3–11 months according to the dose of immunoglobulin received [49]. If immunoglobulin is administered within 14 days of MMR or MMRV administration, these vaccines should be repeated after the appropriate time interval [49]. When immediate protection is required, MMR or MMRV vaccine can be applied to a person who recently received a blood product, but the dose should be repeated after 3 months [48].

50.11.1.4 Altered Immunity

Patients with immunodeficiency diseases and suppressed immune responses due to lymphoma, leukemia, generalized malignancy, or those who have received immunosuppressant treatments such as corticosteroids, antimetabolites, alkylating drugs, or radiation within the previous 4 weeks should not receive live attenuated virus vaccines such as MMR or MMRV [2, 16]. Since vaccinated people do not spread the virus, immunocompromised persons can be protected by vaccinating their close contacts [49, 53].

For HIV-infected children, mumps vaccination recommendations differ according to their immune status. All asymptomatic HIV-infected children and adolescents without severe immunosuppression should be vaccinated with the MMR vaccine [49, 53]. In contrast, severely immunocompromised HIV-infected persons should not receive measles virus-containing vaccines. The quadrivalent MMRV vaccine should not be administered to HIV-infected infants at this time because of this population's lack of safety data [49, 53].

Immunization with the MMR vaccine should be deferred for at least 3 months after finishing immunosuppressive therapy such as chemotherapy for leukemia patients [53]. However, the proper interval for a safe and effective immunization depends on the type and intensity of immunosuppressive or radiation therapies, underlying disease, and other factors, so that a definite recommendation is not possible [16]. According to recommendations of an international consensus conference, allogeneic hematopoietic stem cell transplant recipients may receive two doses of MMR vaccine starting 24 months after transplant if they are no longer on immunosuppressive therapy [54]. Data regarding the safety and efficacy of live virus vaccines in transplant recipients still receiving immunosuppressive therapy were not found to be sufficient in a review [55].

Patients receiving short-term corticosteroid therapy, including intra-articular, bursal, or tendon corticosteroid injections, as well as topical corticosteroid therapy (e.g., skin, nasal), can be vaccinated with the mumps vaccine. However, children receiving immunosuppressive levels of corticosteroids (≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh 10 kg or more, for 14 days or more, as well as those with prolonged and extensive topical corticosteroid application) should wait at least 4 weeks after discontinuation of therapy before they receive live-virus vaccines [2, 16].

50.11.2 Control Measures

Mumps is a reportable disease. Recommendations to prevent transmission include standard and droplet precautions for managing patients with mumps and a 5-day isolation period after the onset of parotitis [56]. For postexposure prophylaxis, mumps vaccine and immunoglobulin are ineffective [16, 48]. However, people without evidence of immunity should receive a mumps vaccine since vaccination will provide protection against the disease after future exposures [48]. Immunization during incubation is not related to an increased risk of adverse events [16]. Therefore, vaccination programs, isolation of patients, contact tracing, and exclusion of unimmunized persons can be implemented to control a mumps outbreak [2]. During an epidemic, the mumps vaccination status of all individuals in the community should be updated appropriately according to age. According to public health recommendations, people with an increased risk for mumps and its complications might receive a third dose of the mumps vaccine [16]. In school settings where outbreaks occur, unimmunized students should be excluded from attendance until 26 days have passed since the onset of symptoms of the last person with parotitis. Excluded students can return to school as soon as they receive a dose of the MMR vaccine [16].

50.12 Conclusion

Mumps outbreaks are still occurring throughout the world. Since mumps is a vaccine-preventable disease, all susceptible individuals should be vaccinated unless contraindicated. Hearing loss due to mumps disease is rare but an important complication. It may be overlooked when HL occurs gradually or as a mild affection. No effective treatment exists for HL due to mumps infection. Although rare, bilateral or severe HL may occur, requiring CI installation. Otological evaluation should be performed to assess HL in children in whom mumps is suspected. Also, because mumps virus infection may be asymptomatic, it should be kept in mind in any patient with sudden HL.

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Epstein-Barr Virus Infection in Children and Hearing Loss

51

Bilge Aldemir Kocabaş, Ergin Ciftci, and Cem Meco

51.1 Introduction

Epstein-Barr virus (EBV) is a gamma herpes virus and can remain lifelong in the latent state after acute infection [1]. The target cell is B lymphocytes in the body, important in terms of their oncogenic potential. Epstein-Barr virus causes different clinical conditions ranging from asymptomatic infection to fatal course. It may present as an asymptomatic or mild viral respiratory tract infection, primarily in infancy. Infectious mononucleosis (IM) with more prominent symptoms may be seen, especially in adolescents.

While vertical transmission is theoretically possible in the intrauterine period, estimating the transmission rate in practice is challenging when the seropositivity rate is more than 95% in adults [1–3]. Therefore, it can be said that primary EBV infection is rare in pregnancy, and the incidence of fetal infection is not significant. There is no definitive data on the relationship between fetal EBV infection and

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congenital anomalies [1–3]. While the relationship between congenital infection and deafness is clear for cytomegalovirus (CMV), there is no clear data for EBV, although they are both herpes group viruses [4–8]. Complications such as central nervous system (CNS) involvement, cranial nerve involvement, and deafness have been reported in acute EBV infections [9–14].

51.2 Etiology

Epstein-Barr virus, also called human herpes virus (HHV) 4, is a double-stranded deoxyribonucleic acid (DNA) virus in the gamma Herpesvirinae subfamily of the Herpesviridae family in the genus Lymphocryptovirus [1, 2]. Type 1 (A) and 2 (B) are two different EBV types; EBV-1 is the most common subtype in the world. Recurrent infections with both types are possible, especially in immunocompromised individuals. No clinical differences between subspecies have been reported [1–3].

51.3 Epidemiology and Transmission

Epstein-Barr virus is primarily transmitted by oral secretions and only from person to person; it does not spread from the environment. Epstein-Barr virus is excreted in oral secretions for 6 months after acute infection, and viral shedding in saliva continues intermittently throughout life, even in healthy individuals [1–3]. Different regions have different seroprevalence rates according to age; In low- and middle-income countries, infection is more common in early childhood, whereas in high-income countries, this rate is reported as 50% in children aged 6–8 years and 30% in adolescents and young adults [1, 2].

While primary EBV infection often progresses as an asymptomatic or mild upper respiratory tract infection in early childhood, it presents as classical IM disease in approximately 50% of adolescents and adults [1–3, 15, 16]. The incidence of IM syndrome is estimated to be 20–70 cases per 100,000 population [1]. Seropositivity increases with age [3]. Infectious mononucleosis does not show seasonal characteristics, and there is no sex predominance [1–3].

Close contact is required for transmission. Infectious mononucleosis is called “kissing disease” because EBV is most commonly transmitted by saliva. Epstein-Barr virus can be isolated from other bodily fluids, such as saliva, urine, breast milk, and female or male reproductive fluids following acute infection. Transmission by blood products and transplantation, sexually and perinatally, have been reported. Although the virus has been shown in breast milk, there is insufficient data on the role of breast milk in the transmission of EBV [1–4].

51.4 Pathogenesis

After transmission with oral secretions, EBV infects epithelial cells in the oral cavity and B lymphocytes in the Waldeyer ring. Envelope glycoproteins (gp350/gp220) on the surface of the virus allow binding to CD3d (CR2 or CD21) complement receptors on pharyngeal epithelial cells and B lymphocytes [1–3]. Infected B lymphocytes provide both hematogenous viremia and lymphatic spread of the proliferating virus. After viral replication and release of new virions, cell lysis occurs, and the virus spreads to neighboring organs such as the salivary glands. This is followed by viremia and infection of B lymphocytes of the peripheral blood and the entire lymphoreticular system, including the liver and spleen. The immune system determines the clinical picture that will emerge after the incubation period of 6 weeks (30–50 days). During the early incubation period, polyclonal CD8+ T lymphocyte activation occurs, then EBV-specific CD8+ T lymphocytes are formed, and natural killer (NK) cells are activated to reduce viral load. Activated CD8+ T lymphocytes constitute atypical lymphocytes in the peripheral blood smear. Cytotoxic (CD8+) T lymphocytes and natural killer (NK) cells are essential in limiting primary EBV infection. This restriction requires a protein called perforin, and the proliferation of EBV-infected B lymphocytes cannot be inhibited in the case of a perforin gene mutation. Insufficiency or loss of cytotoxic T lymphocyte functions causes uncontrolled B cell proliferation, which may result in a malignant course [1–4, 17, 18].

Because the virus resides in memory B cells in a latent state, intermittent viral shedding causes transmission of the infection. While there is no reactivation of the infection, conditions with oncogenic potential may develop due to virus proliferation in cases where the immune system is suppressed.

51.5 Clinical Manifestations

Epstein-Barr virus can cause two different groups of diseases, malignant and nonmalignant. Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin lymphoma, T cell lymphomas, posttransplant lymphoproliferative disorder, lymphomatoid granulomatosis, oral hairy leukoplakia, and leiomyosarcoma are EBV-related malignant diseases [1–4, 15, 16]. Infectious mononucleosis is the most common nonmalignant disease caused by EBV.

Primary EBV infection is often asymptomatic in children, and heterophile antibodies are positive in half of the young children [4, 15]. Conversely, in adults, EBV infection is symptomatic and heterophile antibodies are positive with a probability of 80–90% [3, 4, 15]. There is no correlation between EBV viral load and the severity of symptoms.

The incubation period for IM in adolescents is 30–50 days; this period may be shorter in children. Due to subtler findings, infection is often indistinguishable from upper respiratory tract infections in infants and young children. In the prodromal

period, malaise, fatigue, fever lasting >1 week, headache, sore throat, nausea, abdominal pain, and myalgia are present. The prodromal period is followed by generalized lymphadenopathy. After the development of lymphadenopathy, a classical IM picture (fever, exudative tonsillitis, generalized lymphadenopathy, and malaise) can be mentioned, and it can be distinctive [1–4, 15, 16].

In one third of cases, pharyngeal hyperemia, enlarged tonsils, and white exudate on the tonsils are detected. The tonsils and the overlying membrane become so enlarged that sometimes the tonsils come close to the uvula and may obstruct the airway. This condition is called "kissing tonsils" (Fig. 51.1). Enanthemas are observed at the border of the hard-soft palate in one third of the cases (Fig. 51.2). The more oversized the lymphoid tissue in Waldeyer's ring, the more venous return is blocked. Patients may experience periorbital edema, sleep with an open mouth, snoring, throwing back head, and sometimes apnea. Massive cervical lymphadenopathy (bull neck) may be seen in some patients, requiring differential diagnosis with vena cava superior syndrome caused by lymphoma.

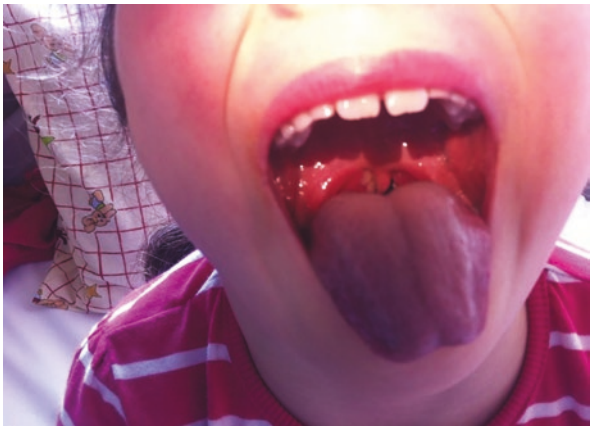

Fig. 51.1 Hyperemic and enlarged tonsils with white exudates which bilaterally close the uvula (kissing tonsils) (Courtesy Bilge Aldemir Kocabaş, MD)

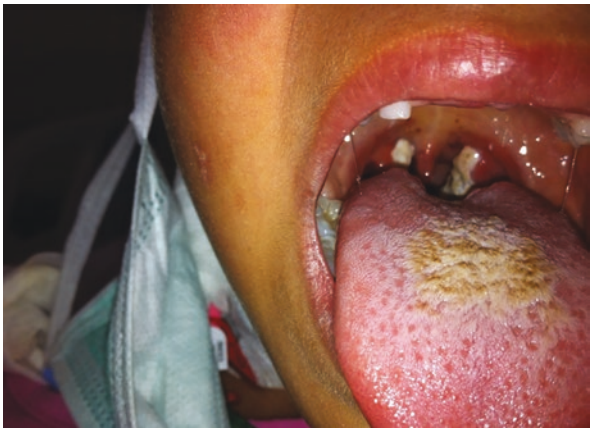

Fig. 51.2 Kissing tonsils and pharyngeal petechiae of primary infectious mononucleosis in an immunosuppressed child. (Courtesy Bilge Aldemir Kocabaş, MD)

Lymphadenopathy is observed in more than 90% of cases [1–4]. It is usually in the form of bilateral cervical lymphadenopathy. The anterior and posterior cervical lymph nodes are often enlarged and the involvement is typically symmetrical. Generalized lymphadenopathy may involve axillary, inguinal, supraclavicular, and even epitrochlear lymph nodes. Enlargement of epitrochlear lymph nodes is considered specific for IM. Enlarged lymph nodes, painless and tender to palpation, do not adhere to each other or the underlying tissue. Abdominal pain due to mesenteric lymphadenopathy and cough due to paratracheal lymphadenopathy may develop [1–4, 15, 16, 18].

Fever usually lasts 1–2 weeks, but it can sometimes persist for up to 4–5 weeks [1, 2]. A maculopapular rash is observed in 3–15% of cases [1–4]. Beta-lactams, especially ampicillin and amoxicillin, may cause a vasculitic morbilliform rash called "ampicillin rash" in patients with IM (Fig. 51.3) [1–3, 19]. Epstein-Barr virus can also cause Gianotti-Crosti syndrome, acute, self-limiting papulovesicular exanthema of the face, extensor surfaces of the extremities, and buttocks. Since tonsillopharyngitis cannot be clinically differentiated from those caused by group A streptococci, these patients have often received antibiotic treatment. Differential diagnosis is possible with systemic examination and peripheral blood smear with atypical lymphocytosis. On the other hand, streptococcal tonsillopharyngitis can be differentiated by neutrophilia, signs of the left shift in the peripheral smear, the presence of only cervical lymphadenopathy, and the absence of generalized lymphadenopathy or hepatosplenomegaly.

Although splenomegaly and hepatomegaly are present at approximately 50% and 30%, respectively, in children aged 4–16 years, the rates are 80% and 60%,

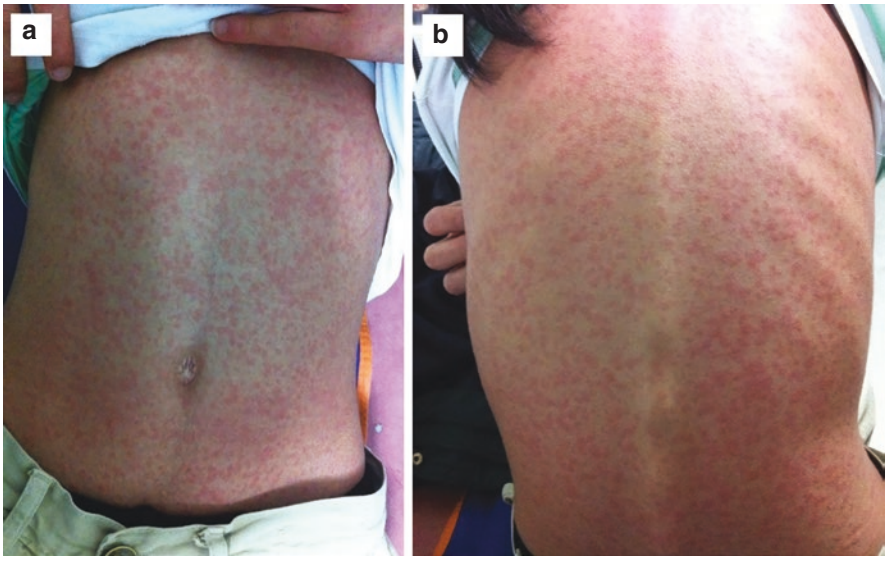

Fig. 51.3 (**a** and **b**) Ampicillin rash in a girl with infectious mononucleosis. A diffuse maculopapular rash on the anterior (**a**) and posterior trunk (**b**). (Courtesy Bilge Aldemir Kocabaş, MD)

respectively, under the age of 4 years [1, 2]. Elevation of transaminases is a common finding, but severe hepatitis and jaundice are seen in a minority of cases [1–4, 20]. While massive splenomegaly is rare, the spleen may also be fragilely enlarged, so care should be taken as pressure palpation may cause splenic rupture. Families should also be informed about spleen rupture and warned to protect their children from abdominal trauma.

Clinical symptoms and findings in IM resolve spontaneously within 3–4 weeks. Organomegaly may persist for 1–3 months, and lymphadenopathy may sometimes last up to 6 months [1–5, 16]. After IM disease, fatigue can be seen in up to 10% of patients for 6 months [1–4, 21]. However, EBV has not been proven to cause chronic fatigue syndrome [1, 3].

Chronic active EBV infection (CAEBV) is a rare condition characterized by hemophagocytic lymphohistiocytosis-like clinical and non-B cell proliferation. This condition is more common in children than adults and has been reported to be more frequent in Japanese. Two forms affect T cells or NK cells. It can be considered the severe form and worse prognosis of hemophagocytic lymphohistiocytosis (HLH). There is a persistent infection of peripheral T cells, with no improvement in classic IM symptoms and signs. Persistence or intermittent recurrence of fever, fatigue, malaise, generalized lymphadenopathy, and hepatosplenomegaly are observed. Neurological symptoms such as encephalitis, malignant findings such as lymphoma, hepatic failure, hemophagocytosis, and other organ involvement such as pneumonia and myocarditis may develop. Typically, CAEBV patients have low or no Epstein-Barr virus nuclear antigen (EBNA) response despite high antibody development against replication-indicating EBV antigens (viral capsid antigen [VCA], early antigen [EA]). Clonal proliferation in EBV-infected T cells and the perforin gene mutation is implicated. In Japan, a milder IM clinic, lower EBV serological responses, high immunoglobulin (Ig) E levels, and lymphocytosis create a different picture. These patients have an abnormal skin reaction to mosquito bites. High rates of EBV-infected CD-56 positive NK cells are detected in peripheral blood and skin lesions [1–4, 22, 23].

Epstein-Barr virus is associated with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis [1–4, 24, 25].

51.6 Differential Diagnosis

Infections such as CMV, *Toxoplasma gondii*, and human immunodeficiency virus (HIV) that cause mononucleosis and can form Downey cells in the peripheral smear, called IM-like diseases, should be considered in the differential diagnosis. Infectious mononucleosis should be differentiated from streptococcal and adenoviral tonsillopharyngitis by producing exudative tonsillopharyngitis and cervical lymphadenopathy. Since ampicillin rash may occur with beta-lactam antibiotics used during IM, differential diagnosis from other childhood rashes is required. The differential diagnosis should consider oncogenic malignancies since lymphomonocytosis, generalized lymphadenopathy, and hepatosplenomegaly can be seen during IM [1–4].

51.7 Complications

Complications are rare and summarized below [1–4, 9, 14, 16, 24, 26].

- Exanthems; ampicillin rash, erythema nodosum, Gianotti-Crosti syndrome.
- Hematologic; hemolytic anemia, aplastic anemia, thrombocytopenia, neutropenia, pancytopenia, and hemophagocytic lymphohistiocytosis.
- Splenic rupture.
- Gastrointestinal tract; parotitis, hepatitis (subclinical inflammation to fulminant hepatic failure, rarely chronic hepatitis), cholecystitis, hydrops of the gallbladder, typhlitis, and pancreatitis.
- Cardiac; myocarditis, ST and T wave changes, pericarditis.
- Renal; proteinuria, microscopic hematuria, tubulointerstitial nephritis, acute renal failure, rhabdomyolysis, nephrotic syndrome, and hemolytic uremic syndrome.
- Respiratory tract; airway obstruction, neck abscesses, interstitial pulmonary infiltration, pneumonia, pleural effusions.
- Genitourinary tract; orchitis, scrotal edema, genital ulcerations.
- Neurologic; aseptic meningitis, meningoencephalitis, cerebellitis, optic neuritis, facial paralysis, brain stem encephalitis, deafness, peripheric neuropathy, convulsions, transverse myelitis, Guillain-Barre' syndrome, "Alice in Wonderland" syndrome.
- Others; include arthritis, thyroiditis, and polyglandular syndrome.

51.8 Epstein-Barr Virus Infection and Hearing Loss

While it is known that CMV shows tropism to fetal neural progenitor cells, vestibular membrane, cochlea, and semicircular canals, it has not been proven whether there is a relationship between EBV and ototoxicity [3, 6, 7]. Moreover, there is no proven data that primary EBV infection causes congenital anomalies in pregnancy. However, there is limited data in the literature that EBV-related hearing loss (HL) may occur during postnatal acute EBV infection [1–4, 12, 14, 27].

In a case report, EBV-associated HLH was diagnosed in an adult patient with sudden HL, and the authors referred to EBV as an etiological agent that may cause HL [28]. On the other hand, when this case is examined, HL has been present for about 1 month, accompanied by vision blur, and EBV infection is not in the acute infection period. Therefore, it is controversial to explain HL with EBV viremia directly. However, this can be explained by the fact that EBV-related autoimmunity may be the progenitor factor.

Another case report belongs to a 3-year-old boy who was being followed up with the diagnosis of neuroblastoma [29]. He had a sudden onset of facial paralysis and HL and was diagnosed with EBV-associated posttransplant lymphoproliferative disease. Likewise, in this case report, the role of EBV in HL has not been demonstrated, indicating that further studies are needed.

Alde' et al. [30] have shown concomitant positivity of serum EBV IgM and CMV IgM antibodies in 5 patients with sensorineural HL (SNHL). Based on this report, the authors suggested a routine audiological examination and periodic follow-up after the onset of symptoms for children with primary EBV infection. However, it should be noted that false seropositivity is a common occurrence in herpes virus infections. In this report, the leading etiologic cause of HL may belong to CMV. Thus, it is impossible to make a definite prejudice without revealing the cause-effect relationship between EBV and HL, and large-scale studies are needed on this issue.

The relationship between cortical deafness and central HL and EBV was demonstrated in another study [12]. In this adult case, the etiologic agent was EBV, but the HL was attributed to vascular damage and ischemia.

Although the EBV and HL relationship is a remarkable finding, many studies should be conducted for the causation, and true etiopathogenesis should be revealed.

51.9 Diagnosis and Laboratory Findings

The diagnosis for IM can usually be made with typical clinical features and peripheral blood smear findings. Serological or polymerase chain reaction (PCR) tests are not mandatory in all patients because of characteristic clinical findings. In cases where the diagnosis is not precise, antibody tests against specific EBV antigens can be used to confirm the diagnosis. The distinctive peripheral smear finding of IM is atypical lymphocytes called "Downey cells" [1–4]. Downey cells are not only specific to IM and can also be seen in some infections such as CMV and hepatitis A virus infections. However, unlike other mononucleosis-like conditions, Downey cells are generally more than 10% in a peripheral smear in EBV-related IM [1–3]. Downey cells are CD8+ T lymphocytes that develop in response to infected B lymphocytes. Downey cell sizes are different from each other, and their cytoplasm is dark blue after Wright staining, vacuolated, and gives the appearance of foam [1–4, 16, 31]. Nuclei are bean-shaped or lobed and do not contain nucleoli (Fig. 51.4).

While heterophile antibody tests are mostly negative in acute infection in infants, viral capsid antibody (VCA) test positivity is approximately 60% [1, 3]. The first antibody formed in primary EBV infection is the IgM antibody against the viral capsid antigen. While VCA IgM antibodies disappear within 4–8 weeks, IgG antibodies to early antigen (EA) generally disappear within 6–12 months. In the acute period, serologically, anti-VCA IgM and IgG antibodies and anti-EA are positive, and anti-EBNA antibodies are negative. Antibodies such as IgG anti-VCA and anti-EBV nuclear antigen (EBNA) persist lifelong. In X-linked lymphoproliferative syndrome seen in males, the antibody response to acute EBV infection is low or insufficient [1, 2]. Reactivation should be considered in the presence of negative IgM anti-VCA, very high anti-EA titer, positive anti-VCA IgG, and anti-EBNA. In the same conditions, if EBNA antibodies are low or undetectable, CAEBV infection is mentioned [1–4, 16, 31]. The interpretation of serological tests used in diagnosing IM is summarized in Table 51.1.

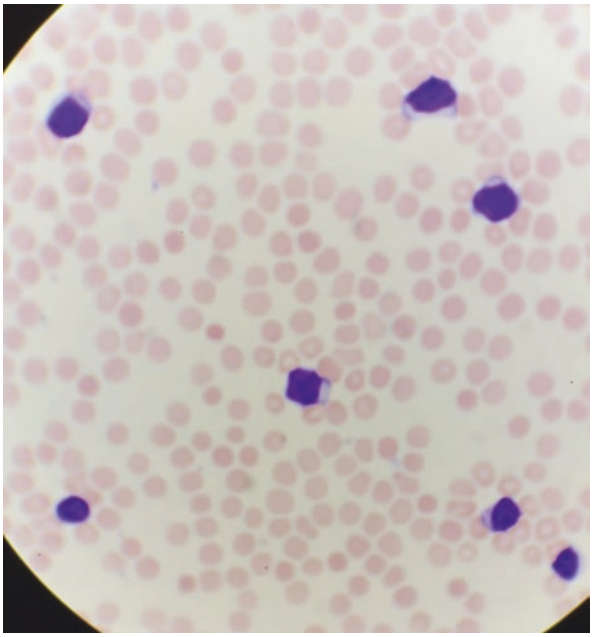

Fig. 51.4 Atypical lymphocytes in the peripheral blood of a child with infectious mononucleosis. (Courtesy Bilge Aldemir Kocabaş, MD)

Table 51.1 Interpretation of serological tests used in diagnosing infectious mononucleosis according to the stages[a]

The early phase of primary infection	VCA IgM[b] VCA IgG EA IgG EBNA IgG	Positive Negative Negative Negative
Acute primary infection	VCA IgM VCA IgG EA IgG EBNA IgG	Positive Positive Positive (high titer) Negative
Convalescent/past infection	VCA IgM VCA IgG EA IgG EBNA IgG	Negative Positive Negative or low titer Positive (high titer)
Reactivation	VCA IgM VCA IgG EA IgG EBNA IgG	Positive Positive (high titer) Positive (high titer) Positive (high titer)
CAEBV infection	VCA IgM VCA IgG EA IgG EBNA IgG	Negative Positive (very high titer) Positive (very high titer) Negative or in a low titer

CAEBV chronic active Epstein-Barr virus, *EA* early antigen, *EBNA* Epstein-Barr virus nuclear antigen, *IgM* immunoglobulin M, *IgG* immunoglobulin G; *VCA* viral capsid antigen

[a] Adopted and modified from Ref. [1, 2]

[b] Sometimes, especially in the early phase of infection, VCA IgM may be negative. In this situation, serum polymerase chain reaction (PCR) testing can be used to confirm the diagnosis, or serological tests can be repeated within a few days

In cases with immunosuppression, where serological tests are not significant or false negative/positive, PCR tests to detect EBV DNA are needed for diagnosis. It is possible to show EBV in tissue samples by in situ ribonucleic acid (RNA) or DNA hybridization methods. It is possible to detect cells containing EBV protein in tissue samples by immunofluorescence methods. Virus isolation tests in tissue cultures are complex, expensive, and used only for research purposes. Especially in oncogenic conditions, EBV virions can be demonstrated by electron microscopy [1–4, 31].

51.10 Treatment

Infectious mononucleosis is a self-limiting disease, especially in immunocompetent individuals. There is no specific treatment except supportive care. Bed rest is essential in the acute phase. It is recommended to use antipyretics for the control of fever and take plenty of fluids. There is no effective antiviral against EBV approved for IM. Although acyclovir, valacyclovir, and ganciclovir show antiviral activity against EBV in vitro, they are not used in the treatment of IM because their effects on clinical findings and disease course have not been demonstrated. However, these antiviral drugs can reduce EBV viral load in immunocompromised individuals [2, 3].

The routine use of corticosteroids for the treatment of IM is not recommended. Its use should be considered in complications, including severe airway obstruction, sleep apnea, myocarditis, hemolytic anemia, hemophagocytosis, massive splenomegaly, and thrombocytopenic purpura. The corticosteroid dose is 1 mg/kg/day, a maximum of 60 mg/day, for 4–7 days. It should be gradually discontinued in use exceeding 7 days [1–3].

The use of beta-lactams such as ampicillin and amoxicillin should be avoided in patients with suspected IM.

Heavy exercise and contact sports should be avoided for at least 21 days after the onset of IM symptoms, as there is a risk of rupture of the spleen. After 21 days, limited, noncontact aerobic sports are permitted only if the symptoms have entirely resolved, and splenomegaly has completely regressed. Active sports should be postponed for 4–7 weeks in contact sports [3, 32]. The decision to start sports can also be made by observing that the spleen size has completely regressed ultrasonographically.

51.11 Prognosis

The prognosis for IM is good, especially in healthy individuals. Neurologic complications such as Guillain-Barre syndrome**,** splenic rupture, myocarditis, HLH, aplastic anemia, hepatic failure, and secondary infections may cause mortality. The most common causes of fatality in EBV-related diseases are immunosuppression and oncogenic malignant conditions [1, 2].

51.12 Prevention

It is recommended to avoid situations such as saliva contact and sharing food and drink with people who have recently had IM. Not only during acute infection but also lifelong intermittent viral shedding in the saliva is seen in healthy individuals. For that reason, only standard precautions are recommended for hospitalized patients infected with EBV. In addition, there is no restriction on returning to school or work for patients who have had a recent EBV infection [1–3].

Some clinical trials have studied a recombinant EBV subunit gp350 vaccine [3, 33].

51.13 Conclusion

Most primary EBV infections are subclinical and indeterminate. It's spread to susceptible persons through close contact with asymptomatic EBV shedders. It is essential to know the complications that may develop during acute infection. Sometimes it is possible to recognize IM with such complications as spontaneous splenic rupture, hepatitis, glomerulonephritis, etc. The target cells of EBV are epithelial cells in the oral cavity and B lymphocytes. So, it is important not to share personal items such as toothbrushes and not to kiss small children on the lips because the disease is transmitted through close contact and saliva. Although EBV mostly causes self-limited disease, it can lead to malignant manifestations, especially in immunocompromised individuals.

Intrauterine transmission of EBV from infected mother to baby is rare; no congenital malformation associated with primary EBV disease has been proven. However, acute EBV infection has reported complications such as CNS involvement, cranial nerve involvement, and deafness. It is unclear whether EBV-associated deafness is central or inner ear-related or is due to direct damage or autoimmunity. More comprehensive studies are needed to draw more attention to the relationship between EBV and deafness and to elucidate the pathogenesis.

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Herpes Zoster Oticus and Hearing Loss

52

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52.1 Introduction

Herpes zoster oticus (HZO), sometimes termed Ramsay Hunt syndrome, refers to an infrequently occurring disorder in which patients present with earache, vesicle formation on the pinna, and peripherally paralysed facial muscles. It occurs when varicella zoster virus lying dormant within the geniculate ganglion becomes reactivated. This condition is equally common in males and females and is seldom seen in paediatric patients. The frequency rises and cases are more severe in individuals who are immunocompromised. Not all features of HZO may initially be seen, which may lead to misdiagnosis. Bell's palsy is more common as the reason for peripheral paralysis of the muscles of the face not caused by traumatic injury, but HZO has a graver prognosis. The frequency of HZO lies between 0.3 and 18%. Among patients with a facial palsy, approximately 12% are attributable to HZO. Cases usually affect one side of the face and no more than around a fifth of cases completely resolve without intervention. The treatment with most supportive evidence at present involves the use of aciclovir and prednisone, but the results remain somewhat disappointing and more effective treatments are still needed [1].

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52.2 Definition

Another term for the herpes zoster virus is shingles. This virus invades the sensory ganglia during the initial varicella episode. HZO occurs where varicella-zoster virus spreads through the nerves of the face to affect all portions of the ear—external, middle, and inner. HZO is also termed Ramsay Hunt syndrome. The clinical presentation involves severe earache, vesicles on the mouth, external auditory meatus and auricle, and potential paralysis of the face. There may also occur auditory loss, vertigo, severe prosopalgia, and ringing in the ears [2].

HZO is the diagnosis in approaching 12% of patients with paralysis of the face. Its symptoms are worse and the outcome less favourable than cases due to Bell's palsy [2–5]. The degree to which normal facial function returns is partly dependent on how severe the initial paralysis is. A number of studies have concluded that total remission of symptoms is only noted in between 10 and 22% of patients where the initial paralysis of the face was severe. One study did note, nonetheless, that if the initial paralysis was partial, two thirds of cases went into total remission [2].

HZO (Ramsay Hunt syndrome) involves a characteristic combination of three features: paralysed facial muscles on the side of the lesion, vesicles within the external auditory meatus or pinna, and otalgia [6–8]. Some other potential presenting features are gustatory abnormalities, glottic lesions, altered auditory function (auditory impairment, ringing in the ears, sounds that appear louder than usual), and tearing more than usual. Balance problems (vertigo) are also a common complaint in HZO [8].

HZO occurs when varicella-zoster virus particles lying dormant in the geniculate ganglion become reactivated [9, 10] and the virus infects the vestibulocochlear nerve. This condition may also be seen when there are multiple cranial nerves affected, in particular the trigeminal, glossopharyngeal, and vagus nerves [6, 7].

In Bell's palsy, the degree of paralysis of the face is generally less marked than in HZO. Bell's cases are caused by herpes simplex virus. In HZO there may occur loss of the nerve supply to the face at a late stage and the chances of the condition completely resolving are lower than in Bell's palsy cases. Antiviral medication is used to treat HZO, despite a paucity of evidence on the best way to manage the condition [11].

Postherpetic neuralgia may also complicate some cases of HZO [2].

Both sexes are affected at the same frequency by HZO. There is a significantly raised risk of HZO occurring in individuals who are older than 60 years of age [2].

52.3 Pathophysiological Features

The initial infection with varicella-zoster virus (VZV) presents clinically as chickenpox (varicella). When the varicella infection resolves, the VZV particles remain in a latent form in the nerve roots of the cranial nerves and within the sensory ganglia. If VZV becomes reactivated, a vesicular eruption may occur in a particular region of the body. This condition is termed shingles (herpes zoster). HZO occurs

when VZV is reactivated and spreads through the sensory nervous supply to the ear. The geniculate ganglion is commonly involved. The fact that HZO can cause auditory impairment and vertigo is usually attributed to VZV entering the vestibulocochlear nerve from the facial nerve at a point where the nerves pass very close to each other (i.e. the cerebellopontine angle), or haematogenously through the small vessels (vasa nervorum) connecting the facial nerve to other cranial nerves passing close by. Another potential explanation, used to account for the involvement of multiple cranial nerves in some cases, is that VZV passes across synapses in an anterograde fashion within the brainstem [1, 3, 4].

52.4 Aetiology

HZO is the result of dormant VZV becoming reactivated in the sensory ganglia of the seventh cranial nerve. The usual site is the geniculate ganglion. If T lymphocytic function is impaired, there is a higher likelihood that HZO will occur and become complicated. Thus, the following factors raise the risk: malignant neoplasia, radiotherapy, chemotherapy, HIV infection, receiving a donor organ, and immunosuppressant treatments. It is frequently claimed that physical or psychological stress may trigger an episode of HZO [2].

52.5 Diagnosis

52.5.1 History

The usual presentation is with a severe earache. Other presenting features are [2]:

- Periotic, facial, oral, or glossal vesicles that cause a burning pain.
- Vertigo, nausea, and vomiting.
- Auditory impairment, ringing in the ears, sounds that appear louder than usual.
- Ocular pain, tearing.

The painful symptoms may occur a few hours or even days before the eruption is visible. Pain without a visible eruption is termed zoster sine herpete. Blisters may occur prior to the facial paralysis, during it or at a later point. Many patients provide a history of chickenpox (varicella), typically when they were a child. Less commonly (under 10% of cases), patients have a previous history of HZO [2].

52.5.2 Physical Examination

When patients are physically examined, a blistering rash is seen, generally in the external auditory meatus, the concha, and auricle. The exanthem may also affect the

skin behind the ear, the side of the nose, the velum, and the front and sides of the tongue.

The patient may have vertigo and auditory impairment of sensorineural type may be observed. There may be paralysis of the muscles supplied by the seventh cranial nerve. Thus, the picture may look like Bell's palsy. Peripheral rather than central paralysis is the cause if the patient cannot wrinkle their brow on the affected side. In central paralysis, the forehead muscles are usually unaffected [2].

Other findings which may be noted are as follows [2]:

- Abnormal gustatory perception.
- The patient may lack the ability to close their eye on the side of the lesion. This may then lead to corneal desiccation and irritation.

52.5.3 Laboratory Investigations

The diagnosis of HZO mainly depends on obtaining a characteristic history and physical examination findings. However, prior to commencing aciclovir, certain baseline investigations are of value, namely [2]:

- Blood urea nitrogen (BUN).
- Blood biochemistry (including creatinine and electrolytes).
- Full blood count.

If a patient is in a high risk category due to immunodeficiency, it may be helpful to perform serology for anti-VZV immunoglobulins M and A.

The diagnostic test with the highest sensitivity in detecting herpes zoster is PCR. It can detect above 95% of cases and is more rapid than cell culture [2].

52.5.4 Imaging Investigations

Where physical examination fails to elicit findings supporting a diagnosis of HZO, computed tomographic imaging of the head may be useful in revealing another cause for facial paralysis [2].

52.6 HZO and Auditory Impairment

The first published description of HZO was by James Ramsay Hunt in 1907. It is therefore eponymously referred to as Ramsay Hunt syndrome. It is caused by dormant VZV viral particles within a sensory root ganglion becoming reactivated years after the initial varicella infection that caused their presence in the neurone. HZO results from this reactivation occurring in the geniculate ganglion, within the sensory division of the seventh cranial nerve. The lesion within the seventh cranial

nerve then causes earache, peripheral paralysis of the face on the affected site, and a blistering rash over the pinna. If HZO is severe, the eighth cranial nerve may also be involved, with 40% of cases having balance-related problems and 10% auditory impairment of sensorineural type.

52.7 Treatment

The treatment for HZO enjoying the highest level of acceptance among clinicians is combined aciclovir and prednisone [4]. Aciclovir has efficacy in preventing the rapid replication of herpes zoster. It is a prodrug that becomes active when in its triphosphate form. This occurs due to the action of a thymidine kinase coded by the virus. The active form interferes with the activity of DNA polymerase of viral origin and the virus cannot then replicate its own DNA [12]. A study using both an oral and intravenous method of administering aciclovir found that any differences in outcome associated with the route of administration were no more than may be expected by chance [12]. Since the virus has increasingly become resistant to aciclovir, more recently developed agents such as valaciclovir, famciclovir, penciclovir, and brivudine are increasingly prescribed for this indication.

Corticosteroids administered adjunctively to treat facial paralysis may be beneficial [13]. A trial where 80 patients with HZO were administered aciclovir in combination with prednisone found that 52% of cases recovered entirely (grade I on House-Brackmann scoring). This outcome was independent of the severity of paralysis before treatment began [4].

Trials have also compared combined aciclovir-steroid with steroids alone and concluded that the former is the superior treatment [13]. Despite this finding, there are numerous warnings in the literature about the risk of corticosteroid therapy allowing VZV to spread more widely, especially when treating vesicles around the eye [14].

Rehabilitatory measures used in cases of facial paralysis involve electrical stimulation of muscles, infrared radiation, and exercises aiming to work the muscles of the face, such as self-massage, relaxation of muscle groups, preventing synkinetic contractions, improving facial co-ordination, and showing emotions via facial expression. If older patients are administered the varicella vaccine, this increases T cell immunocompetence and helps prevent herpes zoster and postherpetic neuralgia [15].

52.7.1 Antiviral Medication

Provided it is administered shortly after disease onset, antiviral medication can shorten the symptomatic period and reduce its severity. It has been demonstrated that aciclovir given within 72 hours of symptomatic onset improves the functional recovery of the seventh cranial nerve and arrests degenerative change. Antiviral

agents, moreover, reduce the likelihood of postherpetic neuralgia and render it less severe when it does occur [16–19].

There is a potential for misdiagnosis of VZV infection as Bell's palsy if there is no accompanying vesicular eruption, i.e. zoster sine herpete. For this reason, it may be advisable to consider using more than one antiviral agent, such as aciclovir, valaciclovir, and famciclovir [11, 20]. Trials comparing aciclovir administered orally and intravascularly have found no difference in outcome when used to treat patients with facial paralysis who are not immunodeficient [21].

Valaciclovir and famciclovir possess greater efficacy in preventing pain than aciclovir, but their safety and efficacy against VZV are similar. Patients may be more compliant when taking valaciclovir or famciclovir than aciclovir, since these agents are administered t.d.s. rather than five times per day, as required for aciclovir [16, 22]. Patients taking famciclovir had a greater likelihood of complete resolution of HZO than if administered aciclovir, once the effects of varying compliance and initial grade of severity were controlled for. There are several potential explanations for this greater efficacy, such as the excellent bioavailability of famciclovir and the fact that absorption is not altered by presence or absence of food in the gut. Aciclovir suffers from low bioavailability when given by mouth and absorption is impaired by presence of food in the gut. Furthermore, famciclovir undergoes metabolism to an active form which persists longer than aciclovir in virally infected cells and enjoys high selectivity for those cells where herpes virus is present [23].

52.7.2 Corticosteroids

It has been demonstrated numerous times that combined corticosteroids and antiviral agents significantly reduce complications in the longer term. Steroids administered systemically reduce pain acutely, lessen vertigo, and render the development of postherpetic neuralgia less probable. Trials of different dosing regimens for corticosteroids in HZO have not provided decisive answers about the optimum schedule to follow. A meta-analysis indicates that aciclovir combined with prednisone is better at ensuring functional recovery of the seventh cranial nerve and decreasing neurodegeneration than aciclovir used alone [17]. Where patients received antiviral agents plus steroid, the outcome improved, as evidenced by shorter times for the eruption to heal, resolution of acute neuritis, a lesser need for painkillers, and quicker return to normal social functioning [24]. Nonetheless, there is no evidence to demonstrate any effect of steroid treatment on reducing the incidence of postherpetic neuralgia [18, 19].

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Enterovirus Infections in Children and Hearing Loss

53

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53.1 Introduction

Enteroviruses (EVs) belong to the Picornaviridae family and consist of coxsackieviruses (CVs), rhinoviruses, polioviruses, and echoviruses. Enteroviruses constitute one of the most common causes of infections in humans worldwide, affecting all age groups and causing a diverse range of diseases, including the common cold, polio, and aseptic meningitis. Enteroviral infections are often self-limiting, though EVs can lead to significant morbidity and economic burden [1].

53.2 Etiology and Classification

The Picornaviridae, one of the largest families of ribonucleic acid (RNA) viruses, includes a range of pathogens infecting humans and animals. Structurally, all EVs in the Picornaviridae family consist of a 15–30 nm icosahedral capsid enclosing about 7400-nucleotides long positive-sense single-stranded RNA (+ssRNA) [1, 2].

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Enteroviruses have different serotypes that can be distinguished from each other by neutralization with specific antisera. Enteroviruses are classified into 4 subtypes based on their host specificity and pathogenicity [3].

- Polioviruses (serotypes 1–3).
- Group A CVs (serotypes 1–22, 24).
- Group B CVs (serotypes 1–6).
- Echoviruses (serotypes 1–9, 11–21, 24–27, 29–33).

Enteroviruses are also classified according to the homology within the RNA region encoding the VP1 capsid protein (4 species, A to D). Since 1970, many new EVs have been identified and characterized by molecular methods, thus increasing the number of known serotypes to over 100.

There are also alternative groupings for EVs in the literature [1]:

- Rhinoviruses and non-rhinovirus EVs.
- Polioviruses and non-polio EVs.
- Rhinoviruses, respiratory EVs, and non-respiratory EVs.
- Human EVs (HEVs) and rhinoviruses.

53.3 Epidemiology

The enteroviral disease is seen in all age groups, but is more common, especially in young children. Zhou et al. [4] reported the annual incidence of EV disease in the whole population as 144,8/100,000, while this rate was 3066,8/100,000 in children aged 5 years and younger. While the proportion of patients aged ≤5 years to all patients was between 82.6% and 95.6% in various studies [4, 5], this ratio was 79% in a study conducted in Türkiye [6].

As the age decreases in children, the risk of central nervous system (CNS) involvement, encephalitis, and myocarditis increases. The most well-known neurotropic EV is the poliovirus. Poliovirus belongs to the EV C strain and has been almost eradicated by vaccination. Non-polio EVs constitute the majority of infections [7].

Most patients with EV infection have very mild or no symptoms. However, during the first EV 71 infection outbreak in Taiwan in 1998, the mortality rate was reported to be 1 to 10 per 100,000 population [8]. There were about 7.2 million cases in China between 2008 and 2012 due to outbreaks of hand, foot, and mouth disease (HFMD) [9]. The EV-A71 was responsible for 80% of approximately 82,000 serious cases and 93% of 2457 deaths.

Enterovirus infections occur year-round, and people living in temperate climates experience higher infection rates in summer and autumn. Immunocompromised patients may experience more severe enteroviral diseases [1, 10].

The incubation period of EV infections is difficult to measure and varies according to clinical syndromes. Studies during PV outbreaks showed that fever and other

nonspecific clinical manifestations develop 3–5 days after exposure. Excretion of infectious virus from the upper respiratory tract and feces lasts for 1–3 weeks and 3–8 weeks, respectively. Maximum contagiousness occurs in the first 2 weeks of infection [3].

53.4 Pathogenesis

Enteroviruses are cytopathic. While tissue-specific cell destruction is likely the cause of most associated diseases, host immune response is considered responsible for some clinical manifestations, such as EV exanthems and myocarditis. Transmission of EVs occurs via respiratory droplets and fecal-oral and transplacental routes. The oropharyngeal epithelial cells and intestinal mucosa are the primary viral replication sites. Although some replication can happen in the upper respiratory tract and lymphatics, most EVs are ingested and transferred to the stomach and then reach the lower gastrointestinal tract. The EV passes through the gut, goes the Peyer's patches in the lamina propria, and viral replication takes place. Viremia may cause a secondary tissue infection. In particular, CNS infection secondary to EV causes meningitis or encephalitis.

Other tissue-specific infections may cause myocarditis or pleurodynia. Widespread infection may lead to exanthems, nonspecific myalgias, or severe multiorgan damage [2].

Rhinoviruses, on the other hand, primarily infect the airway epithelium. When the virion enters the cell, low endosomal pH or receptor binding triggers a conformational change, exposing hydrophobic domains. This is followed by the pore-mediated entry of the viral genome into the cytoplasm, where the host cell ribosomes synthesize the viral polyproteins. Rhinoviruses do not directly cause cell destruction. Instead, they disrupt the epithelial barrier function by stimulating reactive oxygen species production during replication and dissociating zonula occludens-1 from the tight junction complex [1].

53.5 Clinical Manifestations

More than 90% of non-polio EV infections are asymptomatic or result in febrile illness. In the case of more severe disease, the clinical spectrum and severity of the disease vary according to the host's age, gender, and immune status [11, 12].

53.5.1 Central Nervous Infections

Meningitis is the most common CNS involvement. Some EVs, such as polioviruses, E-30, EV D68, and EV A71, target motor nuclei in the brainstem and spinal cord, causing acute palsy in the cranial and spinal nerves [13].

53.5.1.1 Meningitis/Meningoencephalitis

Aseptic meningitis is most common in infants younger than 1 year of age. More than 90% of aseptic meningitis cases in infants are caused by EVs, primarily by group B CVs and echoviruses. Nevertheless, EVs constitute the most common cause of viral meningitis in a broader population, including toddlers, older children, and adults, accounting for more than 50% of all cases.

The most common symptoms in infants are fever and irritability. Aseptic meningitis is usually diagnosed during the evaluation of a child with a fever without a source. In older children, fever, headache, meningeal irritation signs, nausea, and vomiting are observed. Most infants and children recover within 3–7 days, and full recovery usually is the rule.

Enteroviruses are responsible for about 5% of acute encephalitis cases for which extensive diagnostic testing is performed. The most common cause of enteroviral encephalitis is Echovirus 9, followed by echoviruses 4, 6, 11, and 30, and CV B5.

Generally, the prognosis is better than encephalitis caused by other viruses. However, in the last 20 years, severe encephalitis epidemics have been reported in Asia-Pacific countries due to EV A71 (EV-A71), and long-term sequelae have been reported to be related to the severity of CNS involvement or neuronal damage, hypoxia, and young age [11, 13, 14].

53.5.1.2 Acute Flaccid Paralysis

Many EV serotypes have been reported in the etiology of acute flaccid paralysis, and poliovirus types 1,2, and 3, EV D68, and EV A71 are responsible for only a small portion. These viruses infect the brain stem and motor neurons in the spinal cord.

Poliomyelitis-like diseases related to EV A71 and EV D68 have been reported in outbreaks and epidemics. Rare cases of brainstem encephalitis identified during outbreaks due to EV A71 have been reported to be accompanied by non-cardiogenic pulmonary edema and fatality.

The disease caused by wild-type poliovirus infection is now confined to Afghanistan and Pakistan, and its complete eradication is imminent. Rare cases of vaccine-induced paralytic polio continue to emerge in countries that use live attenuated oral polio vaccine for routine infant vaccination and control of wild-type polio [11, 15].

53.5.2 Neonatal Sepsis

Enteroviral infections in newborns can cause a wide variety of clinical manifestations, from asymptomatic infection to fulminant and life-threatening diseases like fatal encephalitis and myocarditis. Newborn infections may be acquired vertically before, during, or after birth, from a family member, or via nosocomial transmission. Although inapparent infection likely occurs occasionally, evidence for this assumption is limited.

Enteroviral infections cause nonspecific febrile and sepsis-like diseases. It is difficult to distinguish from a bacterial infection in infants with nonspecific fever. The sepsis-like disease is characterized by fever, poor feeding, abdominal distention, irritability, rash, lethargy, and hypotonia, and severe fatal disease includes jaundice, hepatitis, disseminated intravascular coagulation, thrombocytopenia, and hypotension. Echoviruses and CV B viruses are the most common serotypes associated with neonatal sepsis. Respiratory diseases have been reported due to neonatal enteroviral infections, including herpangina, rhinitis, pharyngitis, laryngitis, and pneumonia.

In the first week of life, severe life-threatening complications may develop, such as hepatic necrosis with coagulopathy, myocarditis, and meningoencephalitis. The outcome of enteroviral infection in the newborn depends on the virus type, mode of transmission, and the presence or absence of maternal neutralizing antibodies [16, 17].

53.5.3 Exanthema and Enanthema

Non-polio EVs are frequent causes of various exanthemas and enanthemas in summer and autumn. Rashes other than hand, foot, and mouth disease (HFMD) cannot be distinguished from other rash causes.

53.5.3.1 Hand, Foot, and Mouth Disease

Hand, foot, and mouth disease (HFMD) is characterized by vesicular lesions in the anterior mouth and on the hands and feet associated with fever. Hand, foot, and mouth disease is usually benign and self-limiting in preschool children; however, severe complications such as meningitis, encephalitis, and neurorespiratory syndrome may develop rarely. Hand, foot, and mouth disease has caused many epidemics throughout history, mainly by two EVs: CV-A16 and EV 71 [18, 19]. Recurrent attacks may occur in HFMD. The severity of HFMD was not associated with the duration of recurrent episodes [20].

53.5.3.2 Herpangina

Group A CVs are the leading causes of herpangina, affecting mainly children aged 3 to 10 years. Most cases occur during summer outbreaks.

The onset of herpangina is typically characterized by a sudden onset of fever. There is usually no prodromal period. The fever is generally higher in young children between 39.5 and 40 °C. Fever may be accompanied by loss of appetite, sore throat, headache, vomiting, and diarrhea. Oropharyngeal lesions occur during or immediately after fever. The characteristic lesions are vesicles and ulcers seen in the anterior tonsillar pillars. Enanthems can also be seen on the soft palate, uvula, tonsils, and pharyngeal wall. Except for herpangina lesions, the throat appears normal or slightly hyperemic. The duration of illness is usually 3–6 days. Cases of herpangina are usually mild, but serious associated enteroviral manifestations such as aseptic meningitis, acute flaccid paralysis, and encephalitis have been reported [1].

53.5.3.3 Maculopapular Rash

Generalized maculopapular rashes often occur in EV infections, especially those due to CVs A9 and B5 and echoviruses. The fever lasts for 24–36 hours and then subsides with the appearance of the exanthem. The rashes are discrete, nonpruritic, salmon-pink macules and papules, approximately 1 cm in diameter, located on the face and chest [1, 11].

53.5.3.4 Petechial and Purpuric Rashes

Petechial and purpuric eruptions have been associated with echovirus 9 and CV A9. In addition, Del Guidice [21] reported petechial rashes in the extremities of 6 pediatric patients with EV A71. When aseptic meningitis occurs in these cases, the clinical illness is easily confused with meningococcal disease.

53.5.3.5 Urticarial Rash

Urticarial exanthemas are usually due to allergic or dermatological problems. However, when urticaria develops with an acute febrile illness, the cutaneous reaction is due to an infectious agent. Although papular urticaria is most often due to insect bites, similar rashes are seen in CV A and other EV infections. The presence of fever indicates enteroviral infection [11, 22].

53.5.4 Acute Hemorrhagic Conjunctivitis (AHC)

Coxsackievirus A24 and EV 70 may cause a painful and highly contagious ocular infection named AHC. Both viruses have caused outbreaks of AHC. It is self-limiting and rarely causes permanent visual impairment. In severe cases with AHC, keratitis may last for several weeks. The primary therapy is supportive [11, 23].

53.5.5 Pleurodynia (Bornholm Disease)

Pleurodynia is a historically epidemic disease characterized by fever and paroxysmal spasms of the thoracic and upper abdominal muscles. Group B CVs are the leading cause of epidemic pleurodynia; other EVs have rarely been reported. It is mostly seen among adolescents and adults during localized summer outbreaks. The incubation period is 4 days, followed by sudden onset of fever and pain.

The pain is very severe, starts abruptly, and is accompanied by excessive sweating; the patient may appear pale and shocked. Pain and fever usually last for 1–2 days, and spasm periods last for 15–30 minutes. Abdominal pain occurs in the form of cramps, during which the patient has pallor, sweating, and a shock-like appearance. Pleurodynia can be confused with pneumonia, pulmonary embolism, myocardial infarction, acute abdomen, and herpes zoster infection [11, 24].

53.5.6 Myocarditis

Cardiac involvement during EV infection typically presents as myopericarditis and affects the subepicardial myocardium and the pericardium. However, clinical manifestations of either myocarditis or pericarditis may predominate. Group B CVs, especially CV B5, are the most common causative agents. Mortality is unknown, as virological studies are often not performed on cardiac disease due to EVs. In the study in which patients with acute CV myocarditis were followed up, it was reported that myocarditis was completely resolved in survivors. With the development of diagnostic testing, CV B nucleic acid sequences have been found in myocardial biopsy specimens from patients with cardiomyopathy. Studies examining the relationship between cardiomyopathy and EVs show the role of EVs in some patients with dilated cardiomyopathy. Myocardial damage is thought to be the result of the host's cellular immune response, not the direct cytopathic effect of the virus [11, 24].

53.5.7 Respiratory Disease

Enteroviruses cause both upper and lower respiratory tract infections that are clinically indistinguishable from other infectious etiologies. Various CVs and echoviruses have been shown to cause the common cold. The onset of pharyngitis due to CVs and echoviruses is sudden, and the first complaint is fever. The pharynx and tonsils are hyperemic, sometimes covered with exudate. The duration of the disease is 3–6 days.

Croup, due to EVs, has a milder course than croup due to parainfluenza and influenza. Coxsackieviruses and echoviruses are associated with the triggering of bronchiolitis, infectious asthma, and asthma attack in atopic children. It has been reported with a 1–7% rate in children with pneumonia and a positive viral culture.

EV D68 was first isolated from children with lower respiratory tract infections in 1962. All patients had pneumonia and bronchiolitis. Children with asthma and reactive airway disease were frequently affected, and intensive care unit admission was more likely [1, 11, 24].

53.5.8 Chronic Enteroviral Meningoencephalitis (CEM)

Cell-mediated immunity has a primary role in the host's defense against most viral infections. However, the most critical host defense mechanism against EVs is humoral immunity with neutralizing antibodies. Two patient groups, infants and young children and people with antibody deficiency, have an unusual predisposition to develop severe enteroviral infections. Patients with X-linked agammaglobulinemia (XLA) are particularly vulnerable to vaccine-associated paralytic poliomyelitis and CEM. Chronic EV infections do not occur in otherwise normal individuals. Agammaglobulinemic individuals with only B cell deficiencies appear at serious risk for chronic enteroviral infections of the CNS due to unclear reasons.

These cases may present with headaches, hearing loss (HL), weakness, seizures, ataxia, paresthesia, lethargy, or coma. Besides, the EVs clearance time is prolonged in agammaglobulinemic patients, although it is usually an average of 1–6 weeks. The CEM of agammaglobulinemia (CEMA) has a slow and insidious onset of neurological symptoms and altered cognitive function. Although the disease can present a diverse onset, signs and symptoms are eventually similar in nearly all patients.

McKinney et al. [25] reported that in 42 patients with CEMA, the most common complaints were headache, seizures, HL, weakness, ataxia, lethargy, or coma. Peripheral sensory changes (paresthesias), decreased intellectual acuity, loss of developmental milestones, hemiparesis, cranial nerve palsies, episodic states of confusion, and symptoms consistent with transient ischemic attacks were frequent. Personality changes are expected, though challenging to characterize. The most common behavioral changes are depression and emotional variability. Visual disturbances such as dysarthria and aphasia and diplopia occur. Subarachnoid hemorrhage was reported in one patient, and subdural hematoma in another. The two most essential points regarding neurological symptoms are that (1) the presence of neurologic symptoms in an agammaglobulinemic patient may be a reflection of CEMA, and (2) the virus may be present in CNS for a long time before the onset of neurological findings [25].

53.6 Enterovirus Infections and Hearing Loss

Viral infections are considered an important underlying cause of sudden HL. The underlying mechanism can be either acute, caused by host defense response, or latent due to damage induced by reactivation and trigger immune responses. Infections with Herpesviridae family viruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], cytomegalovirus [CMV], Ebstein-Barr-virus [EBV]), mumps, rubella, measles, adenovirus, and other viruses that caused respiratory tract infections have been proposed to play a role in the pathogenesis of sudden HL [26].

Animal experiments have shown that several viruses can cause HL when administered into the perilymph. Some of these have an affinity for specific inner ear cells, such as sensory epithelia and cochlear nerve. Some viruses, such as adenoviruses and CV B, have specific CAR receptors defined on different cell types, while others act by binding to nonspecific cellular receptors.

The relationship between sudden sensorineural HL (SNHL) and enteroviral infection was first reported in 2003 [27]. However, Bachor et al. [28] presented histopathological findings in the temporal bone at the autopsy of a 26-month-old girl with a polio-like syndrome, who had almost pure neural HL due to a probably non-polio EV infection in 2001. Non-polio EVs were identified as a possible etiological factor in this patient, yet no test was performed.

In 2003, Schattner et al. [27] reported a young male presenting with sudden severe bilateral SNHL due to self-limiting EV aseptic meningitis in autumn. The diagnosis was made by polymerase chain reaction (PCR) test for EV in the cerebrospinal fluid (CSF) followed by EV culture in the patient's stool, and the HL

completely recovered on the tenth day. The authors reported that EV infections might cause viral cochleitis and sudden SNHL, even some idiopathic SNHL, besides aseptic meningitis.

Subsequently, in 2003, Mentel R et al. [29] performed serological tests for HSV, VZV, and EV and PCR tests for EV in 55 patients with sudden HL and the control group. They did not find any difference between the patient and control groups in the serological screening for HSV and VZV. However, the reverse transcriptase-PCR (RT-PCR) test revealed specific sequences for EV in 40% of the study group, whereas none were in the control group. The authors concluded that EV infections might be associated with sudden HL.

Groos M et al. [30] analyzed EBV and CMV serology and EV RT-PCR in plasma samples at admission in a prospective cohort study of 48 adult patients with unilateral idiopathic SNHL between April 2004 and March 2005. None of the patients had clinical symptoms consistent with a prior or concurrent viral infection. One patient (2.08%) had RT-PCR evidence of EV infection. Enterovirus infections may be causative of unilateral idiopathic SNHL.

Pyykkö et al. [26] reported a total of 273 patients with Ménière's disease (n 158), recurrent vertigo of unknown etiology (n 56), or HL (n 17), and 43 of whom were controls. Patient sera were evaluated for immunoglobulin (Ig) G antibodies against HSV-1, HSV-2, VZV, CMV, EBV, EV, CV B5, echovirus 22, rotavirus, influenza viruses A and B, RSV, adenovirus, mycoplasma, and chlamydia. Patients with sudden SNHL had higher IgG titers for VZV, adenovirus, CV B5, influenza B, and RSV than controls, and CV B was able to affect the inner ear and induce SNHL in humans.

Kadambari et al. [17] evaluated 668 cases of EV meningitis in infants younger than 90 days of age in 13 months between July 2014 and July 2015 in the United Kingdom and the Republic of Ireland. They reported that none of the patients had SNHL at the 12-month follow-up. The authors concluded their data support the consensus that post-discharge audiological follow-up is not routinely required in infants with EV meningitis well at discharge.

Balasubramanian et al. [31] evaluated short- and long-term (first year) outcomes in 33 neonates with enteroviral meningitis at >32 weeks of gestation, based on CSF enteroviral PCR from July 1, 2002, to June 30, 2012. They performed a neurodevelopmental assessment using the Griffiths Mental Developmental Scales (GMDS), which evaluated 5 areas (locomotor, personal and social, hearing and speech, eye and hand coordination, and performance). All but one infant has normal growth and neurodevelopment in the first year of life; one infant developed cerebral palsy, epilepsy, and progressive hydrocephalus, requiring a ventriculoperitoneal shunt.

In contrast, a study prospectively evaluating 70 children between 1 month to 5 years of age with bacterial and viral meningitis in Fiji reported enteroviral meningitis as the most common (25%) cause of HL in 2 of 8 children at 6 months post-discharge [32].

A literature review of long-term outcomes after discharge of children <16 years of age with viral meningitis (most cases enteroviral meningitis) between January 1, 1990, and December 31, 2018, revealed a high rate of good clinical outcomes following viral meningitis [33].

Meningoencephalitis and SNHL emerge as common neurological symptoms of disseminated enteroviral infection in patients with congenital or acquired B-cell deficiency. McKinney RE et al. [25] evaluated the clinical information of 42 patients with CEMA. The most common pathogens were echoviruses in 37 cases, particularly type 11 in 11 cases. Hearing loss was defined in 16 of 42 patients, but the hearing results of the other 9 patients were not reported. Again, Tekin et al. [34] reported a 30-year-old patient with seropositive rheumatoid arthritis, using rituximab and prednisone, with disseminated enteroviral infection due to CV A9 and SNHL. Apart from severe congenital B cell deficiencies, patients may be exposed to disseminated enteroviral infections due to a profound B cell depletion caused by monoclonal anti-CD20 antibody therapy such as rituximab or obinutuzumab [34]. Sensorineural HL due to EVs is also common in children with congenital and acquired agammaglobulinemia [25].

In conclusion, diagnostic tests for EVs should be performed in children with SNHL because enteroviral infections may be the cause. There are conflicting studies regarding the necessity of routine hearing testing in patients with enteroviral meningitis. However, data are limited, and it seems reasonable to routinely perform audiological evaluation while awaiting more extensive studies. Sensorineural HL due to EVs is common in children with congenital and acquired agammaglobulinemia.

53.7 Differential Diagnosis

The differential diagnosis depends on clinical findings. In the respiratory tract and CNS infections, rashes, newborn and cardiac disease due to EVs, and other viral and bacterial infections should be considered in the differential diagnosis. Guillain-Barré syndrome may cause diagnostic problems in sporadic paralytic diseases. Paralysis is symmetrical, sensory changes are expected in Guillain-Barré syndrome, and albumino-cytological dissociation is typical in CSF.

53.8 Diagnosis and Laboratory Findings

Enteroviruses are detected by RT-PCR test and viral culture on various samples, including stool, rectal, throat, conjunctival, nasopharyngeal swab, tracheal aspirate, blood, urine, tissue biopsy, and CSF samples. RT-PCR testing is rapid and can detect strains difficult or impossible to grow in cell cultures.

In general, serology is not used to diagnose acute enteroviral disease except in cases where infection with a specific serotype is suspected. When using serology, acute and convalescent serum samples taken at least 4 weeks apart are required. The diagnosis of acute infection can be made retrospectively, with a fourfold or greater increase in antibody titers between acute and convalescent specimens. Serum IgM antibodies against EVs can usually be detected in the early stages of the disease, but a positive test is not serotype-specific [2, 11].

53.9 Treatment

There is no specific treatment for EV infections. Intravenous immunoglobulin (IVIG) has been used in life-threatening neonatal EV infections and EV-associated myocarditis [10]. Intravenous immunoglobulin, administered intravenously or intraventricularly, may also benefit CEM in immunocompromised patients. However, IVIG is not approved for intraventricular administration.

Licensed antiviral agents are not present for the treatment of severe enteroviral disease. Pleconaril was initially developed as an inhibitor of host cell receptor attachment and uncoating of picornaviruses, including rhinovirus and EV [35]. A double-blind, placebo-controlled study evaluated the pharmacokinetics and efficacy of pleconaril in infants younger than 1 year of age with meningitis due to EV infection. The trial did not show virological or clinical efficacy, possibly because of the study group's general self-limitation and benign clinical course of enteroviral meningitis [36].

Fluoxetine is the only Federal Drug Administration (FDA)-approved drug with significant activity against EV-D68. This anti-enteroviral activity demonstrated in vitro is independent of its known selective serotonin reuptake inhibitor (SSRI) activity [1]. Further clinical research is required to elucidate its action mechanism.

The development of vaccines against EVs is hampered by the abundance of different viruses, limited cross-reactivity, and difficulty in predicting serotype-specific epidemiological patterns. Effective vaccines have been developed against only PVs [1].

Enterovirus A71 (EV-A71) can cause serious illness in children under the age of 5, especially in infants. It can mainly cause HFMD, herpangina, and severe neurological problems. However, there are no effective antiviral agents for treating these infections. Inactivated whole and live attenuated virus vaccines are under development against EV-A71 [37].

53.10 Prevention

In addition to the standard precautions to isolate the patient with EV infections in the hospital, droplet precautions should also be taken for EV-D68 respiratory tract infections.

Especially hand hygiene and respiratory hygiene (especially for EV-D68) after changing diapers in infants are crucial in reducing the spread of EVs. In addition, proper disinfection of surfaces is required. Detection of HFMD in kindergartens and nurseries may necessitate temporary closure. Chlorination of drinking water and swimming pools can help prevent contamination. In patients with severe B-lymphocyte deficiency, maintenance administration of IVIG may prevent chronic EV infection of the CNS.

53.11 Conclusion

Enteroviruses have caused many outbreaks worldwide and are associated with various manifestations, from mild respiratory tract infections and rashes to life-threatening infections, such as carditis, meningitis, encephalitis, and neonatal sepsis. They usually cause self-limiting infections in children. However, infants, young children, and those with antibody deficiency are predisposed to develop serious enteroviral infections.

Enteroviruses are the most important causes of viral meningitis. Although it is controversial whether EVs cause SNHL, it is an etiological agent in patients with SNHL. Therefore, tests for EVs are recommended in children with SNHL. There are studies supporting and not supporting routine hearing testing in patients with enteroviral meningitis. In addition, SNHL is common in children with congenital and acquired agammaglobulinemia. However, routine hearing testing in children with enteroviral meningitis is more rational.

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COVID-19 in Children and Hearing Loss

54

Nazım Bozan, Cemal Cingi, and Francesco Maria Passali

54.1 Introduction

Beginning in late 2019, the newly emergent SARS-CoV-2 virus began spreading across the entire world, producing what became known as the COVID-19 Pandemic. The clinical features of infection with SARS-CoV-2 ranged in severity from a virtual absence of symptoms to pneumonia of high severity, resulting in acute respiratory distress and multi-organ failure. There were also many cases where the infection resembled a more familiar type of mild respiratory tract infection [1].

54.2 Infection in Children

Case series reported during the initial phase of the pandemic described most infections in children due to contact with an infected adult in the same household [2–8]. These reports may reflect the fact that infections in children were only diagnosed

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after lockdowns were implemented, in which schools were no longer open face-to-face, meaning that the only way the infection could be transmitted was via members of the same household. In other words, the risk of child-to-child transmission was still unknown, given the limitations of the data [1, 9].

Before viral variants with a higher rate of transmissibility had emerged, the rate of infection among children exposed to an infected adult was between 4% and 57%, when an observational methodology was employed [10–15]. A meta-analysis which combined data from 87 studies looking at transmissibility in households and involving 1.25 M contacts across several different countries calculated that the rate of infection in children was 18%, but from adult-to-adult, 30% [16]. The rate of transmitted infection has since increased as viral variants with a greater transmission potential have arisen [17].

There are also reports showing that outbreaks could be linked to healthcare delivery and in educational settings from teacher or other adult to child or between different pupils [18–22]. The risk of becoming infected rises among those who have not yet received vaccination [23].

54.3 Risk Factors for High Severity COVID-19

Despite some case series' identification of immunocompromise in paediatric patients as a risk factor for high severity COVID-19, the way that immunocompromise and high severity of disease are related has not yet been fully elucidated. When studies of small numbers of paediatric patients on immunosuppressants due to renal disease, inflammatory bowel disease or rheumatological disorders examined the pattern of COVID-19 infection, surprisingly the infection was only of mild severity [24–27]. However, a study examining 8 paediatric rheumatology patients ascertained that high disease activity and administration of steroids both predicted COVID-19 of high severity [28].

There is also an association between paediatric neoplasia and more severe COVID-19. A study based on a worldwide paediatric cancer registry noted that, among 1500 patients, COVID-19 was of high severity or caused a critical condition in 20%, while death occurred in 4%. These rates exceeded those in the general paediatric population [29]. High severity of COVID-19 in paediatric patients with malignancies is noted to occur where intensive chemotherapy was administered, the neutrophil or lymphocyte counts were low, another condition was co-morbid, or there was a second infection present [29, 30]. The risk of high severity of COVID-19 in children with blood cancers is no higher than that seen in neoplasia of other types [1, 31].

54.4 Clinical Presentation

54.4.1 Coryzal Symptoms Due to SARS-CoV-2

The management of coryzal symptoms due to SARS-CoV-2 in paediatric patients follows the same approach as with other causes of a cold, namely support and palliation of symptoms [32].

The approach taken in children with risk factors for highly severe COVID-19, such as immunocompromise, being reliant on medical technology for a separate medical disorder, or having several co-morbidities, differs from the standard management and is discussed elsewhere [32].

Paediatric patients who have an actual or potential diagnosis of COVID-19 require clinical assessment (which includes telephone or remote consultation, as well as face-to-face appointments) prior to granting permission for participation in strenuous physical activity (such as training practices, races, sports education, or impromptu sports matches) [32].

54.4.2 Age-Related Factors

Infection with SARS-CoV-2 occurs at every stage in childhood, with boys and girls both at the same risk [33].

The way COVID-19 presents in children varies widely, with some features in common with other paediatric diagnoses, such as pneumonia, bronchiolitis or croup, lung injury secondary to digital cigarette use [34], and gastroenteritis.

Data obtained from case surveillance in American children and teenagers reveal the following common symptoms [1, 33, 35]:

- Pyrexia.
- Coughing.
- Dyspnoea.
- Muscular aches and pains.
- Nasal discharge.
- Pharyngitis.
- Headache.
- Nausea and vomiting.
- Abdominodynia.
- Loose stools.
- Hyposmia and hypogeusia, which may become apparent in a child who is unable to speak as refusing food or an unwillingness to eat [36].

Different symptoms predominate at different ages in children [33]. In the initial stages of the pandemic, more than 60% of children and adolescents diagnosed with COVID-19 reported pyrexia, cough, or dyspnoea. It was more common for patients aged 10 years or over to complain of muscular aches and pains, pharyngitis or headache than for this to occur in children below the age of ten. The rate in the former is between 30% and 40%, whereas in the latter it is between 10% and 15%. Furthermore, hyposmia or anosmia occurs more commonly in older than younger paediatric patients (around 10% vs 1%) [33].

54.4.3 Respiratory Symptoms

Overall, respiratory symptoms occur with high frequency in COVID-19, but the rate of particular symptoms varies according to which variant of the virus causes the infection. At the beginning of the pandemic, the symptoms with the highest recorded rate in children and adolescents were pyrexia, chills, or coughing [33, 35, 37]. At the time when most infections were due to Delta or Omicron variants of SARS-CoV-2, the rate of certain symptoms was higher, namely blocked nose, headache, sneezing, pharyngitis, and paroxysmal coughing. Delta infections are more strongly associated with pharyngitis and hyposmia / anosmia than infections with Omicron [38–44].

54.4.4 Clinical Features

The majority of paediatric patients with acute COVID-19 resulting in mild symptoms recover in no more than a fortnight after the symptoms begin [6, 33, 45, 46]. In a minority of cases, however, there may be an abrupt worsening in clinical presentation which occurs around 7 days after the symptoms. In these patients, medical reassessment should be undertaken urgently. The best place to do the reassessment is a paediatric unit specialising in the treatment of paediatric COVID-19 [47].

A cohort study [46] undertaken prospectively, where an adult acting on behalf of the child utilised a mobile application to report symptoms, found that the average (median) period for which symptoms lasted was 6 days (interquartile range [IQR] 3 to 11 days). The symptoms were reported on a voluntary basis and involved 1734 children in whom SARS-CoV-2 was positively detected. A second cohort, with similar characteristics to the infected children, was used for comparison. These children had a negative test. In the latter group, the period of reporting symptoms lasted on average 3 days (IQR 2–7 days). Around 2% of both groups attended Accident and Emergency or were admitted to hospital. For children aged between 5 and 11 years, the median symptomatic period was 5 days, rather than the average 7 days in children aged between 12 and 17 years [1].

54.5 Complications

54.5.1 Multi-System Inflammatory Syndrome in Children (MIS-C)

Although it is an infrequent complication in paediatric COVID cases, severe MISC may occur. Clinically, this disorder may present in a way that mimics Kawasaki disease and shock syndromes in either Kawasaki disease or toxic states. There is persistent pyrexia, low arterial tension, gut-related symptoms, exanthem, and myocardial inflammation and the laboratory investigations indicate a raised inflammatory response. There may, however, be no respiratory symptoms [1].

54.6 Laboratory Investigations in SARS-CoV-2 Infection

The types of laboratory investigation needed in paediatric COVID cases are chosen according to the clinical presentation, namely whether the symptoms present are those expected in COVID-19, how long they last, when potential exposure occurred, surveillance requirements, and whether the test is to provide documentation of status as required for particular events (such as air travel). Local guidelines and the type of testing offered locally are also relevant to the choice [48].

The standard, officially accepted diagnostic test to confirm acute SARS-CoV-2 infection in children, whether they have symptoms or merely exposure to a known case, is polymerase chain reaction (PCR) amplification of viral DNA [48].

Antigen detection testing has lower sensitivity and may require a second test where the first appears negative, especially if other factors favour a diagnosis of SARS-CoV-2 infection, such as typical symptoms or a history of clear exposure. A meta-analysis has been published which pooled the data from studies of cross-sectional or cohort design on 8 types of antigen detection test used in paediatric patients for a rapid result. This meta-analysis showed that antigen testing had an overall sensitivity of 64% (pooled data from 17 studies, with 6287 patients; CI 57–71%). This sensitivity rose to 72% where symptoms were present (pooled data from 13 studies involving 3407 patients; CI 64–79%), but was only 56% if symptoms were absent (10 studies involving 2431 patients; CI 48–64%) [49]. For each of these groups the tests were 99% specific. One potential limitation on generalising these results is that in 16 of the 17 studies included in the meta-analysis, the test was undertaken by individuals specifically trained to perform the testing. In real world conditions, testing may not be performed in such an optimal way [1].

54.7 Deafness in Cases of COVID-19

54.7.1 Likely Pathogenesis

54.7.1.1 Brainstem Injury

The brainstem is the location of key centres involved in auditory and vestibular processing. Auditory signals pass via the auditory branch of the vestibulocochlear nerve to the cochlear nuclei, lateral lemniscus, inferior colliculus, and medial geniculate body prior to being passed on to the auditory processing areas of the cortex [50]. Vestibular signals also pass via the vestibular branch of CNVIII to the vestibular nuclei, which relay the signals to the thalamic centres. There are several nuclei within the thalamus which are involved in processing vestibular data. These centres process sensory input of varied kinds, including vestibular, proprioceptive, and visual input. These processed signals are then passed to the appropriate cortical regions [51]. There are also other key functions co-ordinated by the brainstem, such as the regulation of consciousness level and sleep, and control of vital functions. Sleep is regulated through the ascending reticular activating system, while the autonomic nuclei regulate vital functions. Since infection with SARS-CoV-2 can produce inflammation within the brainstem, any of its usual functions may be disturbed. This accounts for how COVID-19 may cause sensory deficits (including dysequilibrium and hearing loss), motor problems, cranial neuropathies, obtundation of consciousness, autonomic dysregulation, and respiratory failure [52, 53].

The Role of Inflammation

Inflammation is a key part of immune functioning and is seen in response to pathogenic organisms (viral, bacterial, fungal, or parasitic), in addition to occurring in autoimmunity and many chronic disorders [54]. High levels of generated reactive oxygen species (ROS) in inflammation cause oxidative stress, which may damage DNA, proteins, or lipids within the cell. In the absence of inflammation, cells normally produce relatively low levels of ROS, which assist in preserving cellular homeostasis and ensuring physiological function [55]. High levels of ROS, in addition to specific chemical triggers (both naturally occurring and artificial), may initiate an inflammatory response. During inflammation, pro-inflammatory cytokines are manufactured and released, including interleukins 6 and 1β, as well as tumour necrosis factor–alpha (TNF-α). Many pathophysiological mechanisms depend on the inflammatory response and generation of ROS, which are closely intertwined processes. Accordingly, many diseases have a pathogenesis involving both ROS generation and inflammation, including COVID-19 [56]. It has previously been reported that both acute and chronic inflammation, wherein ROS and pro-inflammatory cytokines are generated, play roles in auditory loss of sensorineural type and in producing tinnitus [57, 58]. Inflammation may also directly injure the inner ear in cases of SARS-CoV-2 infection [59]. Some cases of COVID-19 also result in the so-called “cytokine storm”, a massive mobilisation of the immune system on the systemic level. As a result of such a cytokine storm, the microglia may be stimulated and remain active even following resolution of the primary infection.

This inflammatory response within the nervous system can then cause injury to gliocytes related to the auditory system [52, 60].

54.7.1.2 Dissemination Via the Bloodstream

It has been demonstrated experimentally that SARS-CoV-2 is capable of attachment to haemoglobin and can enter the cytoplasm of red blood cells. This means the virus can be transported around the entire body, coming into contact with the wide variety of tissues which express the ACE-II receptor, which is the usual means of viral entry into cells. There is extensive expression of ACE-II in the central nervous system, including the brainstem and auditory system [61]. Genetic expression of ACE-II has been demonstrated in the murine cochlea [62]. However, so far it has not been definitely shown that SARS-CoV-2 can enter the cells of the inner ear in humans. It has, however, been proven that dissemination of the virus occurs due to the widespread nature of ACE-II receptors within the vascular system—on the endothelium of arteries and veins and in leiomyocytes of the arterial wall [63]. It is possible that SARS-CoV-2 affects the integrity of the barrier between the labyrinth and blood stream and enters the inner ear within macrophages [64]. Red blood cells infected with SARS-CoV-2 have a lower oxygen-carrying capacity and this may produce hypoxic injury to the delicate inner ear mechanism [65]. This hypoxia has been recorded in individuals infected with the virus, even where they are otherwise asymptomatic. This asymptomatic hypoxia, as revealed by pulse oximetry, has been termed “silent” or “apathetic” hypoxia [52, 66].

54.7.1.3 Toxicity to the Ear Secondary to Antiviral Medications

The agents, remdesivir, ribavirin, and the synthetic analogues of quinine (namely chloroquinine and hydroxychloroquinine), have previously been administered to patients with malaria or autoimmune disorders, including systemic lupus erythematosus. These medications are both anti-viral and anti-inflammatory [67]. A recently updated multi-centre randomised controlled trial involving 405 centres and 30 different countries and sponsored by the WHO Solidarity Trial Consortium found that there was no benefit from using these agents in cases of SARS-CoV-2 infection. They did not reduce the death rate, failed to prevent the need for mechanical ventilation, and did not shorten hospital admissions [68]. Furthermore, the synthetic quinine analogues cause a number of adverse effects, including ear toxicity, damage to the retina, neuromuscular damage, and injury to the myocardium. These side effects may manifest as ototoxicity, which may be temporary or irreversible, and result in sensorineural deafness and tinnitus. This occurs whether these agents are used briefly or for longer periods. Chloroquine, in particular, causes permanent ototoxicity [69]. The mechanisms through which ototoxicity occurs may include injury to the inner ear and nervous tissues, including damage to the outer hair cells, spiral cell ganglia, the nerves, atrophy of the stria vascularis, and pathological alterations to the central portions of the auditory system [67]. Furthermore, the level of glutamate in the extracellular space rises due to chloroquine, which stimulates excessive generation of ROS. These reactive oxygen species are themselves acknowledged to cause neurotoxicity affecting the inner ear’s gliocytes [52, 70].

54.7.2 Auditory Impairment

Sudden sensorineural deafness is irreversible and occurs when either the inner ear or auditory nerve sustains injury [71]. It involves a loss of perception of at least 30 dB in three consecutive frequencies and develops in under 3 days [72]. There have been several hypotheses put forward to account for how sudden sensorineural deafness occurs. One hypothesis is that the virus invades the cochlear nerve or the fluid-filled spaces. Other possibilities are that the virus undergoes latency in the inner ear and subsequently becomes reactivated, or that immunoglobulins targeting the virus damage the surrounding tissues [73]. There has not yet been any detailed research published indicating the extent to which SARS-CoV-2 can invade the auditory system, but if this occurs, it may be analogous to the way other viral illnesses damage the auditory system [74, 75].

As well as the possibility that sudden sensorineural deafness is directly caused by SARS-CoV-2, it may also be the case that pharmacotherapy is also ototoxic. This concern applies in particular to the synthetic analogues of quinine, which have previously been shown to cause ototoxicity [76]. The quinine anologues have a long history of use in managing malaria and disorders involving chronic inflammation [74]. It has been reported in the literature that sudden sensorineural deafness, tinnitus, disturbed gait, and dizziness occurred in patients with COVID-19 who were administered hydroxychloroquine [69]. Note that the dosages of quinine analogues employed in treating COVID-19 are considerably above those recommended for malaria and disorders involving chronic inflammation [77].

SARS-CoV-2 may cause sudden sensorineural deafness by directly invading cells of the nervous system. It gains entry into the cells via the ACE-II receptor [78]. Other viral infections act in a similar way. The auditory processing areas of the temporal lobe may be invaded in this manner. The auditory cortex is injured through the action of cytokines, which are released when the virus is detected. The cochlear nerve itself may be invaded, provoking neural inflammation. The response to invasion of the cochleal soft tissues by the virus is again inflammation [79]. Currently, there appears to be evidence that SARS-CoV-2 invades the inner ear, which provides a mechanism for the virus to cause sudden sensorineural deafness. It was shown by Mustafa et al. [80] that the cochleal hair cells were injured in patients with SARS-CoV-2 infection, even where no symptoms appeared. The damage to the cochlea was quantified by looking at the amplitude of transitory-evoked otoacoustic emissions (TEOAE). The findings from the study quoted link sudden sensorineural deafness to COVID-19, even where no symptoms exist to suggest this has occurred. Further data to support the thesis that it is the virus which causes the sudden sensorineural deafness, rather than a drug effect, come from a study by Karimi-Galougah et al., in which cases of sudden sensorineural deafness occurred in patients who had a diagnosis of COVID-19, but did not receive any pharmacotherapy [75, 81].

At present, there is an annual increase of 6000 in the cases of sudden sensorineural deafness registered in the USA [82]. These cases are by no means entirely due to COVID-19 nor its treatment, as there are multiple other recognised aetiologies. A study conducted by Chari et al. just before the pandemic struck ascertained a

diagnostic rate for sudden sensorineural deafness of 1.77% in 4013 patients screened for the disorder. This represented 71 cases in a two and a half month period in mid-2019. When the exercise was repeated during the pandemic in 2020, some 13 diagnoses were confirmed out of 681 patients in whom a diagnosis was suspected, a rate of 1.91%. In this second series, none of the confirmed diagnoses were in individuals who tested positively for SARS-CoV-2 infection [83]. The most likely theory states that sudden sensorineural deafness can occur from many interacting factors, and the extent to which SARS-CoV-2 infection is an additional risk factor remains unclear [75].

Jafari et al. undertook a meta-analysis in which data from four studies were pooled [52, 84–87]. This meta-analysis found that deafness occurred in 3.10% of patients with a confirmed diagnosis of COVID-19. This result is, however, hard to interpret given the heterogeneous nature of the studies included and the fact that some studies had low methodological rigour (such as those lacking a control arm) [88]. These data were also not specific about the degree of auditory impairment (mild, moderate, or severe), the type of deficit (sensorineural, conductive, or mixed), or the likely aetiogenesis. For studies where data rely on patients' own perception of hearing problems, very mild or mild auditory impairment is likely to be underreported, particularly where COVID-19 was of high severity. The discrepancy between studies as a result of methodological differences is analogous to that observed in studies of olfactory dysfunction in cases of SARS-CoV-2 infections, where the rate of occurrence judged by patient report was 36.64%, a small fraction of the rate estimated when extrapolating from studies using objective testing methods (i.e. 86.6%) [52, 89].

54.8 Vaccination

There is no vaccination available which effectively immunises against the common cold generally, although vaccinations are available for some viruses that cause coryzal illness [32].

It is currently advised that all patients above the age of 6 months should be routinely vaccinated against influenza, to prevent the disease and potential complications [32].

The guidelines also suggest that any patient above the age of 5 years may be offered vaccination against SARS-CoV-2 [90].

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Lymphocytic Choriomeningitis Virus (LCMV) Infection in Children and Hearing Loss

55

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55.1 Introduction

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus with an envelope which is within the Arenaviridae viral family. In developed nations, it may infrequently be responsible for infection of the central nervous system [1].

LCMV is found in the saliva, urine, seminal fluid, milk and faeces of rodents. The species which harbour LCMV and can shed virus in this way include rats, mice and hamsters. There is an elevated risk of infection by LCMV in children growing up in poverty, where they may eat food contaminated by infected animal urine, may get contaminated matter into cuts or injuries, or may breathe in viral particles [2].

The first description of LCMV being transmitted vertically via the placenta in an American child was in 1992, although the first report of vertically transmitted LCMV is from England and dates from four decades earlier [2]. Transplacental infection mostly occurs while the virus is detectable within the mother's bloodstream [2]. The peak incidence of infections is over the winter period, as rodents tend to invade patients' homes at that time in search of food and shelter [1].

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55.2 Definition

LCMV (Lymphocytic choriomeningitis virus) is a single-stranded RNA virus. It is within the Arenaviridae grouping. This viral family also includes the Lassa, Argentine, Bolivian and Venezuelan haemorrhagic fever viruses. The reservoir for infection is rodents. In mice, infection with LCMV does not result in any symptoms, although hamsters may sometimes exhibit signs of the infection. The virus can be transmitted to a human host when virally contaminated faecal particles are inhaled, ingested, or brought into close proximity. LCMV causes major teratogenic effects on a foetus and is usually a self-limiting infection producing pyrexia and consisting of two phases. Recently, LCMV has also been recognised as a pathogen which may cause congenital infection [3]. The risk of contracting LCMV is raised in people who live in proximity to infected animals or whose occupation exposes them to contact with rodents. Thus, employees who handle pet rodents or laboratory animals have potential infective exposure. There have also been cases noted in which infection has occurred when an organ was transplanted [4–7].

55.3 Pathophysiology

Once the virus invades the body, whether via the respiratory or gastrointestinal systems or by crossing the skin or a mucous membrane, it enters the bloodstream. If an infected organ is transplanted, this also results in viraemia. The pathogen can then take hold outside the central nervous system and produces a pyrexial episode with no clear focus. Some days later, a second episode of viraemia occurs and LCMV can then commonly invade the central nervous system. When this occurs, the characteristic features of meningitis or meningoencephalitis are observable [4].

The clinical features are considered to be produced by the host response to LCMV. The natural killer cells and cytotoxic T-lymphocytes synthesise and secrete interferon and further inflammatory signalling molecules in response to the virus [8]. Other than vertical transmission, or in the unusual case of organ transplantation, LCMV is not transmitted from one human host to another. Congenitally acquired LCMV is generally of considerably greater severity than when the infection is acquired at a later stage. The features may closely resemble those of toxoplasmosis or cytomegalovirus infection, when transmitted congenitally. As in cases acquired after birth, congenital forms of the disease are greatly shaped by the host response to infection. The T- and B-lymphocytic response is the means by which the host tissues are damaged. It is probable that LCMV transmitted transplacentally has a tropism for nervous tissues, becoming focused in the area of the growing central nervous system and eye [4, 9].

55.3.1 Acquired Infection

In acquired infections, the clinical presentation is non-specific. Pyrexia reaching 39–40 °C is commonly noted. There may also be a degree of bradycardia. The lymph nodes are diffusely enlarged and an exanthem of maculopapular type may also occur. Pharyngitis may be noted, but pharyngeal exudates are not seen. Nuchal rigidity is a frequent symptom where the virus has invaded the central nervous system [4].

There are also a number of other, less frequently encountered, clinical presenting features, such as joint inflammation affecting the metacarpophalangeal and proximal interphalangeal joints, enlargement of the liver and spleen, papilloedema, hearing loss, or paralysis. There may also be features indicating orchitis affecting a single testis, myocardial inflammation of viral type, pneumonitis, psychosis, transverse myelitis, Guillain-Barré syndrome, hydrocephalus (which may be temporary or persistent) and encephalitis [4].

55.3.2 Congenital Infection

Congenitally infected infants are usually of the expected size for their gestational age and are not born prematurely. There are abnormalities of the eye in around 88–93% of cases. These abnormalities include chorioretinopathy, chorioretinitis, cicatrisation, atrophic areas, nystagmus, esotropia, unusually small eyes, cataracts and inflammation of the vitreous humour [10].

Macrocephaly is present in around 34–43% of cases [10]. It was reported that 90% of neonates who underwent imaging had features of either hydrocephalus or intracranial periventricular calcifications. Microcephaly occurred in between 13 and 38% of cases, the condition generally resulting from either dysplasia or atrophy in the developing cortex [10].

Deafness is present in around 7% of infected neonates and generally affects both ears. It is of sensorineural type and it is either severe or total [11].

The fact that LCMV infections principally affect organ systems beyond the central nervous system (except for infrequent involvement of the skin, manifested as a rash, enlargement of the liver and spleen or myocarditis) acts as a valuable diagnostic clue [3, 4].

55.4 Laboratory Investigations

55.4.1 Serological Testing

Serological testing using an immunofluorescent method to detect specifc IgM and IgG antibodies is marketed and is the best technique available [4].

The US Centres for Disease Control and Preventions (CDC) utilise an ELISA (enzyme-linked immunosorbent assay) for detection of immunoglobulins M and G in cerebrospinal fluid. There is a complement fixation assay available, however it suffers from low sensitivity and is not recommended for diagnosis of LCMV infection, whether congenital or acquired [4].

At an early stage in LCMV infection, the virus can be detected in blood samples. As the disease progresses, the virus becomes detectable in cerebrospinal fluid or, in unusual cases, from a urine sample or from a swab of the nasopharynx, if cell culture is used or there is direct injection into the brains of very young laboratory mice [4].

55.4.2 Analysis of Cerebrospinal Fluid (CSF)

CSF may contain abnormally high amounts of protein. In 25% of cases, the glucose concentration is below normal, but in the remaining 75% the glucose level is normal. There is generally an increased white cell count, with elevated lymphocytes. The level ranges from below 30 to above 8000. There is one case reported in the literature in which eosinophilic meningitis occurred [4].

55.4.3 PCR Amplification of Viral DNA

At present, the use of PCR to detect LCMV is confined to research settings, although a method is under development for routine clinical use [12].

55.5 Auditory Impairment

It has already been established by research that fatality is a rare outcome in cases where aseptic meningitis or encephalitis occur as a result of LCMV infection. In humans, LCMV does not appear to produce persistent infections. Following acute infection, there is complete elimination of the pathogen. Nonetheless, in common with other pathogens that invade the central nervous system, especially if encephalitis results, transient or irreversible neurological injury may occur. There are reported cases of sensorineural hearing loss and chronic arthritis following LCMV infections [13].

If a pregnant woman becomes infected with LCMV, there is a risk of vertical transmission. Foetal infection within the initial trimester of pregnancy may have a fatal outcome for the foetus, whereas infections in the middle and final trimester may result in congenital anomalies. These anomalies may be grave and irreversible, such as damage to the visual system, learning disability and hydrocephalus. In some such cases, the mother may give a history of a flu-like episode whilst she was pregnant, but this is often absent from the history [13]. The risk of mortality in the

mother is no higher than 1%, thus the vast majority of patients survive the episode [13].

Lymphocytic choriomeningitis virus (LCMV) is a single-stranded RNA virus with an envelope which is within the *Arenaviridae* viral family. It is increasingly recognised as a cause of congenital abnormalities [14]. The primary hosts for LCMV are rodents, including the house mouse, and these animals act as the infective reservoir [15]. Transmission of the virus to a human host is generally via the mouse's urine, faeces or saliva. Since rodents tend to invade human dwellings at the coldest time of year, winter is the peak period for human infections to occur [3]. Although human-to-human transmission in normal circumstances is very rare, in the setting of organ transplantation, this route of transmission becomes possible [15, 16].

In adult patients who have no immunosuppression, infection with LCMV generally either produces no symptoms or those of an upper respiratory tract infection, namely pyrexia, headache, nausea and vomiting. Aseptic meningitis or meningoencephalitis are infrequent complications. In pregnant women, the highest risk is for spontaneous abortion to occur. Infections during pregnancy, particularly in the initial and middle trimester, have the potential to cause birth defects, especially microcephaly, hydrocephalus, ventriculomegaly, pachygyria, cerebellar hypoplasia, chorioretinitis, periventricular calcification and deafness [3, 15, 17]. Whereas cytomegalovirus (CMV) or rubella infections in the foetus are strongly associated with deafness, visual impairment and microcephaly are considerably more typical of foetal LCMV than deafness. Furthermore, unlike CMV and rubella, LCMV does not result in enlargement of the liver and spleen, which helps to distinguish between the likely causes in congenital deafness [14, 16].

For confirmation of the diagnosis of congenital LCMV, ELISA for detection of immunoglobulins G and M is a suitable laboratory investigation. Auditory impairment in cases of congenital LCMV is somewhat unusual, and the ears may not be equally affected. The hearing loss is of sensorineural type and is severe or profound [14, 17].

55.6 Clinical Management

Ribavirin is an agent sometimes used to treat LCMV infections affecting adult patients. It inhibits RNA synthesis and the addition of the 5′ cap to the RNA string by the virus. Unfortunately, there are no trials in patients which demonstrate definite benefit from use of the agent and there are known adverse effects of ribavirin, especially haemolytic anaemia. Since this medication has been shown to be teratogenic in multiple animal species, it is not suitable for administration in pregnancy [15]. Another agent which may be potentially beneficial in LCMV infections is favipiravir. Since this agent inhibits RNA-dependent RNA polymerase, it may treat a large number of different viruses of RNA types. However, currently, action against LCMV has only been demonstrable in vitro [3, 16].

In suitable candidates, auditory impairment should be compensated using hearing aids or other assistive technologies, according to the child's needs. There may be limited success in remedying the effects of severe or profound auditory impairment of sensorineural type in paediatric patients with congenital LCMV, in whom injury to the eighth cranial nerve explains the loss. This group of patients invariably also have a severe type of visual loss, therefore treatment of hearing loss should at least be tried, as any benefit (even if small) may improve quality of life [16].

There are no specific therapeutic modalities currently available for LCMV infection. The evidence on ribavirin so far indicates that this agent does exert an antiviral action on LCMV in vitro, but this has not yet been satisfactorily established in vivo. Although the evidence base is incomplete, the recommendation in organ transplant recipients found to have acquired LCMV is administration of ribavirin and a reduction in the degree of immunosuppressant treatment [6, 18].

In the future, treatment options may include favipiravir (which is already known to prevent viral reproduction) and agents which inhibit the synthesis of pyrimidines. These latter are still at the developmental stage [3, 19].

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Human Immunodeficiency Virus Infection in Children and Hearing Loss

56

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56.1 Introduction

A wide range of clinical manifestations is associated with human immunodeficiency virus (HIV) infection [1]. Acquired immunodeficiency syndrome (AIDS) refers to an advanced stage of HIV infection based on the criteria of the Centers for Disease Control and Prevention (CDC) for children, adolescents, and adults [2]. There have been significant improvements in the life expectancy of people with HIV infection due to the introduction of antiretroviral therapy (ART) [1, 2].

Neurocognitive functions and learning can be affected by HIV-related conditions. Human immunodeficiency virus-associated neurocognitive disorders affect

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executive function, information processing, motor skills, working memory, language, and hearing [3, 4]. In literature, hearing disorders are prevalent in adults and children with HIV infection, and changes in the auditory system may be seen [5–7]. Several factors have been associated with this population's hearing loss (HL), including high viral loads, viruses that affect the auditory system, ART, and opportunistic diseases. However, the evidence has not been conclusive, as HL may be due to a combination of factors [8].

56.2 Etiology

Human immunodeficiency virus types 1 and 2 (HIV-1, HIV-2) are members of the *Lentivirus* genus of the Retroviridae family, which includes cytopathic viruses causing diverse diseases in several animal species [9, 10]. Retroviruses form a family of single-stranded ribonucleic acid (RNA) viruses. The mature HIV-1 virion consists of a core rounded by a lipid bilayer envelope. The HIV-1 genome contains three major (GAG, POL, ENV) regions. The HIV-2 has structural and genomic similarities to HIV-1 and a comparable life cycle to HIV-1; however, HIV-2 is unlike HIV-1 in its accessory genes [9, 10]. Three distinct genetic groups of HIV are M (major), O (outlier), and N (new) groups. Group M viruses are the most extensive worldwide and contain 8 genetic subtypes, A through K, each of which has a distinct geographic distribution [1, 10].

56.3 Epidemiology and Transmission

There were 37.7 million HIV-infected people, including 1.5 million newly infected, in 2020 [11]. Total AIDS-associated deaths were 680.000 in 2020. Moreover, there were 1.7 million HIV-infected children (<15 years) and 99,000 AIDS-associated child deaths in 2020. Every day, 4000 new HIV-infected cases occur in adults and children; of these cases, 60% are in sub-Saharan Africa, and 10% are among children [11].

Blood, semen, cervicovaginal secretions, and human milk are the primary body fluids in transmitting HIV infection [1]. Globally, the vast majority of HIV-infected children have acquired the virus via vertical transmission [9]. Maternal viral load at delivery, preterm delivery (<34-week gestation), and maternal antenatal low CD4+ T lymphocyte count are the leading risk factors for vertical transmission [6]. Mother-to-child HIV-1 transmission can occur during pregnancy, delivery, or in the postpartum period via breastfeeding. Therefore, the epidemiology of pediatric HIV infection is inseparably related to preventing mother-to-child transmission [10, 12]. The other known types of HIV transmission include vaginal, anal, or orogenital sexual contact, percutaneous blood exposure, mucous membrane exposure to contaminated blood or other body fluids, and transfusion with contaminated blood products [1].

A number of similarities exist between HIV-1 and HIV-2, including their basic gene arrangement, modes of transmission, intracellular replication pathways, and

clinical consequences: both result in AIDS. The HIV-2, however, is less transmissible and less likely to progress to AIDS. Although HIV-2 progresses to AIDS at higher CD4+ T lymphocyte counts, both HIV infections display similar pathological processes when clinical progression occurs. In HIV-2, plasma viral loads and immune activation levels are consistently lower. There may be a "protective" effect in HIV-2, such as a more effective immune response, that explains the better prognosis in HIV-2 [1, 13]. Adolescents (13–24 years of age) compose a significantly growing population of newly HIV-infected people [9].

56.4 Etiopathogenesis and Immunity

Dendritic cells, macrophages, and CD4+ T lymphocytes are the main targets of HIV. Human immunodeficiency virus attaches to one of a group of co-receptors for fusion and enters its target cell. Various co-receptors mediate virus influx into these cells. The two primary chemokine co-receptors for HIV-1 are CCR5 and CXCR4. Human immunodeficiency virus is integrated indiscriminately into the host cell chromosomes through the action of another virally encoded enzyme, integrase, thus establishing HIV provirus. The HIV provirus may proceed transcriptionally inactive (latent) or demonstrate various gene expressions for efficient virus production. The protease encoded by the HIV then catalyzes the cleavage of the gag-pol precursor to produce the mature virion. These infected cells lead to the spread of HIV. The migration of CD4+ T lymphocytes, dendritic cells, and macrophages to regional lymph nodes is followed by the dissemination of the cells to organs via the bloodstream. This dissemination results in an increase in HIV replication and the induction of inflammatory cytokines and chemokines. When HIV replication reaches a threshold, viremia causes acute HIV infection, formerly known as acute retroviral syndrome [9, 14].

Innate and adaptive immune responses play an essential role in decreasing the HIV load level. However, abnormalities in the function of all immune system branches have been described during HIV infection. Different mechanisms for decreasing CD4+ lymphocytes have been proposed, such as HIV-mediated single-cell killing, syncytia formation, natural killer cells, antibody-dependent cellular cytotoxicity, superantigen-mediated T cell activation, autoimmunity, and apoptosis. With their long lifespan, monocytes and macrophages infected with HIV express their role as reservoirs and effectors of organ tissue damage [14–16].

Furthermore, CD8+ T lymphocytes play a critical role in HIV infection. Several ligands are released by CD8+ T lymphocytes that inhibit HIV replication by interfering with the attachment of the virus to the co-receptor CCR5. Viral structural and regulatory proteins are targeted by HIV-specific cytotoxic T lymphocytes, then neutralizing antibodies increase in the infection. Human immunodeficiency virus infection affects the immune system and destroys CD4+ lymphocytes despite early cell-mediated and humoral immune responses. Persistent infection is eventually established by HIV [15–17].

56.5 Clinical Manifestations

Human immunodeficiency virus infection has distinct phases: viral transmission, acute seroconversion, acute retroviral syndrome, recovery and seroconversion, asymptomatic chronic infection, and symptomatic HIV infection or AIDS. Human immunodeficiency virus causes severe immunodeficiency in humans by attacking CD4+ T lymphocytes and ultimately causing their death. Malignancies and opportunistic infections can become more difficult to fight once the CD4+ T lymphocyte count falls too low. Acquired immunodeficiency syndrome is diagnosed in patients with HIV infection who have a CD4+ T lymphocyte count of less than 200/mm^3 or an AIDS-defining illness. Most HIV-positive patients will develop AIDS within 10 years if left untreated [18]. The asymptomatic phase of HIV infection may last for years, suggesting a persistent conflagration between the virus and the host's immune response [19].

Clinical presentations of HIV infection in infants and children are often nonspecific, like in adults. Several clinical findings may be observed in untreated pediatric HIV patients, including failure to thrive, generalized lymphadenopathy, hepatomegaly, splenomegaly, persistent oral and diaper candidiasis, recurrent diarrhea, parotitis, hepatitis, central nervous system (CNS) disease, lymphoid interstitial pneumonitis, recurrent invasive bacterial infections, and opportunistic infections (OIs) [1]. Within the first few weeks of infection, 50% to 90% of adolescents and adults develop acute symptomatic HIV infection. Neurologic conditions, *Candida* esophagitis, and mucocutaneous ulcerations are less commonly seen clinical manifestations nonspecific to HIV infection [13, 17].

Human immunodeficiency virus-infected individuals, even with high CD4+ T lymphocyte counts, are at a higher risk of developing both common and OIs than the general population. However, in HIV patients with CD4+ T lymphocyte counts of less than 200/mm^3, the risk of developing OIs and subsequent death remains the highest. Children under 6 years of age have a CD4+ T lymphocyte count that naturally declines, so the count criteria putting them at risk for OIs are only correct above that age group [20]. These individuals are prone to a wide variety of bacterial, viral, fungal, and protozoal infections, which include *Toxoplasma gondii* (CD4+ count <50 cells/mm^3), *Pneumocystis jirovecii* (CD4+ count <200 cells/mm^3), *Cryptococcus neoformans* (CD4+ count <100 cells/mm^3), *Mycobacterium avium* (CD4+ count <50 cells/mm^3), *Mycobacterium tuberculosis* (all CD4+ counts), cytomegalovirus (CMV, CD4+ count <50 cells/mm^3), herpes simplex viruses (CD4+ count <100 cells/mm^3), and *Histoplasma capsulatum* (CD4+ count <150 cells/mm^3) [21].

Acquired immunodeficiency syndrome is the advanced stage of HIV infection based on specific criteria, with OIs and malignant neoplasms [1, 17]. It is relatively uncommon for children with HIV infection to develop malignant neoplasms; however, leiomyosarcomas and non-Hodgkin B-cell lymphomas of the Burkitt type, including those of the CNS, occur more frequently than in immunocompetent children [1].

The immune reconstitution inflammatory syndrome (IRIS) occurs in HIV-infected patients severely immunosuppressed shortly after receiving ART. The onset of local and/or systemic symptoms is secondary to an inflammatory response due to the restoration of cell-mediated immunity [1].

56.6 Diagnosis

Several diagnostic tests are available for HIV infection, including serologic tests such as serum HIV antibodies and p24 antigens and nucleic acid amplification tests such as plasma HIV deoxyribonucleic acid (DNA) or RNA assays [1]. A two-step process involves detecting HIV, consisting of a highly sensitive screening test followed by a highly specific supplementary or confirmatory test [22]. In adults and older children, serum HIV antibody tests are commonly used to detect HIV infection. The CDC HIV laboratory testing algorithm recommends an initial FDA-approved HIV-1/HIV-2 antigen/antibody combination immunoassay (fourth-generation assay). If an antigen/antibody immunoassay result indicates a positive result, the specimen should be tested with an HIV-1/HIV-2 antibody differentiation immunoassay approved by the FDA [1, 23, 24].

Maternal antibodies may persist until 18 months of age, so antibody tests are unreliable for diagnosing children younger than 18 months. However, these tests are used in this age group for screening if a child has been exposed to HIV [8, 22–24]. The most reliable method for diagnosing HIV infection in infants and children younger than 18 months is virological. The HIV infection in infants younger than 12 months is diagnosed using plasma HIV DNA or RNA assays. Confirmatory testing with a secondary virological test should be done in infants and children with a positive result. The HIV RNA qualitative assay also provides results as a predictor of disease progression and is used for monitoring changes in viral load during treatment with ART [1, 24].

56.7 Treatment

All children with HIV infection should be treated according to the recommendations of the Antiretroviral Therapy and Medical Management of Children Living with HIV Panel [25]. Several studies have demonstrated that early ART initiation within the first year of life is associated with a reduction in the size of viral reservoirs, preserves immune function, prevents clinical disease progression, and shows immune growth and neurodevelopmental benefits [26, 27].

Antiretroviral (ARV) drugs were historically used in the newborn period as a form of prophylaxis since their primary purpose was to prevent the acquisition of HIV. Antiretroviral prophylaxis includes the administration of a single agent, usually zidovudine (ZDV), as well as combinations of two or three ARV drugs as treatment if the neonates are at an increased risk for transmission when their mothers do not receive ART or mothers start late ART in pregnancy, or antepartum treatment

does not result in viral suppression defined as a confirmed HIV RNA (level < 50 copies/mm^3) [25–27].

When determining the initial ARV regimens for children with HIV infection, clinicians evaluate the pharmacokinetics, safety, and efficacy data for drugs available in formulations appropriate for the child's age and weight at the beginning of treatment. New ARV drug options may become available as children grow and learn to swallow pills and as new drugs, drug formulations, and data become feasible [1, 25]. Consultation with an expert in pediatric HIV infection is recommended in caring for HIV-infected infants, children, and adolescents. Current treatment recommendations for HIV-infected infants and children (https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new-guidelines) and adolescents (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescentarv/whats-new-guidelines) are available online (https://www.ncbi.nlm.nih.gov/books/NBK586303/) [1, 25].

56.8 Prognosis

Early diagnosis of HIV infection and early initiation of ART improve the outcomes of infants and children [25, 28, 29]. Some studies show that perinatally HIV-infected infants have a higher risk of mortality and disease progression than older children [27, 30, 31]. Due to the limitations of available drugs, the long-term toxicity of ART, adherence problems, the risk of resistance to ARV drugs, and limited resources, treatment may be problematic in HIV-infected infants and children.

An analysis of data from untreated HIV-infected children in the United States of America (USA) and Europe conducted by the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) indicated that a 1-year-old child with high CD4+ T lymphocyte counts had a six-fold higher death risk as compared to a child aged 5 with high CD4+ T lymphocyte counts [32]. Compared to HPPMCS, the Cross Continents Collaboration for Kids study of untreated HIV-infected African children showed a much lower predictive value of CD4+ T lymphocyte counts in young children after infancy and much higher mortality rates [33]. There is evidence that the timing of HIV transmission from mother to child plays a significant role in the progression of the disease. Some studies show that HIV transmission from the mother within the first 1–2 months of life has a higher mortality rate at 12 months compared to a child infected with HIV later in life [34, 35].

Due to the HIV-mediated depletion of CD4+ T lymphocytes, HIV infection causes progressive immunosuppression and also leads patients to become susceptible to OIs [36]. The progression of disease and immunosuppression are associated with increased susceptibility to OIs, the leading cause of morbidity and mortality in HIV-infected individuals. In HIV-infected children, pneumonia and bacteremia are the most common OIs, followed by herpes zoster, disseminated *M. avium* complex, and invasive candidal infections [37].

The most common long-term morbidities in HIV-infected children and young adults treated are mental health concerns, dyslipidemia, cardiovascular complications, insulin resistance, diabetes mellitus, decreased bone mineral density, and

renal diseases. It is recommended to evaluate HIV-infected patients for possible risk factors, such as atherosclerotic heart disease and diabetes, prior OIs, environmental exposures, and therapeutic and illicit drug use [38–42].

In addition, HIV-positive adolescents adhere to treatment less likely than adults, which results in a lower rate of viral suppression and a lower rate of death decline [43].

56.9 Human Immunodeficiency Virus Infection in Children and Hearing Loss

Hearing disorders associated with HL, tinnitus, and dizziness seem more prevalent in HIV-infected adults and children [44–46]. Studies demonstrated that 24% [47] of children and 49% [48] of adults with HIV infection had clinically significant HL. In a recent review of 17 studies, approximately 33% of HIV-infected children had some form of HL [49]. Wang et al. [50] reviewed 88 studies and reported that the pooled prevalence of HL was 13.1% in HIV-infected children aged 0–18 years. Ensink et al. [51] reported similar results in their systematic review of 21 studies on HL in HIV-infected children and adults. Possibly, this variation can be attributed to methodological differences in assessment measures, assessment environments, and cut-off criteria for determining normal hearing [48]. The HIV-infected individuals have a two-fold higher prevalence of sensorineural HL (SNHL) than uninfected controls [52].

Currently, limited data exist regarding the underlying molecular mechanisms involved in HIV-induced HL [53]. Compared to bilateral HL, unilateral HL is more prevalent in HIV-infected children and may be associated with possible other factors related to conductive HL, such as passive smoking, allergies, attendance, being the third or later sibling, and poor nutrition [50, 54].

The HIV infection may affect the hearing system in various ways [54, 55]. Detectable HL may also result from HIV infection of relevant structures such as the cochlea or CNS. In recent studies, HIV has been shown to infect the cochlea [56, 57]. Studies have postulated that HIV infection may lead to synaptic loss, followed by cochlear damage and CNS disease, as the virus induces local inflammation and degeneration of auditory structures [56–59]. As the central nervous system may act as a reservoir for HIV, the central auditory pathway may also be affected by HIV (AIDS dementia), resulting in deficits in central auditory processing. A recent study showed that despite ART, neurocognitive deficits are seen in HIV-infected individuals [60].

Furthermore, HIV infection leads to profound changes in the composition of the gut microbiome, resulting in gut dysbiosis. Highly active ART (HAART) may further exacerbate gut dysbiosis. As inflammatory mediators are released into the bloodstream during gut dysbiosis, these mediators may enter the cochlea by enhancing the permeability of the blood-labyrinth barrier. These inflammatory mediators can damage cochlear sensory cells, also resulting in SNHL. The role of gut

dysbiosis in HIV-induced SNHL needs to be determined, which will pave the way for developing novel microbiome-based therapies [53].

Although the treatment regimens of HIV-infected children in each study were not described in detail, certain classes of ART, namely nucleoside reverse transcriptase inhibitors (NRTIs), have been linked to hearing impairment in children [61–63]. In vitro studies suggest that several common anti-HIV drugs are likely ototoxic. Some commonly used anti-HIV drugs are toxic to the House Ear Institute-Organ of Corti 1 (HEI-OC1) cells by impairing cell proliferation or inducing cell death. The HEI-OC1 cells, a mouse auditory cell line used for research purposes, are generally considered a good model for screening ototoxic drugs. However, the HEI-OC1 cells are not cochlear hair cells, and further studies with animal models are required to confirm the ototoxicity of the ARV drugs as predicted by this in vitro system [64]. It is important to identify which ART drugs are likely to cause ototoxicity and determine whether the duration of ART use plays a role in SNHL [53].

There is also evidence that Epstein- Barr virus (EBV) and CMV may contribute to SNHL [65], but those co-infected with HIV will have a worse outcome. The inner ear cells, including the hair cells and the temporal bone cells, will become more susceptible to immune cell recruitment when infected with other organisms simultaneously [59, 66].

A study demonstrated that HL is more common in HIV-positive and HIV-negative exposed children compared to matched controls; however, late presentation is associated with an increased risk of HL in HIV-positive children [47]. Patients with frequent ear drainage, ear infections, low body mass index (BMI), or HIV infection with severe progression should receive frequent assessments and auditory function testing [67].

The HIV-related factors such as ART, stage of disease, and current or previous ear infections appear to be associated with HL in patients with HIV infection [49]. A study reported that HIV-infected patients experience more otological and auditory symptoms, especially as the disease progresses toward the advanced stages [68]. As a consequence, all individuals with HIV infection should undergo an assessment of their hearing function by otoacoustic emission (OAE) testing, pure tone and speech audiometry, speech-in-noise testing, or the auditory brainstem response (ABR) test [53, 56].

56.10 Conclusion

Access to ART has reduced HIV-related morbidity and mortality globally and increased life expectancy, including in low-income countries. More HIV-infected patients are surviving, leading to increased awareness of the magnitude of the disabilities related to HIV infection itself, OIs, or medication side effects that can cause these disabilities. The literature shows that children with HIV infection and HL have a significantly higher likelihood of reporting other disabilities.

As the ability to hear is one of the most critical factors in normal brain and speech development, there is an urgent need for improved identification, treatment,

and screening tools for HIV-infected children and follow-up with multidisciplinary teams as early as possible. With the advancement of ART therapy and the transition of HIV from an acute to a chronic disease, more studies need to understand the mechanisms underlying SNHL in HIV-infected individuals. Prospective studies with large cohorts of HIV-infected patients are also required to determine the onset of HL and the impact of ART on the further deterioration of HIV-induced SNHL.

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Lassa Fever and Hearing Loss

57

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57.1 Definition

The Arenaviridae have a genome consisting of single-stranded RNA. They infect rodents without causing symptoms and may be transmitted to humans as a zoonosis from an infected rodent. This usually occurs through contact with rodent urine or faeces. Since the rodents pass the virus on to their offspring, these animals remain a steady reservoir of infection. The Arenaviridae consist of 22 different viruses, with a further 9 types that were recently identified, but have not yet been definitively assigned to a taxon. The first arena virus, which is considered prototypical for the grouping, was discovered in 1934, the lymphocytic choriomeningitis virus (LCMV). At that time the St Louis encephalitis virus made its first appearance in an epidemic. A sample obtained from a patient who died at that time was found by chance to contain the LCMV, too. This became apparent after the virus had been transmitted through several monkeys, one after another. LCMV was the first pathogen found to underlie aseptic meningitis in human patients [1].

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57.2 Classification

Among the Arenaviridae endemic to South America and Africa, there are various viruses which classically cause viral haemorrhagic fevers. There are also certain viral species which do not infect humans or do not cause disease when transmitted to a human being. The majority of the Arenaviridae are still actively being researched [1].

The Arenaviridae are classified into two divisions. One group can infect members of the Murina subfamily, the other group those of the subfamily Sigmodontina, within the family Muridae. The former are found in the Old World (i.e. Eastern Hemisphere), while the latter are indigenous to the New World (i.e. Western Hemisphere). Those Arenaviridae infecting Western Hemisphere rodents are assigned to 3 clades, labelled A, B and C, which reflect different lineages. LCMV can, in fact, infect both the Murinae and Sigmodontinae, but it is taxonomically placed among the Old World viruses. The following list gives the names of the most prominent Arenaviruses and indicates which rodent species serves as the reservoir of infection [1].

57.2.1 LCMV-Lassa Virus Complex (Eastern Hemisphere)

57.2.1.1 Lymphocytic Choriomeningitis Virus

- The reservoir of infection consists of 3 rodent species: *Mus musculus*, *Mus domesticus* (both are house mice) and *Mesocricetus auratus* (the Syrian hamster).
- This virus is found in Europe, Asia and North and South America.
- It is associated with human habitation and grassland.
- Infections occur in September of October.

Human patients come into contact with the virus within houses [1].

57.2.1.2 Lassa Virus

- The rodent reservoir is members of the genus *Mastomys* (the multimammate mouse).
- The virus inhabits West Africa.
- Viruses are associated with areas of Savanna or where trees have been cut down.
- Infections occur between January and April.
- The virus mainly comes into contact with a human within houses [1].

57.2.1.3 Mopeia Virus

- The infective reservoir is *Mastomys natalensis.*
- The viral habitat is Savanna in Southern Africa.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.4 Mobala Virus

- The infective reservoir is members of the *Praomys* genus, the soft-furred rats.
- The viral habitat is Savanna in the Central African Republic.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.5 Ippy Virus

- The infective reservoir is members of the *Arvicanthus* genus, the Nile grass rat.
- The viral habitat is grassland and savanna of the Central African Republic.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans [1].

57.2.1.6 Lujo Virus

- The reservoir of infection is not yet known.
- The habitat is an unknown location within Zambia. It probably occupies a similar ecological niche to Lassa virus.
- It is unclear at what time of year infections usually occur, nor is it known how the virus usually comes into contact with humans, but similarities with Lassa virus are suspected [1].

There are also a number of other Eastern Hemisphere members of the Arenaviridae, namely the South African Merion Walk virus, the Tanzanian Morogoro, the Guinean Kodoko and the Australian Dandenong [1].

57.3 Pathophysiological Features

57.3.1 Characterisation of the Virus

The Arenaviridae are spherical particles, wrapped in an envelope of plasma membrane derived from the host and with a diameter of between 50 and 300 nm. The spherical form coexists with other shapes. The virion is encased by an envelope studded with irregularly spaced glycoproteins, which appear as clubs or spikes, and are named GP1 and GP2 [1].

The arenavirus genome consists of 2 subgenomic segments, which contain 2.4Mbp and 1.3Mbp. The former is referred to as the L (=large) segment, the latter as the S (=small) segment. The genome contains predominantly anti-sense sequences, but there are positive sense sequences at the 5′ end of both the subgenomic segments. Thus, although arenaviruses are generally classed as anti-sense viruses, they may be more properly considered ambi-sense viruses. The L and S segments contain a long open reading frame, with no overlap, but read in opposite directions. There is a viral RNA-dependent RNA polymerase encoded within the L segment, as well as the Z protein. This molecule plays a key part in viral budding

from the host cell as well as other roles inside the host cell. The nucleocapsid protein (N) and glycoprotein precursor polypeptide (GPC) are both encoded on the small subsegment. The GPC undergoes cleavage at various points and lycosyl residues are added, thereby producing the glycoprotein spike proteins. The viral N protein provokes the most vigorous antibody response. Immunoglobulins targetting the N protein are detected with an indirect fluorescent antibody (IFA) test for diagnostic purposes [1].

The Arenaviruses get their name from the presence of grain-like structures within the virus when visualised using electron microscopy. These structures are between 20 and 25 nm across and resemble sand (arena = sand in Latin). They are in fact ribosomes belonging to the host and captured, while the arenavirus buds off from the host cell. No functional role has yet been assigned to the ribosomes captured in this way.

57.3.2 Lassa Virus (The Cause of Lassa Fever) [1]

Lassa fever is an endemic disease in West Africa. The first cases were reported in Nigeria, but there have since been cases in Sierra Leone, Liberia and Guinea. The Lassa virus was first identified in members of the genus *Mastomys*. These rodents are often found in human dwellings, which they actively seek to enter. The dry season corresponds to when Lassa fever becomes frequent. Lassa fever is unusual among arenoviruses insofar as human-to-human transmission is possible. The viruses endemic to South America also possess some capability of human-to-human transmission [2–4]. Lassa fever takes between 3 and 16 days to incubate. The risk of a fatal outcome overall is 1%. However, for pregnant women in the last trimester, there is a greater than 80% risk of death, and foetal loss virtually invariably occurs. Aborting the foetus makes maternal death somewhat less probable [1].

57.4 Clinical Presenting Features of Lassa Fever

In 80% of patients with Lassa fever, the clinical features are sufficiently mild that the diagnosis may be missed. It has been estimated that Lassa fever affects multiple systems and is of high severity in 20% of cases overall. There is an incubation period lasting between 1 and 3 weeks. The disease has an insidious onset, with symptoms of pyrexia, weakness, feeling generally unwell, arthralgia and lumbar pain [1].

If the severity is high, the patient may be unable to rise from bed, become dehydrated and experience pain in the abdomen. There may be swelling of the face and cervical region [1, 5, 6].

57.5 Physical Examination

The majority of cases present with mild pyrexia, headache and feeling generally unwell. If Lassa fever is of high severity, respiratory distress and features of shock are potential manifestations. There may be swelling of the face, with bleeding from the gingiva, nose and oral cavity. Furthermore, the patient may be severely nauseous and vomit. There may be pain in the chest, back and abdomen. Central nervous system involvement may appear as a tremor, cognitive disorientation, encephalopathy and fits. There should be no localising signs [1].

The cerebrospinal fluid does not show any abnormalities [1]. The aminotransferases in serum are sometimes raised. The only cause of viral hepatitis in which the aspartate aminotransferase level is well above that of alanine aminotransferase is Lassa fever. This pattern of abnormality would normally indicate alcoholic hepatitis. No more than 15–20% of cases feature haemorrhage. Where haemorrhage does occur, it is from the mucous membranes and is not severe [6].

57.6 Complications

The complication which occurs with highest frequency in Lassa fever, irrespective of disease severity, is hearing loss. This complication is present in approximately 30% of cases and is commonly irreversible [1].

Pregnant patients are at elevated risk of a fatal outcome. The death of the foetus occurs in approaching 95% of cases [1].

Overall, mortality from Lassa fever is between 15 and 50% [6].

57.7 Clinical Management

For patients infected with an arenavirus of any sort, if the disease is of mild severity, no particular treatment is indicated [7]. Infections with arenaviruses leading to haemorrhagic fevers do, however, need to be treated specifically and with attention to alleviating symptoms [1].

Palliation of symptoms is all that is required in cases of LCMV [1]. By contrast, where Lassa fever is symptomatic or in the haemorrhagic fevers of South America, patients require aggressive clinical interventions if the risk of severe morbidity or a fatal outcome is to be diminished [1].

Careful management of the arterial tension, as well as ensuring adequate hydration and satisfactory electrolyte balance has the potential to prevent fatal outcomes.

Ribavirin, an antiviral agent, is utilised for the treatment of Lassa fever, in addition to the haemorrhagic fevers of South American type.

Benefit has been demonstrated for convalescent human plasma in treating infections with Junin virus. However, this use of plasma does not offer similar benefit in Lassa fever. The most probable explanation for this situation is that the neutralising immunoglobulins in Lassa fever cases are present at a lower concentration and do not begin to be synthesised in large numbers until after the main illness has passed [1].

57.8 Auditory Impairment

Deafness of sensorineural type affecting one or both ears and of acute onset is seen in around 1 in 3 cases of non-fatal Lassa fever. In many cases, this hearing loss is irreversible [8]. According to calculations by the WHO (World Health Organisation), globally there are 368 million people living with hearing loss, mostly in developing countries [9]. Sudden-onset sensorineural deafness occurs through trauma to the hair cells of the cochlea or the nervous tissue of the inner ear. By definition, it must involve a loss of at least 30 dB affecting 3 or more frequencies and develop in 72 hours or less [10]. Therapy involves fitting hearing aids, or, in certain patients, a cochlear implant [10]. Unfortunately, in the countries where Lassa fever is endemic, hearing loss of this type cannot usually be treated [9, 11]. There are numerous reasons for deafness to develop in adults, including medications with ototoxicity, occupation-related hazards, neoplasia, otitis and viral infections. The latter category includes measles, mumps, rubella or HIV. Lassa fever is another cause of deafness, but its true prevalence is unknown in the countries where it mostly occurs [12].

At present, Lassa fever is a threat to a population of around 37.7 million [13]. As foreign travel increases and epidemics become more likely, as well as the possibility that Lassa virus may be weaponised, research into the pathogenesis of sudden sensorineural deafness secondary to Lassa fever is more needed than ever. An important piece of missing information is the prevalence of this complication. A deeper knowledge of the pathogenesis would guide the development of vaccinations and medications for use in Lassa fever and help direct therapy for Lassa fever-associated hearing loss [14].

57.9 Pathogenetic Mechanisms Involved in Sensorineural Deafness Secondary to Lassa Virus

Cummins et al. undertook a study examining any association between Lassa fever and auditory impairment [8]. The study used a case-control design, with 3 different groups involved: cases where the patient was admitted to hospital with pyrexia, healthcare workers, individuals whose serology was positive for Lassa fever and people living within a particular region of Sierra Leone (the Eastern Province) with acute onset hearing loss. In the hospitalised patients, the rate of acute onset uni- or bilateral hearing loss in those with positive Lassa serology was 29% in the period 5 to 12 days following resolution of pyrexia. Seroconversion was invariably present

prior to the first manifestations of deafness. In 17.6% of those with sudden sensorineural deafness secondary to Lassa fever, the condition was irreversible. Sensorineural deafness did not occur in any of the patients with pyrexia whose Lassa serology was negative. In the group consisting of healthcare staff and first-year doctors who had a positive result on serology for Lassa fever, if the individual had positive serology for anti-Lassa virus immunoglobulins, there was a 17.6% risk of sensorineural deafness. This rate was elevated compared to a rate of just 3% (2 of 74 ears tested) in those individuals who had negative serology for Lassa virus. Meanwhile, some 81.2% of the individuals living in the Eastern Sierra Leone Province who had evidence of sensorineural deafness had positive serology for Lassa virus, whereas only 18.8% of those without sensorineural hearing loss had positive serology. Of the cases with positive serology and sensorineural deafness, the severity of impairment was at 71.9% (either unilaterally or bilaterally) [8, 14].

The possibility that sensorineural deafness following recovery from Lassa fever is due to ribavirin has also been researched, since this agent is known to be ototoxic [15]. Neither the prognosis nor the way the deafness developed was found to fit with the pattern of ribavirin use, however, which implies that ribavirin is not responsible. The fact that use of ribavirin does lower the level of viraemia but does not prevent sensorineural deafness from occurring shows also that the circulating virus level does not explain the auditory deficit. Indeed, there is no correlation between the risk of sensorineural deafness and the circulating viral titre, liver function tests, or clinical severity. Taken together with the timing of the onset of deafness, these facts have been taken as evidence that sensorineural hearing loss in Lassa fever is not a direct result of the pathogen, but rather of the immune system's response [8, 14].

A Nigerian study of case-control design examined longer term outcomes in cases of Lassa fever where sensorineural hearing loss developed within the acute stage of the illness [16, 17]. Sensorineural deafness of early onset and affecting both ears was found in 13.5% of patients where Lassa virus was confirmed by reverse transcriptase DNA amplification, but in none of the controls who had pyrexia but no confirmation of Lassa virus infection. Some 60% of patients with sensorineural deafness following Lassa fever had positive serology for immunoglobulin M. The death rate, notably, was also more elevated in cases of Lassa fever where sensorineural deafness developed than in cases without hearing loss (60% vs. 21.9%, respectively). The study authors pointed to the fact that immunoglobulins were not detectable in all cases of Lassa fever-associated deafness and that deafness was a risk factor for a fatal outcome, using this to argue that sensorineural deafness was probably not solely due to the immune response but was also directly caused by the pathogen itself [17]. There are, however, significant differences between the definitions used by Cummins et al. and this study, in particular the use of a time-based criterion for diagnosing early onset of sensorineural deafness (i.e. in under 21 days), rather than the use of seroconversion or entering convalescence, which were relied upon by Cummins et al [8, 17] There is a need for future research to standardise the definitions of Lassa fever-related sensorineural deafness when investigating the pathogenetic mechanism by which hearing loss occurs and to allow a more rational approach to treatment. Treatments which have been attempted for sensorineural

hearing loss in Lassa fever include corticosteroids, hyperbaric oxygen delivery, vasodilation of the labyrinth vessels and vitamin supplementation, alongside fitting of hearing aids. No benefit has been demonstrated for any of these treatments so far [17]. It is possible that the lack of benefit from these interventions is due to the fact that Lassa virus produces widespread nervous injury and only cochlear implantation has the potential to improve deafness [14, 17].

One proposed way in which sensorineural deafness may be caused by the immune response is by immunoglobulins accidentally targetting self-antigens in the cochlear, resulting in the loss of hair cells [18, 19]. This explanation cannot, however, account for where sensorineural deafness manifests but no seroconversion occurs [17]. Cochlear hair cells have been noted to sustain minimal damage, which may be directly attributable to the virus. Mice which are deficient in Stat1 generate CD3+ lymphocytes and suffer sensorineural hearing loss, whereas mice deficient in the R gene produce Interferon alpha/betagamma and do not develop deafness. This evidence may corroborate the pathogenetic mechanism proposed by Cummins et al., which attributes injury to the immune response [8, 20]. However, further studies will be required to full understand the details of such a pathogenetic mechanism [14].

The Lassa virus mainly attacks monocytes, macrophages and dendritic cells, thereby disrupting their co-ordinated action. Cells of the myeloid series infected with Lassa virus cease triggering a response by the adaptive arm of the immune system [21]. Furthermore, Lassa virus attacks the human hepatic and renal tissues, as well as the spleen, adrenal glands and bone marrow [22]. Lassa virus is detectable in cerebrospinal fluid of both humans and other species, which indicates that the pathogen can invade the central nervous system [23, 24]. It is common for patients who survive Lassa fever to mount a swift and vigorous T-lymphocytic response, absent in those who go on to die from the disease [21]. As is the case with LCMV, survival is enhanced by a rapid T-lymphocytic response, albeit at the risk of secondary injury due to immune overreaction [25]. It has been demonstrated, using an animal chimaera, that T-lymphocytes play a key role in the pathogenetic mechanism of Lassa fever. In this model, even when the circulating viral level was elevated, reducing the numbers of CD8+ T-lymphocytes was an effective way of preventing a fatal outcome [14, 26].

Sudden onset of sensorineural deafness may also occur with medications of known ototoxicity; the likely way this occurs is also through an immune mechanism. ROS (reactive oxygen species) are generated by activated B-lymphocytes in which the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) has been translocated to the nucleus following stimulation by proinflammatory cytokines, notably interleukins 1β and 6. Eventually, the mitogen-activated protein kinase (MAPK)–c-Jun N-terminal kinase (JNK) pathway becomes active and this then causes cochlear hair cells to undergo apoptosis. Moreover, the atonal transcription factors Atoh1 and Hath 1, which govern growth of the cochlear hairs, are inhibited, preventing them regrowing [14, 19, 27, 28].

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Dengue Haemorrhagic Fever and Hearing Loss

58

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58.1 Introduction

The clinical term dengue refers to a viral disease-causing pyrexia which occurs after a patient is bitten by a mosquito of the *Aedes aegypti* or *Aedes albopictus* species. There are four types of flavivirus which may cause dengue, namely dengue viruses 1, 2, 3 and 4 (hereafter abbreviated as DENV-1 etc.). Infection with any of these types can cause dengue haemorrhagic fever or dengue shock syndrome, both of which are severe illnesses. Dengue has endemic status in at least 125 different countries within the tropics or subtropical zones. There are thought to be 390 million cases each year, of which 96 million are symptomatic [1].

The risk that dengue will be of high severity is most elevated in patients who have already been infected by one of the four dengue viruses and then become infected by a second type. This situation is referred to as secondary (or heterotypic) infection [2]. Due to this phenomenon, the severity of dengue is highest where different dengue virus subtypes co-exist. Survivors of dengue virus infections acquire

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long-term immunity against the specific virus type causing the infection, but any immunity acquired in this way is only transient in preventing reinfection with the other dengue viruses [3].

58.2 Background

In humans, the most frequent and significant viral disease spread by an arthropod vector (i.e. an arbovirus) is dengue. There are between 2.5 and 3 billion people who inhabit areas where dengue is endemic. It affects some 112 countries directly. The precise incidence of dengue infections is unknown, since data are lacking for many regions and some cases may be misdiagnosed, but it appears probable that there were some 3.2 million infections worldwide in 2015. The four dengue virus serotypes (DENV-1, -2, -3 and -4) are all flaviviruses. This viral genus consists of RNA viruses with a single strand genome lacking segmentation. Homotypic immunity (i.e. immunity to a single serotype), once acquired following infection, lasts for the individual's lifetime. However, resistance to the other serotypes (i.e. heterotypic immunity) is more transient, ending in around 2 years. Thus, patients may be infected by all 4 viral serotypes in the course of a lifetime. Furthermore, at any one time several serotypes may be involved in an epidemic [4].

The mode of transmission involves a mosquito vector, specifically members of the *Aedes* genus. These insects have a wide range, covering both the tropics and adjacent subtropical regions. Patients infected with the virus can transmit it back to another mosquito if the second bite occurs within 12 days (average = 4–5 days) of the first. The virus incubates for between 5 and 10 days in the mosquito before becoming transmissible. Once in this state, the mosquito remains a vector until it dies. *Aedes* mosquitoes generally live for between a fortnight and 1 month. The *Aedes albopictus* species has a greater ability to survive cold temperatures than *Aedes aegypti* and is therefore the usual vector in subtropical areas, such as Southern Europe or the USA [4].

There has been a dramatic rise in the worldwide frequency of dengue infections over the last 20 to 30 years. Currently, this disease potentially affects nearly half (40%–50%) of the global population, spread over 128 countries [5–7]. It is a disease that principally afflicts Asian and South American nations. In these countries it is a major cause of hospital admission and mortality. In 2019, the WHO (World Health Organisation) considered dengue to be among the ten most serious problems affecting human health worldwide [8].

There is some variety in the way dengue infection presents clinically. Between one half and 90% of cases lack symptoms, while the remainder show non-specific features of a pyrexial illness or exhibit the classic features of dengue fever. In the classic presentation of dengue fever, there is marked pyrexia that develops rapidly, headache, pain behind the eyes, somatic aches (muscular and bony), debility, vomiting, pharyngitis, dysgeusia and an exanthem of maculopapular type spreading towards the extremities. Pain can be so intense that dengue is sometimes termed "breakbone fever" [4].

In a minority of cases, there is haemorrhage and leakage from the blood vessels. This occurs in an individual who has previously been infected with one dengue

serotype and then is infected with a different type. The WHO-approved term since 2009 has been "severe dengue", although older texts may use the terms "dengue haemorrhagic fever" or "dengue shock syndrome".

Severe dengue may also be referred to as dengue vasculopathy. The loss of flood from the vessels in this condition causes the blood to become overly concentrated, serous effusions may occur and there is a risk of circulatory failure. Circulatory collapse which co-occurs with severe bleeding may cause shock. Shock is more threatening to life than haemorrhage alone [9].

There are two ways in which dengue viruses are transmitted, namely epidemically and hyperendemically. The disease is considered transmitted epidemically when a single event brings a specific viral serotype into a particular area. Provided there are sufficient arthropod vectors and children and adults without immunity, the infection rate can grow exponentially, with a quarter to a half of the population becoming infected. For disease outbreaks of this sort, three factors play a key role in development: reducing the mosquito vector numbers, the development of herd immunity and alterations in weather. It seems that the epidemics generally start in built-up areas before reaching the rural population [10]. At present, this mode of transmission predominates in Africa and Latin America, as well as those regions of Asia where dengue has reappeared, and on some of the smaller island countries. If patients travel to such areas while an epidemic is in progress, they may also acquire the infection [4].

The situation in which dengue is transmitted hyperendemically is somewhat different. For this to occur, there need to be large numbers of human hosts lacking immunity, many mosquitoes able to transmit the infection and several viral serotypes present at the same time. Hyperendemic transmission is more common worldwide than epidemic transmission. Where it occurs, serology titre should rise with patient age, such that the majority of adults become immune. This mode also raises the risk of dengue haemorrhagic fever. The risk to travellers of acquiring dengue is higher when visiting an area of hyperendemic status than an area where an epidemic is occurring [11].

58.3 Dengue Fever

The usual presentation of dengue resembles that of several other infections caused by bacteria or viruses. Pyrexia usually commences on day 3 of symptoms. It lasts for 5–7 days, reducing as the number of viral particles in the blood decreases. The patient's temperature may rise to 41C°. In a few patients, a saddleback fever pattern emerges, especially in paediatric cases. In these children the pyrexia ceases for 24 h before recommencing. Saddleback fever is more frequent as a part of the presentation of dengue haemorrhagic fever [4].

Frequent abnormalities on full blood count include leucopenia and low levels of lymphocytes towards the end of the pyrexial period. Low platelets are also common. These abnormalities are thought to be due to a direct destruction of precursor cells within the bone marrow by the virus. As the virus multiplies and destroys the osseous tissues, it creates the bony pain associated with dengue fever. In around 1 in 3 cases of dengue fever, a mild degree of haemorrhage occurs, such as petechial

bruising, bleeding gums and positivity of the tourniquet test. In the tourniquet test, positivity is defined as more than 20 petechial bruises within a square of skin measuring 2.5 cm along the side. It is unusual for patients to die from dengue fever [4].

58.4 Severe Dengue (Aka Dengue Haemorrhagic Fever)

Although only a minority of cases of dengue fever present as severe, this condition is more dramatic clinically. In the majority of severe cases in Asia countries, the patient is a child. Indeed, Asia is where the first descriptions of severe dengue were reported. In Latin America and North America, as well as recently in Taiwan, cases of severe dengue are evenly distributed across the age range [4].

The presentation of severe dengue is usually no different from that of mild dengue at the outset. As with dengue fever, there is an acute pyrexial phase, where the patient's temperature does not exceed 40 °C, with a duration of between 2 and 7 days. The development of severe dengue becomes clear when this pyrexia recurs after a pause, giving a saddleback or biphasic appearance to a plot of temperature vs time [4].

There are also other signs indicating dengue is severe, such as a progressively worsening thrombocytopenia, a rise in haematocrit (of 20% compared to before the illness) and hypo-albuminaemia. These abnormal blood parameters indicate impending circulatory shock. The tourniquet test is positive in at least half of patients and worsening effusions are noted in the lungs or abdomen. There are raised numbers of lymphocytes in the blood, frequently including atypical cells, before the pyrexia abates or shock develops. Liver function is also abnormal, with a slight increase in the transaminases or, if acute hepatitis has occurred, enlargement of the liver and a transaminase level reaching the thousands. On clotting profile, a decreased fibrinogen and raised level of cleaved fibrin indicate disseminated intravascular coagulation. Metabolic acidosis may be severe and circulatory failure supervene [4].

The most important element to consider in cases of severe dengue is leakage of plasma out of the capillaries. The capillaries become abnormally permeable and this may become apparent as haemoconcentration, pleural effusions and abdominal fluid accumulation. Haemorrhage results from damage to the smallest calibre vessels, as well as low levels of circulating platelets. The skin may exhibit petechiae or there may be potentially fatal haemorrhage in the gut [4].

Hepatic injury is shown by raised transaminases (alanine and aspartate aminotransferases), hypoalbuminaemia and abnormal clotting (seen in the prothrombin and partial thromboplastin times) [12, 13]. Where hepatitis secondary to dengue is fatal, above 90% of the hepatocytes and stellate macrophages appear infected, while the cytokine levels are very low (in particular tumour necrosis factor-alpha and interleukin-2). This pattern of hepatic injury resembles that produced by yellow fever and Ebola, when these infections result in death [12].

Severe dengue shock, as may be inferred from the title, refers to a presentation where patients with dengue haemorrhagic fever go on to develop circulatory failure.

It manifests as a low arterial tension, narrow pulse pressure (less than 20 mmHg), which then develops into shock and causes death unless clinical intervention prevents this. Once there are indications of circulatory collapse, death may follow within 8–24 h. Clinically, the condition usually manifests as low body temperature, pain in the abdomen, vomiting and agitation [4].

58.5 Signs and Symptoms

The mean time at which symptoms of dengue appear following infection (i.e. the duration of incubation) is 4–10 days, with a range of 3–14 days. Symptoms typically have a duration of between 2 and 7 days [4].

In many cases, dengue infection does not result in symptoms. There is, however, likely to be a 2- or 3-day prodromal symptom consisting of chills, an exanthem, reddened and mottled skin and flushing of the face. Up to the age of 15 years, dengue fever generally presents as a non-specific pyrexial episode, with a possible accompanying exanthem of maculopapular type. Features of the presentation that should prompt a differential diagnosis of dengue include the following: pyrexia reaching 40 °C, pain behind the eyes, myalgia and arthralgia, nausea, swollen lymph nodes, vomiting and a skin eruption. There should also be a history of travel within the preceding 2 weeks to an area where dengue is epidemic or hyperendemic, or potentially so [4].

The following symptoms may also be present in cases of dengue [4]:

- Pyrexia.
- Headache.
- Pain behind the eyes.
- Severe muscular aches, particularly affecting the lumbar regions and limbs.
- Joint pains, generally affecting the knees and shoulders.
- Nausea and vomiting. Diarrhoea seldom occurs.
- Exanthem of maculopapular or macular confluent type. The distribution is facial, thoracic and covers the flexor surfaces. There are areas of skin without any rash.
- Debility. The patient feels generally unwell and lethargic.
- Dysgeusia.
- Loss of appetite.
- Pharyngitis.
- Evidence of bleeding, such as petechial rash, gingival haemorrhage, nose bleeds, menorrhagia or blood in the urine.
- Swollen lymph nodes.

58.5.1 Severe Dengue (Dengue Haemorrhagic Fever, Dengue Shock Syndrome)

Severe dengue begins in a way resembling both dengue fever and other pyrexial illnesses caused by different viruses. Pyrexial onset is typically between 2–7 days

after other symptoms manifest. Just after the patient becomes pyrexial, there are signs that plasma is being exuded from highly permeable capillaries, in addition to haemorrhagic events, e.g. excessive bleeding from small injuries, bleeding in the gut or blood in the urine. Some cases may also feature abdominodynia, ongoing vomiting (including haematemesis), tiredness and, in paediatric patients, febrile convulsions [4].

Once this stage is reached, the following 24 h are a critical period. Without treatment, haemorrhagic fever evolves into circulatory shock. Signs that shock is developing include abdominodynia, vomiting and agitation. The circulatory collapse also causes its own presenting signs, in particular pallor, raised respiratory and cardiac rate, vertigo and obtunded consciousness [4].

58.6 Diagnosis

There are several laboratory methods available for diagnostic confirmation of dengue virus infection. The viral DNA or antigens may be detected, or the immunoglobulins produced in response to infection, or these tests may be combined [4]. Tests include the following:

- Comparison of paired serum samples for levels of immunoglobulins G and M specific to antigens found on dengue virus. If the second sample antibody level is at least four times elevated, the diagnosis is confirmed.
- For post-mortem confirmation of the diagnosis, tissue can be stained using immunohistochemical or immunofluorescent markers. Serum may also be subjected to enzymatic immuoassay, such as MAC-ELISA, IgG ELISA, non-structural protein 1 (NS1) ELISA, EIA.
- Reverse-transcriptase polymerase chain reaction amplification can be used on serum, cerebrospinal fluid or post-mortem tissue to detect viral RNA. This method has a high specificity and is rapid.
- Virus may also be directly isolated from samples of serum, plasma, infected white cells or post-mortem material, but this method is not often employed.

At the first stage of dengue fever (i.e. up to day 4 or 5), the virus may be isolated from serum, plasma, cells from venous blood or the tissues. Isolation of the virus, RNA detection or detection of viral antigens are suitable diagnostic methods at this stage. After the initial phase, however, serological methods are most suitable for diagnosis [5].

There are several other laboratory investigations which are valuable in cases of suspected dengue fever, namely [4]:

- Full blood count.
- Metabolic panel.
- Quantification of protein generally and albumin specifically, in serum.
- Liver function tests.

- Clotting profile, which may include screening for disseminated intravascular coagulation.

The typical results of laboratory investigations in dengue are the following [4]:

- Deficiency of platelets. The count is below $110 \times 10^9\ L^{-1}$.
- Leucopenia.
- The transaminases are raised slightly or moderately.

In cases of severe dengue, the expected abnormalities are [4]:

- Raised haematocrit as a result of plasma leakage from the vessels, possibly in conjunction with bleeding into third spaces.
- Low plasma protein.
- Lengthened prothrombin time.
- Lengthened activated partial thromboplastin time.
- Low levels of fibrinogen.
- Elevation in the level of cleaved fibrin.

Stool should be tested for occult blood with the guaiac method for every case where dengue is a potential diagnosis. Haematuria can be confirmed by urinalysis.

There are also some imaging investigations required, namely [4]:

- Chest X-ray.
- Computed tomographic imaging of the head minus contrast helps to identify bleeding within the cranium or oedematous swelling of the brain in severe dengue.
- Ultrasonographic examination can identify fluid in the thorax or abdomen, a pericardial effusion and thickening of the gallbladder wall. These are potential findings in severe dengue.

58.7 Auditory Impairment

Although dengue does cause some otorhinolaryngological issues, it does not usually cause deafness. Sudden hearing loss is the term used to describe auditory impairment of sensorineural type that develops abruptly in a patient with no previous history of deafness. The potential connection between specific pathogens and sudden hearing loss is the subject of ongoing research, including the possibility that dengue can cause deafness of this type. At present, however, it is unclear whether dengue is a cause of sudden sensorineural deafness [14].

Two cases of sensorineural-type auditory impairment of a mild degree after dengue have been reported by Soni et al. [15]. The impairment was persistent at follow-up undertaken 3 months after recovery from dengue. In one of these cases, the loss affected high frequencies [15].

58.8 Clinical Management

Patients who are diagnosed with dengue but have no indications of impending severe disease nor comorbidities (as detailed above) may be safely managed without hospital admission. This applies to the majority of patients with dengue, for whom it is a mild condition [3].

Clinicians need to educate patients to recognise symptoms heralding the onset of severe dengue, warning them about the critical period between 1 and 2 days after pyrexia ceases, when a sudden deterioration in clinical condition may occur. While the patient has pyrexia (generally for between 2 and 7 days), in the 1–2 days after defervescence, daily monitoring of hydration status and other parameters which alter in severe dengue should be undertaken. The full blood count should be obtained on several occasions and checked for the signs of haemoconcentration (rising haematocrit and abrupt onset of thrombocytopenia). If this is noted, it implies the capillaries are leaking and the danger of haemorrhage rises [3].

Pyrexia may be treated with paracetamol, but NSAIDs or aspirin should be avoided, since they inhibit the aggregation of thrombocytes and therefore raise the risk of haemorrhage [3].

The advice to patients and their carers is to ensure adequate fluid intake. They should be aware of the signs of dehydration, such as reduced urine production, dry eyes, dry mouth and lips, sunken eyes, apathy or disorientation, coldness or clamminess of the hands and feet and, in infants, a sunken fontanelle. If these signs appear, the patient should seek medical assistance without delay. As defervescence begins (generally between 3 and 8 days after symptoms first appeared), patients should know to look out for the following ominous signs: abdominodynia of high severity, persistent vomiting, exanthem, gingival or nasal haemorrhage, haematemesis, dark stools, feeling drowsy or becoming irritable. The skin may exhibit pallor or feel cool, and breathing may become laboured [3].

In areas where dengue is endemic, precautions should be taken to avoid individuals being bitten by infected mosquitoes. Wherever feasible, mosquitoes should be killed in houses and the windows and doors fitted with insect screens. Any containers remaining filled with water should be covered or drained. When a patient actually has dengue, he or she should break the chain of infection by using mosquito repellent during the day and a bed tent at night. These measures help to stop mosquitoes becoming infected with dengue, which may then be passed on to other patients [3].

Admission to hospital is required if patients show signs of impending severe dengue, the patient's condition is already severe, or there are other risk factors present, such as being pregnant, the patient is an infant, the patient is diabetic, living conditions are poor, the patient is elderly or the patient has kidney failure. Every patient admitted should be examined to determine if shock is developing. The majority of patients who are under clinical care before shock occurs and who are administered fluid resuscitation make an uneventful recovery.

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Part VI

Fungal Infections

Fungal Infections in Children and Hearing Loss

59

Ali Seyed Resuli, Nihat Susaman, and Bert Schmelzer

59.1 Introduction

Otomycosis is a term used to denote infection of the external auditory meatus by a fungus. Otomycosis may occur as primary infection, or be secondary to external otitis of bacterial origin, generally following antibiotic treatment. Around 9% of infections affecting the external auditory meatus are due to a fungal pathogen [1]. The most frequent causative pathogens in general are *Aspergillus niger* and *Candida* species. However, there is some geographic variability in the frequency of different fungal pathogens. Otomycosis occurs more commonly in tropical and subtropical regions, where the atmosphere is more humid [2]. Other risk factors for otomycosis include swimming, scratching the external meatus and cleaning the ear. There have been warnings that over-reliance on antibiotics may predispose patients to fungal overgrowth. So far, however, there have been no alterations in the frequency of fungal infections, nor change in the pathogens involved, even though topical antibiotics have been employed for more than 30 years [3].

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Otomycosis typically present with pruritus of the canal, otalgia, otorrhoea or the sensation of something lodged in the ear canal [4]. Pruritus is deep in the canal and is the most distressing feature for patients. Otalgia is generally of lesser intensity than that seen in bacterial infections of the external canal [3].

The medial portion of the external auditory meatus is the most common location for infection to occur. The inferior tympanic recess is found at this location, and may act to allow debris to gather within the canal. Furthermore, the medial aspect of the meatus offers a more optimal environment for fungi to grow, as it is more shaded and has a higher temperature than the lateral aspect [3].

The oedema associated with otomycosis is of lesser severity than with bacterial otitis externa. The fungi can be readily recognised within the canal, particularly where the operating microscope is used. There are delicate fungal filaments and spores, which are familiar to anyone who has noticed mould forming on out-of-date food items. The spores of *A. niger* resemble a dusting of coal powder in the auditory meatus. These organisms sometimes also look like damp newspaper or blotting parchment. Infections with *Candida* produce white, sebaceous material of a soft consistency and sometimes, if severe, of sufficient volume to block the meatus. A pseudomembrane frequently forms along the sides of the canal, removal of which exposes a membrane of friable, granular type [3].

59.2 Definition

Otomycosis is a fungal infection affecting the external auditory meatus. It often comes to the attention of ENT specialists, where diagnosis is generally made on the basis of physical examination, although the clinician must be alert to the possibility to avoid missing the diagnosis. Otomycosis has a sub-acute and acute presentation. The canal is inflamed and itching, with scale formation and severe otalgia. The presence of the fungal pathogen causes an inflammatory response, with accumulation of sloughed epitheliocytes and fungal hyphae. This lesion causes pain. The patient may suffer some auditory impairment and feel the ear is full, resulting from the piled-up debris within the meatus. According to one study, as many as 93% of cases may report itching of the canal, making it the key presenting feature [5, 6]. It has also been found to be the main (77%) symptom in a sample of 108 patients. The fungal species identified with the highest frequency in otomycosis are *Aspergillus* or *Candida* species [7, 8]. In clinical practice, otomycosis secondary to candidal organisms may be less readily diagnosed, since they lack the recognisable features of *Aspergillus* infections and may seem to be simply an ear discharge caused by a bacterial pathogen and exhibiting treatment resistance to topical antibiotics [9]. Diagnosis of candidal infection of the canal frequently depends on mycological culture results. There have been numerous studies investigating which antifungals are most efficacious for treatment, based on in vitro data, but a clear consensus on treatment has not yet emerged [10, 11].

59.3 Pathophysiology

Otitis externa (OE) refers to an infection of the external auditory meatus affecting the superficial layers of the skin. The following scheme of classification is generally accepted [12]:

- Acute diffuse otitis externa. This type of OE is the most frequently occurring, especially in swimmers. The condition develops rapidly (usually within 2 days) and patients complain of symptoms related to the external auditory meatus, such as earache, pruritus and aural fullness. There may be an accompanying auditory impairment or pain affecting the jaw. The tragus and pinna are tender to touch and the ear may be diffusely swollen or reddened. Other possible presenting features are a discharge from the ear, swollen regional lymph nodes, reddening of the ear drum and cellulitis affecting the pinna [13].
- Acute, localised OE. An alternative term is furunculosis. It occurs when a hair follicle becomes infected.
- Chronic OE. The features match those of acute diffuse OE, but over a lengthier timescale, i.e. more than 6 weeks.
- Eczematous/eczematoid OE covers a variety of different skin disorders, such as allergic dermatitis, psoriasis, systemic lupus erythematosus and eczema, which may involve the external auditory meatus and lead to OE.
- Necrotising OE. This may also be termed malignant OE. In these cases, the pathogen invades the deeper structures in the vicinity of the meatus. It mainly affects adults with immunocompromise, as may occur in diabetes mellitus or AIDS. It seldom affects children. Malignant OE may develop into cellulitis or osteomyelitis. In these cases, imaging investigations are required.
- Otomycosis is a fungal infection of the external auditory meatus. The usual pathogens responsible are *Candida* or *Aspergillus* species [12].

59.4 Aetiology

The most frequently occurring infections causing OE are bacterial. However, OE may also be the result of a fungal infection, when it is termed otomycosis, or be secondary to eczema and psoriasis [14]. One study found that bacterial pathogens accounted for 91% of cases [15]. However, other studies conclude that up to 40% of the time, no specific pathogen can be identified as responsible for OE. The bacterial pathogens most frequently isolated in cases of OE are *Pseudomonas* spp., Staphylococci, anaerobic bacteria and Gram-negative species [12]. Some 38% of cases can be linked to *Pseudomonas* [14].

Otomycosis may arise following excessive use of topical antibiotics within the external auditory meatus, or may be triggered by damp conditions within the canal. *Aspergillus* accounts for between 80 and 90% of cases. Candidal species plus certain other fungi account for the remaining 10–20%. The characteristic finding is the

presence of long, white filamentous hyphae extending from the surface of the skin. Redness and swelling of the canal are common, as is ear discharge. If otomycosis is exceptionally severe, the canal may be stenosed by growth of the soft tissues. The infection may track along the skin to affect the pinna and tragus [12].

Eczematoid or psoriatic OE has an association with several other disorders, namely [12]:

- Eczema.
- Seborrhoea.
- Neurodermatitis.
- Contact dermatitis, related to hearing aids or wearing earrings.
- Otitis media producing pus and perforated ear drum. The infection then drains via the canal. Although the presentation of purulent otitis media may resemble otitis externa, the key differences are that this form of otitis media does not generally cause ear pain, nor oedema of the auditory meatus.
- Reactions to topically applied treatments used in the meatus.

Chronic OE occurs relatively frequently and may arise when acute OE has not been adequately treated [16]. This condition is more commonly due to the ear canal being touched excessively, such as to clean it or relieve an itch. The result of constantly touching the canal is to set up low-grade inflammation, which then provokes further pruritus. When this situation lasts a long time, the skin becomes thicker and may start to render the external auditory meatus stenotic.

Malignant OE affects patients with immunocompromise. It is, in fact, an osteomyelitic lesion of the temporal bone.

There are a number of risk factors for malignant otitis externa, such as the following [12]:

- Having previously had the same condition.
- Swimming, diving or other water-based activities.
- Earplug usage or placing objects in the ear/such as a cotton wool bud. This may be because such actions cause injury to the meatus.
- High temperatures and humidity.
- Hearing aid usage.
- Co-morbid allergic dermatitis, allergic rhinitis or asthma.
- Other, systemic conditions, notably diabetes mellitus, AIDS, leucopenia or being malnourished.

59.5 Hearing Loss

It is frequent for the ear drum to be perforated and for serous otitis media to develop in cases of otomycosis. These conditions usually respond well to therapy. The tympanic perforation most likely occurs secondary to disruption of the blood supply caused by thrombotic events triggered by the presence of the fungus [11]. It has

been estimated that the ear drum perforates in around 20% of cases [6]. No clinical risk factors have been found to correlate with tympanic perforation. The tympanic membrane probably becomes infected by fungal inoculation from the medial portion of the external auditory meatus or by the infection spreading directly from the adjoining skin [11].

59.6 Clinical Management

59.6.1 Antifungal Agents

Although the number of cases of otitis externa due to otomycosis is small compared to cases overall, these infections with *Aspergillus* or other fungal species should not be overlooked. In some patients, acidifying otic solutions are adequate for treatment. However, where these treatments fail to resolve the problem, antifungal antimicrobials are required. The majority of antifungal agents affect either the manufacturing of components of the cell membrane (e.g. by inhibiting processes involved in sterol synthesis), or change how permeable the membrane is, such as the polyenes [12].

59.6.2 Clotrimazole 1% Ear Drops

Clotrimazole is available as a solution specifically formulated for use in the ear. This agent has a wide spectrum of activity and causes changes in the permeability of the fungal cell membrane, resulting in destruction of these organisms [12].

59.6.3 Nystatin Powder

Nystatin is a naturally occurring compound produced by *Streptomyces noursei*. It possesses both fungicidal and fungistatic abilities. A number of different yeast or yeast-like organisms are sensitive to it. This agent binds to sterol compounds in the fungal cell membrane, making the membrane leaky. The yeast loses essential contents from the cytoplasm. When applying nystatin, it should not be discontinued until 48 h after the patients symptoms have fully abated. When nystatin is topically applied, the growth of yeasts is inhibited [12].

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Cryptococcal Meningoencephalitis Infection in Children and Hearing Loss

60

Asif Selimoğlu, Begüm Yılmaz, and Ahmed El-Saggan

60.1 Background

Cryptococcus neoformans is a capsule-bearing yeast. The first mention of this organism was in 1894, when the pathologist Otto Busse presented a paper to the Greifswald Medical Society, in which he described the isolation of the organism from the tibia of a female patient aged 31 years. The yeast was noted to resist destruction by sodium hydroxide. The same patient was described in a case report, also published in 1894 [1]. Another report describing the event was published at the same period by Abraham Buschke, leading to the eponymous term Busse-Buschke disease [2]. The existence of this organism and its role as a potential pathogen was thus established on the basis of a single original case.

More recently, it has been recognised that *Cryptococcus neoformans* can provoke a wide range of responses by the host, ranging from asymptomatic carriage of the yeast in the airways of laboratory personnel, where its presence can only be revealed by positivity of skin testing, to cases where the yeast causes a disseminated infection and/or meningitis. There are pathogen-associated factors which partly determine the virulence of cryptococcal species in infecting animal and, potentially,

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human hosts, but these are of much less significance than the competence of the host immune response [3].

Cryptococcal infections generally reach their highest severity in patients where the cellular immune response is impaired. Thus, highly severe infections with cryptococci occur in cases of AIDS, organ transplant recipients, neoplasia of the reticuloendothelial system, patients receiving steroids and cases of sarcoidosis. There is no association between neutropenia or lack of specific antibodies and severe cryptococcal infections, however [3].

As AIDS has become a major worldwide problem, the frequency of cryptococcal infections has now risen to the level where cryptococcosis now represents a significant risk for mortality in HIV+ patients.

60.2 Mycological Features

There are a minimum of 50 different species contained within the *Cryptococcus* genus. However, the only species which are thought to possess significant pathogenic potential in humans are *C. neoformans* and *C. gattii*. Earlier researcher concluded that *C. neoformans* had two distinct varieties, but more recently, studies of microbial genetics have revealed that *C. neoformans* and *C. gattii* are in fact separate species. *C. neoformans* consists of three serovars, namely A, D and AD, whereas *C. gattii* consists of two serovars, B and C [3].

In temperate regions worldwide, including the USA, the most frequently isolated *Cryptococcus* species is *C. neoformans*. It can be isolated from old droppings of pigeons. Although this is now changing, *C. gattii* used to be located mostly in areas of the tropics or subtropics. There is no association between *C. gattii* and avian species. This organism is mainly found in the leaf litter of particular species of the eucalyptus tree (namely *Eucalyptus camaldulensis* and *Eucalyptus tereticornis*). A Colombian study, carried out in Bogotá in 2016, employed an epidemiological design. It was ascertained from this study that *C. neoformans* is also liable to be found in eucalyptus litter, as is the case for *C. gattii* [4].

Globally, the A serovar of *C. neoformans* is responsible for the highest number of cases of cryptococcosis in patients with deficient immune systems, such as HIV+ individuals. It is unusual for *C. gattii* to cause infections in HIV+ patients or other individuals with defective immunity, although the reason for this remains unclear. Where *C. gattii* does produce an infection, the patients usually have no signs of immune deficiency, but treatment takes a long time and there is a danger the organism may create mass lesions within the brain, especially cryptococcomas. An epidemiological study dating from 2016 noted a raised frequency of cryptococcal meningitis in Zimbabwean cases of HIV, caused by *Cryptococcus tetragatti* (AFLP7/VGIV), considered a possible genotype of *C. gattii* using the wide definition of the species [3, 5].

60.3 Pathophysiological Features

Despite there being at least 50 different members of the genus *Cryptococcus*, most cryptococcal infections in humans are the result of just two species, *C. neoformans* and *C. gattii*. The pathogenetic features of infection by cryptococci and the host response to attack have mostly been studied using animal models. There are two modes of infection. In the first, an individual with deficient immunity is exposed to *C. neoformans*, which then causes a rapid systemic cryptococcal infection. In the second type of infection, the infection enters a latent period, after which the pathogen becomes reactivated and is able to disseminate around the body. It has been proven that this second mode occurs in *C. neoformans* infections [6]. The pathogen enters the body via the respiratory tract. There is no direct human-to-human transmission.

Cryptococci may be inhaled as spores, which can then reach the pulmonary alveoli. The alveoli are a hostile environment, with a pH of 7 or greater and with raised levels of carbon dioxide. If the spores can withstand this environment, they undergo phagocytosis by macrophages. For the *C. neoformans* pathogen to be able to withstand extracellular conditions, it needs to possess functioning glucosylceramide synthase [7]. Once the alveolar macrophage has engulfed the spore, however, this enzyme is no longer required for pathogenic survival. The lower pH of the macrophage cytoplasm is a less hostile environment for the yeast [3].

Yeasts which lack a protective capsule are easily engulfed and destroyed by phagocytic cells, but the presence of a capsule makes phagocytic destruction much harder for the host. The polysaccharide coating on the capsule of the *Cryptococcus* is able to inhibit phagocytic destruction and also potentially inhibits immune reactions. The capsule prevents phagocytic cells from recognising the presence of the invading pathogen and inhibits recruitment of white cells towards the area where the fungus is growing [3].

The immune system activates both cell-based and humoral defence mechanisms in response to invading Cryptococci. From animal studies, it appears that natural killer cells are involved at an early stage in destroying the pathogen. They may also play a role in immunoglobulin-guided attack on the yeast. It has been demonstrated in vitro that activated monocytes (i.e. macrophages), natural killer cells and T cells can each inhibit cryptococcal activity or destroy the invader. The signs indicating that the host is successfully eliminating cryptococci are a rise in Th (T-helper) cells, conversion on skin testing and lower levels of viable yeasts within the tissues. Alongside studies of cell-mediated immunity, there have been studies reported detailing the role of anti-cryptococcal immunoglobulins and other components of the humoral response. Immunoglobulins specific to antigens of cryptococcal origin are essential for augmenting the part played by macrophages and lymphocytes in creating immunity to the pathogen. Using a murine model, it has been possible to create passive immunisation against *C. neoformans* by administering extraneous monoclonal immunoglobulins with specificity for the polysaccharides of the fungal capsule [3].

60.4 Cryptococcal Infections of the Central Nervous System (CNS)

CNS invasion by cryptococci usually produces meningitis or meningoencephalitis, which may present subacutely or chronically.

Once CNS invasion has occurred, death is inevitable unless the lesion is correctly treated. Mortality is possible at any point from a fortnight to years after the first symptoms appear.

There is considerable variety in how cryptococcal meningitis presents clinically and how it progresses. This variety is a function of co-morbidities (such as diabetes mellitus or sarcoidosis), immunosuppressant use (e.g. glucocorticoids) and the health of the patient's immune system [3].

Cases most often present with headache and alterations in the mental state, such as an alteration in personality, disorientation, feeling lethargic, reducing consciousness level or coma.

Patients frequently experience nausea and vomiting, which are linked to the raised pressure within the cranium. Pyrexia and nuchal rigidity, which are indicative of a highly vigorous immune inflammatory reaction, occur with lower frequency [3].

In certain cases where the patient is HIV+, there may be very few symptoms initially or they may provide few clues to the underlying diagnosis. Pyrexia is frequently absent, and, if present, may cause only a mild increase in body temperature [3].

Some cases present with blurring of vision, photophobia or double vision. These symptoms indicate arachnoiditis, papilloedema, neuritis of the optic nerve or chorioretinitis.

Other potential features of CNS involvement are auditory impairment, convulsions, ataxia, speech problems and choreoathetoid movements [3].

Dementia may develop as a complication, which may point to the development of hydrocephalus at a late stage in the disease [3].

60.5 Physical Examination

Despite the respiratory tract being the portal of entry for *C. neoformans*, it is when the organism invades the CNS that clinical signs mostly present, regardless of whether the patient has fully functioning or incompetent immune responses. After the pathogen enters the lungs, it is able to disperse widely around the body and may invade any organ. The organs in which *C. neoformans* can most often be detected are the CNS, osseous tissues, prostate, ocular tissues or skin. Before amphotericin B became available in 1955, there was an 80% likelihood that cases where the yeast had entered the CNS would end in the death of the patient [3].

When the central nervous system is entered by cryptococci, both the nervous tissues and meninges are affected, which creates a diffuse pattern of disease. In patients without immunodeficiency, the involvement of the CNS manifests as meningitis or the formation of focalised lesions known as cryptococcomas. Where

cryptococcomas form, there are generally localising neurological signs, whilst meningitis presents a less distinct clinical picture of changes in mental state or vomiting [3].

60.6 Laboratory Investigations

Histopathological investigation using fungal stains on biopsied tissue and microbiological culture is needed for lesions affecting the cutaneous system.

Venous and CSF samples should be submitted for mycological culture and detection of antigens of cryptococcal origin [3].

Caution is needed in interpreting results as routine laboratory screening tests, such as full blood count, haematocrit determination and erythrocyte sedimentation rate may appear normal, in spite of underlying disseminated cryptococcal infection [3].

For suspected involvement of the CNS, analysis of CSF is vital for diagnostic confirmation. Each time a lumbar puncture is performed, the pressure of the CSF should be quantified. A raised CSF pressure (equal to or above 250 mmHg) is correlated with poor outcome. If the pressure is at this level, some CSF will need to be drained off to re-establish the CSF pressure at no more than 200 mmHg. Before any such drainage is attempted, however, imaging using either computed tomography or magnetic resonance imaging is essential to be aware of any intracranial mass, which may cause herniation to occur [3].

CNS cryptococcosis usually results in a low glucose concentration and raised level of protein in the CSF. The white cell count is generally at least 20/μL and mostly comprised of lymphocytes. In some patients, such as those with AIDS, in whom the inflammatory response is muted, or if the infection is at an early stage, there may be no abnormality detectable on CSF analysis. Nonetheless, an Indian ink preparation or screening of CSF for antigens of cryptococcal origin will often demonstrate the presence of the pathogen [3].

Blood and CSF samples should also be submitted for serology in every patient with suspected CNS cryptococcosis [3].

Antigen detection methods are often financially unfeasible in developing countries, which leads to many undiagnosed cases. In response to such difficulties, a lateral flow method underwent development in 2009. This method was intended to be useful diagnostically. One Thai study compared the new method with the established techniques of mycological culture and enzyme immunoassay (EIA). In a large number of cases, the lateral flow method gave the same answer as EIA. The study concluded that lateral flow tests would be beneficial as a bedside method where resources were limited [8]. Since then, a study conducted at a university hospital in France has also examined the sensitivity and specificity of lateral flow testing in suspected cryptococcosis. The lateral flow method was found to possess excellent characteristics in correctly identifying cases where cryptococcal antigens were absent despite clinical suspicion. Furthermore, the test was easy to undertake and gave a rapid answer. For these reasons, lateral flow tests for cryptococcal

antigen detection seem to offer a suitable method to replace EIA where the latter is not feasible [9].

Even in cases where examination of CSF reveals no apparent abnormality, it may still be beneficial to undertake mycological culture. In cases where the disease slowly intensifies and remits alternately, there may be ongoing abnormal results from CSF analysis, showing that cryptococcosis is still present. In 2016, a study was undertaken on the use of the polymerase chain reaction method, coupled with use of restriction enzymes. This test helps to distinguish between infections with *C. neoformans* and those due to *C. gattii*. Discriminating between the pathogens responsible has potential benefits in choosing appropriate pharmacotherapy [10].

60.7 Auditory Impairment

Deafness frequently results from cryptococcal meningitis. It may occur in patients with no previous health issues. Deafness may result from damage to the cochlea or to another site within the CNS. There is some debate about whether injury occurs through a direct action of the pathogen or via the immune system's response to the invader, potentially occurring even after the pathogen has been eliminated. On average, the auditory function is more impaired in cases where cryptococcal antigens are not detected in CSF but imaging reveals enhancement of the internal auditory meatus [11].

There are reports in the literature concerning audiological complications of cryptococcal infection, both in otherwise healthy cases and in cases where immunodeficiencies were noted. This evidence base is limited, however. Most reports are in the form of case studies or cohort studies which failed to report detailed objective audiometric data [12–14]. Histopathological studies examining the temporal bone report the presence of cryptococci in the internal auditory meatus, with neurodegenerative features within the cochlear and vestibular branches of the vestibulocochlear nerve, the organ of Corti, and the semicircular canals, saccule and utricle [15]. The clinical details vary from case to case in the reports; however, most cases involve deafness of sensorineural type and involve the cochlea or nerve supply, both ears are affected at the same time, and the loss either progressively worsens over time or is of fluctuating intensity [12–14].

A study by Wang et al. examined 26 patients, none of whom were HIV+, but all of whom suffered cryptococcal meningitis. Auditory loss of sensorineural type and of at least mild severity affected eight patients once the infection had been eliminated [13]. Another study examined associations between a number of different clinical parameters and raised risk of sensorineural auditory impairment. The factors correlating with heightened risk were a raised level of antigens of cryptococcal origin, visual loss accompanying the hearing loss and enhancement of the meninges on FLAIR magnetic resonance scanning following contrast [11].

60.8 Treatment

Treatment for cryptococcal meningitis is made up of three separate stages, namely induction, consolidation and maintenance treatment. In the induction stage, the therapeutic aim is to sterilise the CSF as quickly as possible. The effectiveness of the intervention used may be quantified by examining the fall in the number of organisms per mL CSF each 24 hours. This rate is known as the early fungicidal activity (EFA). There is an association between a slower rate of elimination of the cryptococcus from CSF and increased risk of death at 2 and 10 weeks after the onset of symptoms [16, 17].

At present, the recommended initial approach to treat cryptococcal meningitis is a 2-week course of intravenous amphotericin B, at a dose of between 0.7 and 1.0 mg/kg daily, plus flucytosine 100 mg/kg daily [18]. A recently conducted trial has been highly influential in establishing that the combination of amphotericin B and flucytosine creates benefit in terms of a reduction in mortality [19]. The trial compared three different treatments, namely a 4-week course of amphotericin B at high dose only; amphotericin B at high dose with flucytosine regular dose for 2 weeks; or amphotericin B plus fluconazole, both at high dose, for 2 weeks [19]. At the 10-week mark, mortality had fallen by 40% with use of combined amphotericin B and flucytosine. The benefit was still apparent at the 6-month point, and clearance of the fungus was also higher than when amphotericin alone was used. Unfortunately, although amphotericin B plus flucytosine has been demonstrated to be more efficacious than other treatments, in many of the global regions with the highest levels of cryptococcal meningitis, this treatment is not available [20]. There is political pressure from clinicians to make flucytosine more widely available [16, 21, 22]. For clinicians facing a lack of flucytosine, the best option will be to combine amphotericin B with fluconazole [16, 18].

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Part VII

Parasitic Infections

Parasitic Infections in Children and Hearing Loss: An Overview

61

Mehmet Akdağ, Taylan Bilici, and Mümtaz Taner Torun

61.1 Introduction

Protozoal and helminthic infections are relatively rare but essential diseases. Although these infections are eliminated in many developed countries, they still exist in some parts of the world.

61.2 Giardiasis

Giardiasis is a cause of diarrhoea of major global significance. This disease is caused by a flagellated protozoal organism, *Giardia intestinalis*. This parasite used to be known as *G. lamblia* or *G. duodenalis*. It is the most frequent cause of intestinal parasitic infestation in the USA [1, 2], as well as the most frequently occurring parasite of protozoal type to infect humans on a global scale [3–7]. Children are more prone to becoming infected than adults [8, 9].

Infection with *G. intestinalis* may result in no symptoms of infection (i.e. colonisation), or diarrhoea, which may present acutely or chronically. Up to 80% of

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untreated water samples taken from lakes, streams or ponds contain *G. intestinalis*. It may also be present in up to 15% of samples of water that has been passed through a filter [10, 11]. Within developing nations, giardiasis is a frequent reason for chronic diarrhoea and slowing of growth in paediatric patients.

Giardia infection mostly occurs as a zoonotic illness, with the parasite passed from animal to human or vice versa. Canine, feline, beaver and primate stool specimens have all been found to contain *G. intestinalis*. It is likely that the beaver is a significant infective reservoir for this pathogen [12–14]. There are other members of the *Giardia* genus which cause infections in rodents, amphibians, avian species and voles or muskrats. *G. muris* infects rodents, *G. agilis* targets amphibian species, *G. psittaci* and *G. ardeae* are found in avian species and *G. microti* parasitises voles and muskrats [15–17].

There is endemicity of *Giardia* in regions lacking adequate sanitary infrastructure. In the developing world, giardiasis is a major contributor to the illness burden in populations. Mass infections frequently occur through ingestion of contaminated water or food. The minimal infective dose for *Giardia* is a mere 10 cysts, with the result that, in developed countries, infections frequently occur in children attending daycare facilities or individuals living in care homes or other institutions. Giardiasis is especially concerning in patients who are malnourished, immunodeficient or have cystic fibrosis [18].

The *Giardia* cysts are often present in high numbers in the stools of individuals who exhibit no symptoms. There are several risk factors for diarrhoeal illness following ingestion of *Giardia*, notably low stomach acid, immunodeficiency of different types, possession of blood group A and being malnourished. The duration of incubation ranges from 1 to 2 weeks, but lasts on average 9 days. Across the entire age range, symptoms last for between 3 and 10 weeks on average [18].

61.2.1 Life Cycle of the Parasite

The giardial life cycle lacks the complexity of many other parasites affecting humans. There are just two stages composing the life cycle, a trophozoite stage and a cystic stage. The trophozoites inhabit the small intestine, whilst the cyst can survive ejection outside the body. A single host is all that is required to complete the life cycle [18].

When a new human host ingests food or liquid contaminated with the giardial cysts (see the accompanying illustration), the parasite escapes from its protective cyst within the stomach or duodenum, under the influence of stomach acidity and digestive enzymes secreted by the pancreas. The released trophozoites migrate to the small intestine. There they divide repeatedly, each division taking between 9 and 12 hours. Trophozoites which enter the colon are exposed to a neutral pH and bile salts which have been metabolised by bacterial action. This triggers the parasite to re-enter the cystic stage. Cysts leave the host in the stool, ready to parasitise the next host [18].

61.2.2 Mechanism of Injury

The pathogenetic mechanism connecting infection with the parasite and the ensuing diarrhoea and malabsorption from the gut is complex and remains insufficiently understood [19]. Several hypotheses have been proposed to account for the injury to the host, such as damage to the brush border of the intestinal cells, production of enterotoxins, the response of the immune system or the actions of raised adenylate cyclase levels, leading to changes in gastrointestinal motility and over-excretion of fluid into the gut.

It has been shown that the epithelial lining of the intestine becomes more permeable when trophozoites adhere to the surface. The parasite causes a reduction in the absorptive surface area of the microvilli, the villi become shorter, the disaccharidases are less efficient and the balance of different bacterial species in the gut is disturbed. Although these changes certainly occur as a result of giardial infection, it remains to be shown exactly how these changes produce the specific clinical features of the disease [18].

Biopsy specimens from patients who have a proven infection with *Giardia* but no clinical symptoms exhibit atrophic villi in some areas, which may be marked or moderate in intensity. As well as the effect of giardiasis on the epithelial lining, there may be other pathophysiological effects which underlie malabsorption and explain why diarrhoea occurs [8, 20]. Interestingly, biopsy specimens of the small bowel may exhibit no histopathological abnormality in patients with giardiasis in whom diarrhoea is a presenting feature [18].

61.2.3 Diagnosis

The traditional way for giardiasis to be confirmed is through microscopic examination of stool. The stool ova and parasites (O&P) test is to identify trophozoites or cysts of *G. intestinalis*. More recently, tests which do not rely so much on interpretation by the laboratory staff have become more common, such as immunoassays or techniques to amplify the parasite nucleic acids, and the demand for O&P testing is declining [21].

For the purposes of stool microscopy, a fresh specimen may be used or a specimen preserved with polyvinyl alcohol or 10% formalin. Preserved specimens require a stain to be used for microscopy. The best way to perform the test is on three samples from separate days, since the parasite may be present at different levels at different times. Microscopic techniques find the parasite in 50–70% of cases if only a single sample is submitted, but in at least 90% if three samples are submitted [18].

Microscopic examination of the stool is beneficial in diagnostic confirmation of *Giardia* infections between 80 and 85% of the time. Microscopy remains the standard for comparison with newer techniques. Some cases have been diagnosed by showing the presence of *G. intestinalis* in the contents of the duodenum, following their aspiration. However, stool microscopy is both less invasive then duodenal

aspiration and may be more sensitive for diagnostic purposes, as has been shown when the two techniques were compared in studies [18].

Another potential investigation is enzyme-linked immunosorbent assay (ELISA) [22]. The cost of ELISA and O&P are comparable, and ELISA is 88–98% sensitive, as well as 87–100% specific. The most suitable way to employ ELISA is for screening potential cases at high risk, such as those in daycare, or to identify infected individuals in epidemics. It is not appropriate to substitute ELISA for O&P, however [18].

61.2.4 Clinical Management

The standard approach to managing giardiasis is prescription of antimicrobials [23, 24]. There are reports indicating some strains are resistant to particular agents.

Within the USA, the antibiotic used with highest frequency in giardiasis is metronidazole. This agent successfully eradicates 85–90% of infections.

Tinidazole is also a treatment of choice in countries other than the USA. Although not the first choice in the USA, this agent does have a license for use. Tinidazole is administered as a single dose, which is stated to eliminate 90% of infections. The gastrointestinal adverse effects of tinidazole are less of a problem than those with metronidazole. Gastrointestinal upset frequently occurs. In a meta-analysis of trials where paediatric patients were treated for giardial infections with either tinidazole or albendazole, with data for 403 cases, tinidazole exhibited statistically significant superiority to albendazole [25].

The recommendation for treating pregnant women with giardiasis is paromomycin, since this agent has a low level of systemic absorption. It does have the disadvantage that fewer infections are eradicated than when other antimicrobials are administered.

There are several agents for which efficacy is claimed, but which are not licensed for use in the USA. Quinacrine is able to eliminate the parasite in between 90 and 95% of cases, but is an orphan drug in the USA. It is associated with several side effects, such as nausea and vomiting and cramps in the abdomen. These side effects are more common than yellow discolouration affecting the skin, whites of the eyes and urine, which may sometimes occur. Quinacrine is not appropriate in patients with a proven allergy to the drug itself or analogous compounds, if there is a medical history of psoriasis or there has previously been any evidence of psychosis [18].

61.3 Toxoplasmosis

Toxoplasmosis in children may be vertically transmitted or acquired after birth, and may present as an acute or chronic illness. This condition is caused by infection with the protozoal parasitic organism *Toxoplasma gondii*. If the host is otherwise healthy, infection with this organism usually does not provoke symptoms. *T. gondii* is very widespread [26].

Congenitally occurring cases of *Toxoplasma* infection are the most concerning, along with those affecting patients with deficient immunity. Congenital toxoplasmosis occurs by vertical transmission. The parasites within the maternal bloodstream are able to cross the placenta into the foetus. The gestational age of the foetus influences how severe the effects of toxoplasmosis will be on the child. The key abnormalities associated with toxoplasmosis are injury to the visual and nervous system. These abnormalities may be detectable despite any other indications/symptoms of infection with *T. gondii*.

The damage done by congenital *Toxoplasma* infection may become apparent during intrauterine, neonatal or early childhood life. Retinal injury is especially likely to complicate the disease and may not become evident until the child becomes an adult. Severe and complicated toxoplasmosis is a higher risk in patients with immunocompromise, particularly where this affects cell-mediated immunity, as occurs in AIDS.

It is possible to prevent the occurrence of congenital toxoplasmosis. Women should be screened before conception (if possible) and serological follow-up arranged. If a woman presents with negative serology at first screening, advice should be provided [27].

61.3.1 Aetiology

Congenital toxoplasmosis occurs through vertical transmission from the mother. The parasite crosses the placenta into the foetal host. The other forms of toxoplasmosis result from recent infection with *T. gondii* or from a latent infection becoming reactivated. Infections may be linked to eating meat products contaminated with the parasite cysts or coming into contact with cat faeces in which oocysts are present. Risk factors for toxoplasmosis therefore include living in insanitary conditions and eating uncooked or insufficiently cooked meat. It is also possible for the parasite to be transmitted when a blood transfusion is given or an organ is transplanted [28].

Immunodeficiencies in the host, particularly where they involve cell-mediated immune function, as occurs in HIV infection, also raise the risk of developing toxoplasmosis of high severity [29].

Congenital toxoplasmosis occurs when the *T. gondii* protozoon crosses the placenta into the foetus from the maternal bloodstream during a primary infection of the mother. There is only a 40% chance that symptoms of *Toxoplasma* infection appear if the mother is healthy overall. Any symptoms that do occur are generally of mild severity. The usual clinical presentation is of excessive tiredness, feeling generally unwell, low-grade pyrexia, enlargement of the lymph nodes and muscular aches and pains [29]. Toxoplasma parasites are only reactivated in pregnancy, leading to congenital toxoplasmosis in the foetus, if the mother has deficient immunity (typically as a result of AIDS) [29].

There is a classic triad of signs which occurs in congenital toxoplasmosis, namely chorioretinitis, hydrocephalus and calcified lesions within the cranium. However, this is not reliable as a diagnostic criterion, as many cases occur without

manifestation of the triad. Congenital toxoplasmosis cases may present in any of the following ways [29]:

- During the newborn period
- Toxoplasmosis in the initial months following birth
- Complications or reactivation of a previous infection that has not been recognised
- Asymptomatic infection

Congenital toxoplasmosis in newborns resulting in clinical signs is of high severity. During the pregnancy, the foetus may be spontaneously aborted, delivered prematurely or be still born. There are generally non-specific indications of an infection, for example [29]:

- Restricted intrauterine growth
- Pyrexia
- Chorioretinitis (generally both eyes)
- Calcified lesions in the brain
- Abnormalities in the cerebrospinal fluid (xanthochromia and increased cell count)
- Emesis
- Raised eosinophil count
- Abnormal haemorrhage
- Icterus
- Enlargement of the liver and/or spleen
- Enlarged lymph nodes
- Exanthem

There are invariably neurological signs and they indicate a severe lesion. Neurological signs that may be observed include [29]:

- Micro- or macro-cephaly
- Tense fontanelle
- Nystagmus
- Alteration in muscular tone
- Seizures
- Missed milestones in development

61.3.2 Physical Examination

In cases of congenital *Toxoplasma* infection where the presentation is subacute, the presence of symptoms may not be realised until some period has elapsed after delivery [29].

In patients whose immune function is intact, the most frequently presenting clinical feature of acute toxoplasmal infection is lymphadenopathy. Lymphadenopathy usually affects only one group of nodes (especially those in the neck region) and

results in firm, non-tender nodes. As well as the cervical nodes, other potential sites for lymphadenopathy are suboccipital, supraclavicular, axillary or inguinal [29].

Further physical signs to check for include pyrexia (low-grade), exanthem and, in certain cases, enlargement of the liver and spleen. The following may also occur: anaemia, disseminated intravascular coagulation, hepatic inflammation, cholestasis, calcified lesions within the liver, enlargement of the liver and/or spleen, icterus, myocardial inflammation, pneumonitis, premature delivery, exanthemata (of maculopapular, petechial, purpuric or blueberry muffin type), features indicating sepsis, fluctuating temperature and low platelets [29].

Since there may be multiple focal lesions within the brain and spinal cord, the presentation may be similarly varied. The mental state may change or seizures may occur. Motor weakness, cranial neuropathies, changes in sensory perception, cerebellar signs, meningismus, abnormal movements or neuropsychiatric abnormalities may all occur if immune function is compromised. Mass lesions or calcified areas may be noted in the central nervous system. The CSF often exhibits increased cellularity (especially raised lymphocytes and eosinophils), with high protein and low glucose concentrations. Ordinary development may be delayed, hydrocephalus of obstructive type may occur and there may be floppy muscular tone, evidence of micro- or macro-cephaly, nerve palsy and auditory impairment of sensorineural type [29].

61.3.3 Laboratory Investigations

Laboratory-based diagnostic testing for suspected congenital toxoplasmosis involves serological tests, PCR amplification of protozoal DNA as well as other investigations. These tests provide diagnostic clarification and quantify the pathogenic load. These values at baseline help in evaluating how successful eradication using antimicrobials has been. It is possible to isolate *T. gondii* organisms from samples submitted to the laboratory, but this is a time-consuming process and is only undertaken at specific reference laboratories [30].

If the parasite can be demonstrated in blood or other body fluids (including urine or CSF), this confirms toxoplasmosis. Congenital toxoplasmosis may be proven by histopathological methods or by detection of parasitic DNA. This should then be put alongside serological evidence and the clinical picture in confidently diagnosing congenital toxoplasmal infection. Serology is, however, a more commonly employed investigative technique than histopathology, which generally calls for a biopsy to be performed.

Toxoplasmal organisms may also be recovered from amniotic liquor or tissue samples of foetus or placenta and then inoculated into a mouse, allowing the parasite to be isolated alive. In adult patients, activation of lymphocytes when a challenge is performed using toxoplasmal antigens proves the patient has previously been exposed to *Toxoplasma*. Blood or other fluids may be analysed using an ELISA technique (to show toxoplasmal antigens are present) or PCR nucleic acid amplification (indicating presence of the pathogen). Both these methods show

toxoplasmosis is acute. Skin testing with a result indicative of a delayed hypersensitivity response to toxoplasmal antigens has value in screening potential cases.

Other laboratory investigations needed included full blood count with differential white cell counts, liver enzymes, lumbar puncture, creatinine quantification in serum, urinary analysis, viral culture of urine for the presence of cytomegalovirus (CMV), serological quantification of specific antibodies and screening tests to rule out other congenital infective causes, notably CMV, rubella, *Treponema pallidum*, congenital lymphocytic choriomeningitis virus and zika virus [31].

The standard reference test to establish a diagnosis of toxoplasmal infection is the Sabin-Feldman dye test. It is a neutralisation test with high sensitivity and specificity. The test quantifies immunoglobulin G. A high titre for immunoglobulin G indicates acute toxoplasmosis. Since the Sabin-Feldman dye test calls for live toxoplasmal organisms to be present, it is not feasible for the majority of laboratories to undertake testing [29].

An alternative way to quantify the immunoglobulin titre is the indirect fluorescent antibody (IFA) test. The results of the IFA test accord well with those obtained by the Sabin-Feldman test. IFA is a suitable method for measuring immunoglobulins of class M, especially within a week of first infection. It should be noted, nonetheless, that immunoglobulin M levels first rise then fall after a few months have elapsed. The method of measuring immunoglobulin M with the highest sensitivity and specificity is the double-sandwich IgM ELISA method [29].

61.3.4 Clinical Management

The T. gondii organism assumes two different forms, a tachyzoite and a bradyzoite (encysted) form. At present, all recommended treatments principally target the former, whilst being ineffective against the latter. For eradication of the parasite to be adequate, two antimicrobials should be co-administered. To prevent the bone marrow becoming suppressed by treatment, folinic acid (Leucovorin) needs to be supplied along with the antimicrobials. The drug with the highest ability to destroy *Toxoplasma* is pyrimethamine. This agent is therefore recommended in most cases. For the second agent, suitable choices include sulfadiazine, atovaquone and clindamycin. Only if specific contraindications exist should monotherapy be attempted. Two agents not licensed in the US are also potential options, sulfamerazine and sulfamethazine [32].

It is uncertain how efficacious azithromycin, clarithromycin, atovaquone, dapsone and co-trimoxazole (which consists of trimethoprim together with sulfamethoxazole) monotherapy is. Accordingly, these agents must be used in conjunction with an agent of established efficacy, i.e. pyrimethamine. The combined treatment with the highest eradication rate involves pyrimethamine with either sulfadiazine or trisulfapyrimidine. Trisulfapyrimidine consists of a mixture of sulfamerazine, sulfamethazine and sulfapyrazine. This treatment targets tachyzoites. The combination of different agents exhibits synergy.

In cases of toxoplasmal infections occurring during pregnancy, the most suitable medication to administer is spiramycin. This agent is not marketed in the USA, however. Spiramycin is also sometimes required for patients in whom there is a contraindication to pyrimethamine and sulfadiazine [30].

61.3.5 Toxoplasmal Infection and Auditory Impairment

T. gondii is a protozoal organism with an obligate intracellular parasitic lifecycle. It is the pathogen responsible for toxoplasmosis. This condition may be acute or chronic in presentation. The symptoms exhibited in cases of toxoplasmosis include enlarged lymph nodes, encephalitis, inflammation of the myocardium and pneumonitis [33, 34].

Unless there is a degree of host immunodeficiency, acute toxoplasmosis rarely results in symptoms. Indeed, in both adult and paediatric cases of acquired toxoplasmosis, the presence of the parasite is not suspected some 80–90% of the time. Congenital toxoplasmosis involves the crossing of the placenta by toxoplasmal organisms in the maternal circulation. In the later stages of pregnancy, the chances of vertical transmission increase. However, the earlier in the pregnancy the foetus becomes infected, the more severe foetal toxoplasmosis becomes [34].

There is a demonstrated association between toxoplasmosis and damage to the auditory pathways. Calcified lesions are found in the brains of paediatric cases of congenital toxoplasmosis. Furthermore, there are lesions resembling these within the spiral ligament and cochlea. Auditory impairment is noted in approximately one fifth of patients with congenital toxoplasmal infection [35].

61.4 Helminthic Infection

Globally, the helminthic infections which occur with highest frequency are ascariasis, trichuriasis (aka whipworm), hookworm, schistosomiasis and lymphatic filariasis [36]. Hookworm infections are the type most likely to result in a profoundly anaemic patient [37].

Hookworm infections mostly occur amongst older children, but they do sometimes also occur in infants. The usual presenting symptoms are melaena and anaemia. Infant cases may be diagnosed late due to the fact that such infections are relatively rare. Endoscopic examination of the upper gastrointestinal tract (including the oesophagus and duodenum) may reveal the presence of *Ancylostoma* organisms. Treating infants with hookworm infection using albendazole resu

lts in resolution of the anaemia and melaena [38].

The helminthic parasites are a group of worms belonging to two distinct phyla, namely the Nematoda (also known as roundworms) and the Platyhelminthes (i.e. the flatworms). There are two divisions of the flatworms, the Cestoda and Trematoda. The former are also referred to as tapeworms, whilst the latter are often termed flukes.

Helminthic infestations represent a significant threat to the health of populations in all parts of Asia, sub-Saharan Africa and North and South America. The estimated global prevalence of infection with one or more species of helminthic parasites is one billion individuals. The rate of co-infection by at least two different species is also thought to be very high [39, 40].

61.4.1 Hookworm Infestations

There are two different species which are described as hookworms, capable of infecting humans, namely *Necator americanus* and *Ancylostoma duodenale*. The territory inhabited by the former is North and South America, Africa below the Sahara and a portion of Asia. The range of *A. duodenale* is the Mediterranean basin, some of the Middle East and Asia. The prevalence of infection by these two species globally has been suggested to lie between 740 million and 1.3 billion cases [36, 41].

The eggs of hookworms may be detected in soil where faeces has been deposited. Once the eggs have hatched, the larval form grows in the soil prior to entering a human host by penetration of the skin. Migration of these larval forms in the cutaneous system may provoke an exanthem that causes itching. There then occurs haematogenous spread to the pulmonary tissues. The larvae escape from the blood into the alveoli and are carried into the upper part of the respiratory tract. When the host swallows the organism, they penetrate as far as the small intestine, undergoing maturation there and producing the principal symptoms associated with the helminthiasis. The parasite has sharp hooks at the mouth end, and these permit attachment to the lining of the duodenum. Following attachment in this way, the parasite secretes peptides which inhibit coagulation and the action of serine proteases. The inhibition of coagulation allows anaemia to occur, whilst malnutrition is partly the result of the action of the serine proteinase inhibitors.

A hookworm attached to the duodenal wall potential drains 0.3–0.5 mL blood daily from the host [42, 43]. In cases where multiple parasites are attached, the resulting anaemia may be very severe. There is also a loss of protein, leading the patient to be malnourished and anasarca to develop. In the regions where hookworms are normally located, patients are frequently parasitised by several different helminthic organisms, which results in even more severe malnourishment [36].

61.4.2 Roundworm Infestations

The most prolific helminthic parasite feeding on humans globally is *Ascaris lumbricoides*, which is believed to infect between 1.2 and 1.5 billion individuals [36]. The organism enters the human gut when its eggs are inadvertently consumed. These eggs hatch within the small bowel. In an analogous fashion to the hookworm, the larval forms disseminate via the bloodstream, entering the pulmonary tissues, where they can enter the respiratory tract and eventually be swallowed. The presence of *A. lumbricoides* in the lungs may trigger pneumonitis, a situation referred to as

"Loeffler syndrome". Like the other helminthiases, infestation with A. lumbricoides causes inhibition of growth in children, malnutrition and impairs the patient's cognitive abilities [44].

The gastrointestinal tract may become obstructed due to the sheer volume of worms that may be present in cases of helminthic infection and the length of gut they occupy. It has been reported from a specialist facility in Kashmir that infestation with *A. lumbricoides* was the number one reason for gastrointestinal obstruction in paediatric patients [45]. A different study found that intestinal obstruction secondary to *A. lumbricoides* most frequently affected children under the age of 5 years [46]. Inflammation of the gall bladder, pancreas or liver are all possible, if the parasite ascends the biliary tract.

61.4.3 Trichuriasis

Trichuris trichiura is a soil-transmitted helminth of major importance in the paediatric population. When the eggs are ingested, they pass into the small bowel, where the larval forms develop. These larvae then pass into the colon. The behaviour of these parasites differs from that of hookworms and roundworms insofar as they do not enter the pulmonary tissues to re-enter the gut. Infection with *T. trichiura* leads to severe inflammation of the large intestine. Dysentery follows. If the patient is very young, the rectum may also prolapse [37].

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Angiostrongylus cantonensis (the Rat Lungworm) Infection and Hearing Loss

62

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62.1 Introduction

Eosinophilic meningitis has an association with infections caused by three major incidental parasites of humans, namely, *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, and *Gnathostoma spinigerum*. Both *A. cantonensis* and *B. procyonis* have a tropism for neural tissues in their usual host as well as in humans. *G. spinigerum* is capable of infecting both the meninges and the regions external to the meninges. When these parasites infect humans, the infection usually progresses only to a certain point, as the parasite remains in the larval form, unable to reproduce or undergo maturation into the adult form. As the larvae enter the nervous system they provoke an eosinophil-dominated inflammatory response which is also reflected in high numbers of eosinophils in the peripheral circulation [1].

A. cantonensis is a species of nematode within the metastrongyloidea superfamily. Cases of eosinophilic meningitis are frequently due to infection with this organism. The common name for *A. cantonensis* is the rat lungworm. Rats are the definitive hosts, whilst snails or slugs are intermediate hosts. Certain other host

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species also transport the parasite. The region of maximum prevalence for infections with *A. cantonensis* is the Asia-Pacific region, although there are sometimes outbreaks or isolated infections in other parts of the world. Currently, nine members of the Angiostrongylus genus are recognised, with the most significant, from the point of view of their ability to produce disease in humans, being A. cantonensis and A. costaricensis [2, 3].

The parasite most likely to produce eosinophilic meningitis is *A. cantonensis* [4, 5]. The larval forms of this pathogen exhibit a preference for inhabiting nervous tissues [6].

62.2 Aetiology

The definitive host species for *A. cantonensis* is the rat. Adult parasitic worms penetrate into the rat's circulatory system and undergo maturation within the bloodstream. Sexual reproduction occurs within the host, leading to the laying of fertilised eggs, which are released into the circulation. These eggs are eventually deposited in the narrow calibre blood vessels within the lungs and they then hatch at this site. The first stage of larval development sees the parasitic larvae penetrate into the airways and pass upwards towards the upper respiratory tract and pharyngeal region. The larval forms are swallowed into the gut, passing through the host and being deposited externally when the rat defaecates. The intermediate host stage then begins. The parasite is ingested by a snail or slug, and enters this organism. If a rat then eats an infected snail or slug, the lifecycle of the parasite is then completed. The parasitic larvae are by now at their third stage. The parasite preferentially migrates to the brain of the rat, where maturation into the young adult occurs. These organisms then re-enter the venous portion of the rat's circulation, being transported to the lungs, which are the site of sexual maturation. The female nematode produces eggs which hatch in the pulmonary tissues. There are some other potential stages in the lifecycle of the parasite. Paratenic hosts (also referred to as transport hosts) are organisms which harbour the parasite but are not crucial for it to complete its lifecycle. They ingest the parasite in larval form from the true intermediate host and are then themselves eaten by the definitive host (i.e. a rat). Paratenic hosts include carnivorous snails, frogs, lizards, prawns, crabs or freshwater shrimps. If vegetable matter is contaminated with snail slime, the parasitic larvae may also be ingested from this source [2, 3, 7].

Human beings are not definitive hosts for *A. cantonensis*, but they may act as incidental host if they ingest parasite-infected intermediate or paratenic species, or snail slime containing parasitic larvae. The behaviour of the parasite in the human resembles that seen in the definitive host. Faecal-oral transmission is a key component. The ingested parasites penetrate the circulation via the mucosal lining of the gut. In the bloodstream, maturation occurs, the adult nematode worms depositing her eggs in the smallest calibre vessels of the pulmonary circulation. Once these eggs hatch, there is larval migration up to the pharynx, causing coughing. The larvae are then ingested once again and progress through the gastrointestinal tract, leaving

the body when the patient defaecates. Intermediate hosts (snails or slugs) ingest the larvae, which are at the first stage of their development. If a rat or human consumes the intermediate host when the larvae have reached the third stage, these larvae can penetrate the circulation and preferentially migrate to the central nervous system. In nervous tissue, the parasite finally assumes its adult form. The adult worms migrate via the veins draining the brain towards the heart, then into the lungs, where full sexual maturity occurs. They are then lodged in the smallest calibre vessels of the pulmonary arterial circulation. The female deposits eggs here.

Whilst the parasite inhabits the brain, particularly the subarachnoid space, it triggers a powerful inflammatory response by the host, with eosinophils predominating. This is manifested as acute eosinophilic meningitis. If the parasitic load is high, there will be other sites of inflammation in the patient, resulting in different clinical pictures, namely radiculitis, neuropathies of the cranial nerves, myelitis, encephalopathy and coma. In some cases, mortality of the host ensues. However, since the nematode itself perishes within the brain of patients, whatever the clinical outcome, there is no direct human-to-human transmission [8]. Generally speaking, the infection incubates for between 1 and 3 weeks, but in some cases, the incubation may last up to 6 weeks [2].

62.3 Epidemiology

The principal areas where cases of eosinophilic meningitis secondary to infection with A. cantonensis present are located is Southeast Asia, especially Thailand and Malaysia. Cases also occur in the south of Vietnam and across the Pacific region, such as Indonesia, the Philippines, Taiwan, China, Japan, Papua New Guinea, Hawaii, and some of the small islands which are abundant in this region. The range inhabited by *A. cantonensis* has been extended by ships on which infected rats have been carried, such that cases have been recorded in African and South American countries, Australia, Cuba, Puerto Rico, and on other Caribbean islands [6, 9–15]. The continental United States has also witnessed cases, beginning in New Orleans, then extending into Louisiana and the states of the Southeast more generally [16]. Isolated cases have also been reported from European countries and parts of the USA remote from Louisiana. In some cases, there was a history of travel to an endemic area, but in others no such connection was established [6, 16, 17].

As described above, the lifecycle of *A. cantonensis* is relatively complex. The cycle starts when the adult nematode lays its eggs in the pulmonary artery of the definitive host, the rat [18]. Larvae emerge, which move towards the pharyngeal region, then pass down through the length of the gut, emerging when the rat defaecates. The third larval stage occurs within the intermediate host, a snail or slug. They enter the intermediate host when the snail ingests the larvae within the rat stool. This invertebrate host may then be eaten by another rat, at which point the nematode larvae penetrate into the central nervous system. Here, maturation into the adult occurs. The adults re-enter the circulation, entering the pulmonary vasculature, where again the cycle begins.

A human host may be infected if a person eats uncooked or insufficiently cooked snails or slugs harbouring third stage nematode larvae [19]. Infected larvae may also be found on vegetable matter that has not been cooked [20]. The larvae, as described above, may also be ingested if a paratenic host is eaten. Examples of paratenic hosts eaten by humans include crabs, freshwater shrimps or centipedes [21]. When humans are the incidental host, the parasite still exhibits a tropism for the nervous, or occasionally, pulmonary tissues, but is unable to lay its eggs, so the infection does not pass on from the human.

The average incubation period for rat lungworm infection is from 1 to 3 weeks, but the reported range is from 1 day to above 6 weeks [22].

For children, playing in the dirt in countries where the parasite is endemic represents the main risk. There is also a risk from eating some local delicacies in endemic regions (such as raw caterpillars) [23]. However, even in those regions where *A. cantonensis* has endemic status, it is unusual for outbreaks to occur. The literature contains a report of an outbreak of eosinophilic meningitis secondary to *A. cantonensis*, acquired as a result of travel to Jamaica [1, 11].

62.4 Clinical Features

The larval forms of *A. cantonensis* exhibit tropism for the brain or the eye. Nervous system involvement manifests from 2 days to 5 weeks after infection begins. The usual presentation is as short-lasting meningitis. A somewhat less frequent presentation is with severe disease of the central nervous system and roots of the nerves [5, 24, 25]. The most frequent symptom at case presentation, manifested in above 90% of cases, is an extremely severe headache, generally localised to the frontal or occipital regions or both temples. When a lumbar puncture is performed, the severity of the headache usually decreases. It is common to find that the initial CSF pressure is raised [26].

Patients frequently exhibit nuchal rigidity, complain of nausea and vomiting and experience paraesthesiae. Pyrexia may not occur [27]. A study reporting on an outbreak affecting 12 patients found that three quarters of cases featured paraesthesia or hyperaesthesia affecting the limbs and/or truncal region [11]. In some cases, there is persistence of paraesthetic or hyperaesthetic symptoms beyond the point where resolution of other symptoms has already taken place. In 4–9% of cases, the extraocular muscles or the nerves supplying the face are paralysed, although the paralysis typically is not permanent [28–32]. Mortality seldom occurs [33]. A study which looked at the outcomes in 484 patients presenting with eosinophilic meningitis discovered that a fatal outcome occurred in fewer than 0.5% of patients [34].

The central nervous system is more frequently affected than the eyes, although the larvae may invade the vitreous humour. If this occurs, the patients may complain of blurred vision in one eye, but there may be no signs of meningitis [1, 35, 36].

62.5 History and Physical Examination

The clinical presentation in cases of infection with *A. cantonensis* result from the vigorous inflammation triggered by the parasites, which is triggered by their death. The most frequently occurring clinical syndrome to result from infection with *A. cantonensis* is eosinophilic meningitis. The most common symptoms are headache, nuchal rigidity, nausea and vomiting. Paraesthetic or hyperaesthetic symptoms may persist for a number of weeks. Although eosinophilic encephalitis occurs rarely, it is life-threatening, since treatment is generally too late. Invasion of the eyes by the parasite may present as feeling there is something in the eye, when the anterior chamber is involved, and vision is blurred, if the vitreous humour is the site of invasion [37–39].

The central nervous system manifestations include a headache of high severity of a type the patient has not previously experienced, coupled with paraesthetic symptoms, including burning, tingling sensations or being overly sensitive to touch. The headache is not relieved by NSAID treatment. A distinctive feature of the presentation is a shifting paraesthesia. This tends to follow a track along the truncal region and limbs, although it does not correspond to the distribution of specific nerves or dermatomes. There may occur a palsy of the abducens or facial nerves. For unclear reasons urinary retention may also occur. The gut is generally affected before the onset of clear symptoms of neurological involvement. The incubation period is typically from 1 to 3 weeks, but may be extended up to 6 weeks after inoculation. At this initial stage, there may be poorly localised abdominodynia, nausea and vomiting. These symptoms are triggered by invasion of the parasite through the lining of the gut. Neurological symptoms begin when the larval parasite has invaded the brain via the circulatory system. Since it takes a minimum of 1 week for the parasite to enter the brain via the bloodstream, there may potentially be a period during which symptoms do not occur, if the gastrointestinal symptoms quickly resolve. Vomiting may also be triggered by irritation of the meninges. There may also be other symptoms of a more general kind, such as loss of energy, mild pyrexia, insomnia or confusion. Paediatric cases generally manifest gastrointestinal disturbance more prominently than symptoms indicating nervous system involvement. When examining the patient physically, the abdominal and neurological examination require extra focus [2].

62.6 Diagnosis

In the majority of cases, diagnosing nervous system infection with *A. cantonensis* depends on an appropriate clinical history and examination, CSF analysis indicating raised eosinophils and a history revealing potential contact with the infective larval forms of the parasite [1].

CSF analysis should show raised numbers of eosinophils. There is generally a degree of cloudiness to the CSF, but not to the extent where frank turbidity or xanthochromia are observable. The white cell count is in the range 20–5000 cells per

cubic millimeter, typically between 150–2000 cells per cubic millimetre. The eosinophils generally represent between 20 and 70 per cent of the total white cells. In 95% of cases, eosinophils will account for at least 10% of CSF leucocytes [28–31]. The protein level is also generally high, whilst the glucose level is either normal or very slightly above normal [28–31].

There is adequate sensitivity for amplification of *A. cantonensis* DNA by polymerase chain reaction on samples of CSF [40]. Two studies which reported on cases of eosinophilic meningitis found a sensitivity of 67% for detection of parasite DNA in CSF taken from patients with eosinophilic meningitis [40, 41]. Potentially, sensitivity for detection of pathogenic DNA has now risen, thanks to the newer techniques now in use [42, 43].

Another diagnostic test of potential value is ELISA (enzyme-linked immunosorbent assay) [44]. The latest immunoassay techniques have the sensitivity to distinguish between eosinophilic meningitis secondary to *A. cantonensis* and that due to *Gnathostoma* infection [45, 46]. There is still, nonetheless, restricted availability of the latest techniques.

A small number of case reports detail the way next-generation molecular sequencing has been employed to analyse CSF samples [47, 48].

Diagnosis of eosinophilic meningitis secondary to *A. cantonensis* does not call for isolation of the parasite. In any case, this has rarely proven possible except where fatality has occurred [1].

Venous eosinophilia is generally seen in conjunction with the raised numbers of eosinophils in the CSF. For most cases, eosinophils account for more than 3% of the white cells. There is no direct correlation between eosinophil levels in the circulation and in the CSF, nor does the blood level reflect the clinical condition of the patient [1].

62.6.1 Radiological Investigations

There are few features of note on CT imaging, however, the fact that there are no foci of disease does help to differentiate cases of eosinophilic meningitis secondary to *A. cantonensis* from those due to *Gnathostoma* or *Taenia solium* [49]. When magnetic resonance imaging is performed, the signal from the globus pallidus and cerebral peduncle may be heightened on T1 weighting. If T1 weighting is used together with gadolinium enhancement, the leptomeninges are enhanced, the ventricles appear enlarged and there are points within the cerebrum and cerebellum with an abnormally enhanced character. T2 weighting shows hyperintense signals [50–52].

62.7 Auditory Impairment

There are differences in how nervous stem infections with *A. cantonensis* present in adult and paediatric patients [5]. In 95% of adults the presenting symptom of neuroangiostrongyliasis is a headache of high severity [53, 54]. The pain is typically perceived throughout the head and lacks any focus. It is often described as feeling like the head is exploding. The usual duration is between 1 and 7 days [55]. Some 40% of patients exhibit nuchal rigidity, which is an indicator of more severe disease [53, 56]. In around 40% of patients, paraesthesiae are reported, usually with a duration of no more than 14 days [30]. Paraesthetic sensations include numbness, pruritus or feeling as if there were worms moving under the skin. Vomiting occurs in 38% of cases and nausea in 28%, in conjunction with a headache. Problems with vision, including double vision, is noted in between 38 and 92% of patients [57]. Pyrexia is observed in 32% of adults with neuroangiostrongyliasis, but only 10% have pyrexia of high grade (i.e. between 38 and 39 °C) [54]. Palsies affecting the abducens and facial nerves are uncommon, as are auditory impairment, gastrointestinal obstruction, or indications that the spine is affected [5, 55, 58, 59].

In paediatric cases of eosinophilic meningitis secondary to infection with *A. cantonensis*, nausea and vomiting are considerably more frequent, being seen in 82% of cases. Pyrexia occurs in 80% of children, 80% exhibit sleepiness, 76% are constipated, 40% suffer abdominodynia, there is weakness of the extremities in 20% and seizures or twitching are more liable to be observed than in adult cases [54]. Furthermore, more than half of paediatric cases present with projectile vomiting, but this typically ceases in less than a week [30]. In comparison with adult cases, paediatric cases have a decreased incidence of paraesthetic symptoms or nuchal rigidity [5, 57].

It is difficult to account for the mechanisms underlying these symptoms, since neither the extent of central nervous injury caused by the migrating parasite nor the immune system response to the presence of living or complete parasitic larvae correspond in severity to the symptoms observed. The immune response is less than might be expected [60, 61]. However, it is clear that the dead (as opposed to living) parasites do mainly account for the eosinophil-dominated immune response. The presence of dead parasites triggers the increased expression of certain inflammatory signalling molecules (both cytokines and chemokines) which act to recruit and attract eosinophils to an area, namely interleukins 5, 12 and 33, as well as eotaxin (CCL11). T helper 2 cells orchestrate this response [62–65]. The resulting inflow of cellular immune mediators and fluid into the brain causes the CSF tension to rise, triggering headache [5, 30, 34].

62.8 Treatment

How severe and how long neuroangiostrongyliasis lasts depends on the number of parasites present in the host. The majority of cases resolve with conservative/supportive treatment alone. The therapeutic aim is to lessen the degree of irritation to the meninges and lessen the CSF tension by draining CSF, whilst offering palliative treatment of headaches. The use of corticosteroids in the form of prednisolone or dexamethasone, with the aim of damping immune reactivity has been shown to lessen the time for which headache occurs and decrease the need for CSF to be repeatedly removed by lumbar puncture [66]. In the past, it was advised that anti-helminthic agents were best avoided, as they may trigger massive release of parasite antigens, causing a more severe inflammatory response by the host immune system. However, it has since been demonstrated that anti-helminthic agents can be safely employed for this purpose and should be potentially employed if the parasitic burden is high. Nonetheless, no additional benefit has been shown to result from adding anti-helminthic agents to corticosteroids [67, 68].

Parasitic invasion of the eyes has a frequency of 1%, when the literature describing cases of *A. cantonensis* is considered as a whole. This invasion is into either the anterior or posterior chamber of the eye. Precisely how this invasion occurs has never been established, but one likely mechanism is for the larvae to migrate along the retinal artery lying adjacent to the optic nerve and its sheath. Generally a single parasitic larva is involved. The associated symptoms are blurring of vision, loss of vision and ocular discomfort. Most such patients also have eosinophilic meningitis. If the larva has penetrated the eye, it needs to be destroyed using a laser and then removed by surgical means [2].

No body has yet published guidelines for the management of neuroangiostrongyliasis. The following recommendations are, however, supported by the evidence base. Real-time PCR DNA amplification can be undertaken on CSF to confirm the presence of *A. cantonensis*. If the initial PCR is negative but clinical suspicion remains high, the lumbar puncture should be repeated and PCR undertaken once again. It is not recommended that serology be undertaken for specific immunoglobulins, either in CSF or blood.

Therapeutic measures should include administration of corticosteroids to lessen the severity of the immune reaction to dead or dying parasites. Albendazole is suitable as an anti-helminthic, but should not be administered without accompanying steroids. In patients with diabetes mellitus, there needs to be careful adjustment of the blood glucose during treatment [2].

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Part VIII

Prion Diseases

Prion Diseases and Hearing Loss

63

Alaattin Zirek, Nurten Küçük, and Nuray Bayar Muluk

63.1 Definition

There are multiple prion diseases which affect humans as well as other animals. They all share the feature of neurodegeneration [1]. Creutzfeldt-Jakob disease (CJD) and Gerstmann-Sträussler-Scheinker (GSS) are prion diseases affecting humans. Cattle may suffer from bovine spongiform encephalopathy (BSE, colloquially referred to as "mad cow disease") and sheep may succumb to scrapie. Prion diseases also affect wild animals, notably chronic wasting disease (CWD) in mule deer and elk. Prion diseases are characterised by lengthy incubation followed by a rapid deterioration shortly after symptoms first appear. At present, prion diseases invariably result in death, and no therapy has proven efficacy. Nonetheless, growth in scientific knowledge about the pathogenetic basis of prion diseases means that avenues for potential therapeutic intervention are now becoming clearer [2].

A unique feature of prion diseases is how they appear to be heritable, may occur sporadically or may be linked to an infective event. In prion diseases, there is a glycoprotein produced by the host which folds in an abnormal way, forming the prion protein, which acts as the agent of infection. Prion proteins replicate by inducing a

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conformational change in normal glycoproteins of the same type, so that they too become prion proteins. The normal proteins have a structure with mostly alpha helical elements, whereas the prion protein configuration results in beta sheets predominating [3].

63.2 Pathophysiological Features

The neuropathological characteristics of the prion diseases show many similarities to each other. The grey matter within the brain and spinal cord is the most affected area, leading to loss of neurones, proliferation of the glia and spongiform change, with characteristic microscopic appearances. The neuropil forms vacuoles, which are also seen within the neurones themselves [2].

Plaque formation is also seen neuropathologically in many prion diseases. These plaques stain in a way characteristic of amyloid. Congo Red-stained plaques exhibit apple-green birefringence using polarised light. Around 10% of cases of CJD are found to have amyloid plaques in the cerebellar or cerebral regions. GSS invariably results in the formation of multicentric plaques in the cerebellum. When immunoglobulins specific to the prion protein are applied, they adhere to the plaques, but immunoglobulins with specificity for other proteins that form amyloid deposits, e.g. amyloid beta, which is present in Alzheimer-type dementia, are non-adherent [2].

63.2.1 Prion Protein

The normal (non-disease causing) form of the prion protein (PrP^C) is located within both neurones and cells of other types within the human central nervous system. It is bound to cellular membranes by glycophosphatidylinositol [4, 5]. It is a cellular protein (hence the "c" in the abbreviation). The neuronal cell membrane contains this protein, which may be abundant in the region of the membrane forming synapses [6]. Part of the PrP^C molecule spans the plasma membrane, forming the transmembrane domains. The protein undergoes intracellular degradation by first being endocytosed and then broken down within vesicles with a high pH. Some of the PrP^C is not dismantled, but instead returned to the cell membrane [7]. There is also secretion of PrP^C [8].

63.2.2 Molecular Biology of the Non-pathogenic PrP Protein

The PrP protein is encoded in the PRNP gene located on chromosome 20. The protein contains some 253 amino acid residues. PrP^C is a glycoprotein which is attached to the outer cell membrane by glycosylphosphatidylinositol. Its function within the cell is currently not understood, although potential roles include intercellular adhesion or signalling. It has been speculated that PrP may be involved in the movement or metabolism of copper ions, since a portion of the N-terminal region consists of

an octapeptide sequence that is repeated five times. This octapeptide sequence binds copper ions strongly. Furthermore, it now appears that the early stages of prion diseases involve dysequilibrium of copper metabolism [9]. Since the PrP^{C} protein sequence is largely unaltered in mammalian species and the protein occurs in every vertebrate, it is likely to perform a vital role of some sort [10, 11]. Yeast have also been found to express the proteins PSI and URE3, which resemble the prion protein [12].

Although expression of PrP occurs in the majority of human tissues, the highest concentrations are found within the brain, especially in neurones. Many immune cells also produced PrP. In murine models, where the PrP gene has been excised from the genome, there does not appear to be any resulting disease [13] other than some unusual features in how the synapses function [14], in sleeping behaviour and processes following a circadian pattern [2, 15].

63.2.3 The Route by which Prions Enter the Central Nervous System

Transmission of prion diseases may occur via the peripheral tissues. Prions may enter via the mouth or cross through the cutaneous barriers. The route and mechanism by which prions enter the brain is of considerable importance to understanding the pathophysiology of prion diseases. The manifestations of prion diseases all affect the nervous system. However, it is clear that there are important events which occur on the route towards the brain, but before the infectious agent enters the nervous system. In particular, the peripheral lymphoid organs appear to play a role [16].

Researchers have understood for several years that the lymphoid organs play a role in the pathogenesis of prion disorders [17–20]. It has been demonstrated that the PrPSc proteins replicate initially in the spleen and lymph nodes. Intracerebral challenge also causes significant alterations in the spleen and lymph nodes. In studies where the spleen was surgically excised or lymphoid organs were removed in various ways, the ability of prions to enter the central nervous system was significantly delayed compared to where the lymphoid organs remained fully functional [18].

It has also been demonstrated that transfusing blood from an infected sheep to another sheep is a way of transmitting BSE. This indicates that prions can enter the central nervous system via the blood [20]. It has also been recorded by the Health protection Agency that three patients developed new variant Creutzfeldt-Jakob Disease following transfusion of whole blood. The transfusions all involved donor blood which had not been depleted of its white cells [2].

The first case of transfusion-associated new variant CJD (vCJD) was described in 2003, some 6.5 years after a transfusion from an individual who died 3.5 years after donating the blood. The cause of death of the donor was vCJD. A second individual died 5 years after receiving blood thought to contain prions, although death in the recipient was not due to vCJD. A postmortem examination showed prion accumulation in the spleen and lymph nodes of the neck. The brain did not contain

lesions consistent with vCJD, nor were there other histopathological features suggestive of prion disease. The donor of the infected blood became symptomatic with vCJD 1.5 years after donation. In the last case noted, vCJD was diagnosed in 2006 in the recipient of blood from an individual who was also diagnosed with vCJD some 20 months after having donated the blood [2].

The apparent necessity for B cells to be present for prions to invade the nervous system from the blood has been demonstrated [21]. Nonetheless, for prions to invade the CNS, it does not appear necessary for the B lymphocytes to express the prion protein. Their role may therefore relate to their interactions with follicular dendritic cells [22]. Most recently, studies suggest that neither cell type plays an essential role in the pathogenesis of prion disorders [23]. Some other studies have produced evidence to link neuroinvasive behaviour by prions to CD11c + dendritic cells [24, 25].

Another way in which neuroinvasion may occur is via the parasympathetic division of the tenth cranial nerve [26]. When prions are introduced artificially into the peritoneal cavity, the onset of prion disease is more rapid when the lymphoreticular organs are hyperinnervated but slower if a sympathectomy is performed [2, 27].

63.3 Aetiology of Prion Diseases

The exact nature of the infective agent in prion disorders has been widely debated, with various candidates advanced, such as nucleic acid or protein alone, a combination of protein with nucleic acid or a polysaccharide. Currently, however, the majority view is that a protein alone is the infectious agent. This was the theory first articulated by Griffith [28] and later described in greater detail by Prusiner [29]. Prusiner coined the term “prion” to describe an infectious particle consisting of a protein responsible for scrapie [30].

The prion theory to explain these disorders was at first strongly rejected by many researchers, only gradually winning acceptance. Prusiner was actually awarded the Nobel Prize for Physiology or Medicine in 1997 for this work. The theory states that the prion lacks any nucleic acid component. The abbreviated term used to refer to a protein-only infectious agent is PrPSc (Sc stands for scrapie). PrPSc consists of the same amino acid sequence as a normal protein found within cells, namely PrP^{C}, but which has adopted an abnormal conformation, changing its function. The normal form, PrP^{C} is a membrane protein expressed physiologically in a variety of cells, especially neurones. The prion protein, upon encountering PrP^{C}, causes it to refold into the prion form, which then generates more abnormal protein, such that it continuously builds up [29]. It appears from one study that the C-terminal region of PrPSc plays a necessary role in turning the protein into an infectious prion [31].

Other theories have been advanced to account for prion pathophysiology. One such is the virino hypothesis [32]. According to the virino hypothesis, the infectious agent is formed from a nucleic acid coated in PrPSc of host-origin. The PrPSc would then be a kind of protective coat. This hypothesis may account for the absence

of an apparent immune inflammatory reaction to the presence of the prion. Different sequences of nucleic acid may explain why there are several different and quite distinct strains of scrapie. Evidence from recent research may be supportive of the virino hypothesis, as it has shown that pure PrPSc has a low infective potential. Furthermore, entry and exit of nucleic acids across cell membranes appears to be modulated by this protein. The PrP protein can attach itself to nucleic acids and initiate reverse transcriptase activity. PrP may be bound to retroelements, and variety in these retroelements may be an explanation for why there are so many different forms of transmissible spongiform encephalopathy [2, 33].

63.4 Diagnosis

GSS may be diagnosed on the basis of sequencing the PRNP gene. In all cases so far, GSS is always associated with mutation of the gene. Genetic testing has satisfactory sensitivity and specificity. In a case reported where familial GSS was already suspected, it proved possible to identify the mutated gene in an embryo before implantation could occur [34].

The central nervous system should only be biopsied if the suspected diagnosis is a condition for which treatment is available [35].

Laboratory-based and radiological investigations are of more benefit in diagnosing sporadic CJD than for the diagnosis of GSS. In most patients with GSS, the levels of tau and 14–3-3 protein are normal in cerebrospinal fluid (CSF). The CSF real-time quaking-induced conversion (RT-QuIC) test is positive in some cases, but RT-QuIC has lower sensitivity in GSS than in sCJD [36]. Electroencephalography (EEG) in cases of GSS potentially reveals slowing, but there is no corresponding abnormality in GSS to the periodic sharp wave complexes that are so typical of sCJD [35].

Magnetic resonance imaging of the central nervous system in these patients lacks both sensitivity and specificity, but potential abnormal findings include decreased signal on T2 weighting in the striatum and midbrain for certain patients [37], and the cerebellum and cortex may exhibit structural abnormality, i.e. they are non-specifically atrophied [38]. In rare cases of GSS, hyperintensity on fluid-attenuated inversion recovery (FLAIR) and/or diffusion-weighted imaging (DWI) sequences in the basal ganglia and/or cortical ribbon may be demonstrable. These abnormal appearances frequently occur in cases of sCJD [35].

It is not usual to undertake more advanced imaging studies of the central nervous system in cases of suspected GSS but various techniques may sometimes be used. SPECT (single-photon emission computed tomography) may show a widespread increase in the flow of blood to the brain. According to one study, early stage GSS can be detected by reduced flow of blood to the occipital lobe and spinal cord [39]. This finding has a high attached sensitivity. Although neuropathological findings include formation of amyloid plaques in cases of GSS, there is no corresponding apparent uptake of amyloid tracers on positron emission tomography [35, 40].

63.5 Clinical Presenting Features

The clinical presentation in CJD is the subject of chapter _____ in this volume.

63.5.1 Gerstmann-Sträussler-Scheinker Disease (GSS)

63.5.1.1 Epidemiological and Genetic Characteristics

Gerstmann-Sträussler-Scheinker syndrome (GSS) is a very infrequently occurring inherited prion disorder affecting human beings. There are between 1 to 10 cases per 100 million population noted each year [35].

GSS demonstrates an autosomal-dominant pattern of inheritance and is highly penetrant. There are a number of distinct point mutations responsible, in addition to repetitive insertions of an 8-peptide repeated sequence. Globally, a minimum of 24 unrelated kindreds have been discovered. Although the mutation occurring with the highest frequency is P102L [41–43], there are multiple other known mutations associated with GSS [44–49].

63.5.1.2 Neuropathological Features

The characteristic neuropathological findings in cases of GSS are multicentric plaques composed of amyloid and found in various locations within the brain, although especially in the cerebral cortical areas, basal ganglia and cerebellum [50]. Although spongiform degeneration is frequently noted, it is not always seen in every case. Microscopy of the brains of cases from multiple different kindreds reveals neurofibrillary tangles and neuropil threads indistinguishable from the ones noted in dementia of Alzheimer type [51, 52]. The prion protein in cases of GSS differs biochemically from that found in CJD. GSS-associated PrP forms short fragments at the C and N-terminal ends which resist degradation by proteases [35].

63.5.1.3 Clinical Presentation

The classic clinical presentation of GSS features progressive deterioration of cerebellar function with parkinsonian features and occurring in individuals in early middle age (on average between the ages of 43 and 48 years). Dementia is also noted. In a few cases, these symptoms may not begin until a decade later (i.e. between the ages of 54 and 58 years).

Dysfunction of the cerebellum is noted clinically as clumsy, uncoordinated movement with an ataxic gait. At an early state, dysaesthesia may be observed. The reflexes are reduced and the proximal muscles of the lower limbs are weaker than usual [39]. Myoclonus is not usually a feature, but it may be seen at a late stage of the disease. There is some variation in the extent to which dementia affects different families afflicted with GSS, or different family members [52–54].

63.6 Diagnosis

GSS may be diagnosed on the basis of sequencing the PRNP gene. In all cases so far, GSS is always associated with mutation of the gene. Genetic testing has satisfactory sensitivity and specificity. In a case reported where familial GSS was already suspected, it proved possible to identify the mutated gene in an embryo before implantation could occur [34].

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63.6.1 Auditory Impairment

There are case reports in the literature concerning GSS. Three describe the clinical findings, whilst two supply information on the histopathology. GSS is a subacute spongiform encephalopathy with a very low frequency. To date, the disorder has only been diagnosed in 52 individuals. There patients came from four large families. The patients became symptomatic between the ages of 33 and 50 years, with death

occurring 4–5 years after the onset of symptoms. There are descriptions of symptoms indicating involvement of the cerebellum, myoclonia and eventual dementia. Furthermore, symptoms indicating damage to the bulb and pyramids are also said to be characteristic. In two cases, there was impairment of both visual and auditory function. Analysis of blood and CSF did not reveal any abnormalities in these cases. Electroencephalographic studies indicated a generalised slowing that kept worsening, but no periodic dysrhythmia. Evoked potentials were not consistent with loss of myelin. The principal way to reliably distinguish between GSS and CJD is by histopathology. Cases of DSS are distinguished in the majority of cases by the presence of kuru plaques and in all cases by multicentric plaque formation. The cortex indicates spongiform degeneration with some neuronal loss and neurogliosis. The blood vessels supplying the cortex have some degenerative changes, but these are of a very mild degree [55].

63.6.2 Fatal Familial Insomnia

63.6.2.1 Epidemiological and Genetic Features

Although the first cases of fatal familial insomnia (FFI) diagnosed were all in families in Italy, there have subsequently been several disease kindreds identified globally [55]. FFI follows an autosomal pattern of inheritance. Its cause is a missense genetic mutation on the 178th codon within the PRNP gene and a methionine substitution on the 129th codon. This gene is found at the location 20p13 [56–60].

There is also a sporadic form of fatal insomnia (sFI). In these cases, the clinical picture and histopathological appearances are highly similar to those seen in the familial form. Genetic testing does not, however, reveal a mutated allele as seen in FFI [57–60].

63.6.2.2 Neuropathological Features

There is a loss of neurones accompanied by proliferation of neuroglial cells, appearances which are consistent across the range of patients with FFI [60–63]. These alterations are most pronounced in the thalamus, but may also be seen in the cortical region of the cerebellum, in the cerebellar nuclei and in the nuclei of the olive. There may be sparing of the cerebral cortex, which may result in a falsely negative result to preliminary brain biopsy [35].

In FFI, the extent of the inflammatory reaction is generally considerably less than that observable in prion disorders of other kinds. Usually inflammation is only visible in the entorhinal cortex [62–64]. Whereas spongiform degeneration is virtually ubiquitous in other prion disorders affecting humans, it is seldom noted in cases of FFI, especially if both mutated alleles code for methionine [35, 62].

63.6.2.3 Laboratory and Radiological Investigations

It is unusual to note any distinctive features for cases of FFI when imaging is undertaken using computed tomography or magnetic resonance imaging. Positron emission tomography (PET) using 18-F fluorodeoxyglucose indicates that the thalamus

consumes less glucose that usual. This feature may be apparent even where the patient is still asymptomatic [65–67].

Analysis of CSF generally provides few clues. The total tau protein content is not raised nor is 14-3-3 protein present. RT-QuIC is not generally positive [68, 69].

There are no sharp wave complexes identifiable on electroencephalography [35].

63.6.3 Variant Creutzfeldt-Jakob Disease (vCJD)

The last few decades have witnessed the emergence of a novel form of prion disease related to bovine spongiform encephalopathy, which led to the death of above 160,000 cattle in the UK [70]. The evidence seems to indicate that this epidemic arose after cattle were given agricultural feed manufactured from sheep infected with scrapie or other cattle infected with BSE. Amongst the cases of BSE there are also cases of CJD with novel features, termed vCJD [71]. This novel prion disease also affects human beings, with two cases dating from 1995 found to have resulted in death. The victims were two teenaged patients in the UK [2, 72, 73].

At present, there have been only four reported cases of sporadic CJD in teenaged patients. The peak age at which sporadic CJD occurs is between 60 and 65 years. Therefore, the occurrence in teenaged patients is highly unusual. Furthermore, the neuropathological features of vCJD are unusual. There are multiple amyloid plaques, which resemble the PrP amyloidosis seen in cases of kuru [74, 75]. Florid amyloidosis also occurs in chronic wasting disease [2, 76].

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Sporadic Creutzfeldt-Jakob Disease and Hearing Loss

64

Çiğdem Fırat Koca, Turgut Celik, and Emmanuel P. Prokopakis

64.1 Introduction

Prion diseases of the central nervous system share the distinguishing characteristic that their aetiology is a proteinaceous infectious agent, namely a prion. One specific prion disease, Creutzfeld-Jakob disease (CJD), has been known for more than 100 years. This disease has seldom been reported to cause an initial presentation with manifestations affecting the ear, nose or throat. However, although the usual presenting features include irreversible, progressive cognitive decline, defects in the visual fields and ataxia, it is possible for patients with underlying CJD to present with vertigo or auditory impairment [1].

CJD is an infrequently occurring spongiform encephalopathy. Cases of CJD initially feature constitutional signs, but cognitive decline and abnormalities of movement then become apparent. From an ENT perspective, the most frequent symptom is vertigo. The number of case reports available that list acute deterioration in hearing as the initial presenting complaint is very small [2].

The most frequent ENT-related presenting complaint described in case reports is vertigo. At present, a mere handful of case reports mention auditory loss as the

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principal symptom at first presentation [1, 3]. A case of auditory loss of a progressive type and affecting both ears was described by Tobias et al., and deemed to be of cortical type since the patient produced phonological mistakes indicative of an abnormality in the way language was processed centrally [3]. In another case, the presenting complaints were feeling the ear was full and alteration in the ability to hear [1]. When audiometry is undertaken, the results may show a characteristic pattern, namely that the pure-tone auditory loss is less than what may be expected on the basis of word discrimination testing [4].

Sporadic CJD (sCJD) invariably leads to insomnia and death. It is a prion disease with a varied degree of sensitivity to the action of proteases [5]. Amongst the human prion disorders of sporadic type, sCJD has the highest frequency (90% of cases) and is the most well understood [6].

There are a number of neuropathological features which all the prion disorders found in humans have in common, such as the death of neurones, neurogliosis, lack of evidence of immunoreactivity, vacuolation of the neuropil giving rise to the spongiform appearance and evidence of prion accumulations. These prions are generally not degradable by the action of proteases [5].

64.2 Epidemiological Characteristics

Whilst CJD is the prion disorder in humans with the highest incidence, it is still a very infrequently occurring condition. There are several forms of CJD, such as sporadic (sCJD), genetic (gCJD), iatrogenic (iCJD) and new-variant (vCJD). Most cases of CJD are due to sCJD, which accounts for 85–95% of known cases. The genetic form of the disease may be responsible for between 5 and 15% of cases, whilst the iatrogenic and new-variant types typically occur in at most 1% of cases [7, 8]. The yearly incidence of sCJD is around 1 or 2 per 1,000,000 people. Cases occur in every population and are found across the entire world [9].

The average age at which CJD occurs is around 62 years, with a range that covers both young adulthood and the ninth decade of life [8, 10–13]. The age range for new-variant and iatrogenic CJD cases is considerably younger on average, which has been taken to imply a different way for the prion to be transmitted in such patients. The mean age at which gCJD presents is similar to sporadic cases, albeit slightly younger [5, 14].

Male and female patients are equally likely to be affected by CJD. In the USA, people of Caucasian ancestry are at a higher risk than those of African or Native American (including Alaskan indigenous) origin. This apparent discrepancy may be an artefact of how cases are diagnosed, however [15, 16]. There are certain regions where the incidence of CJD is between 30 and 100 times that of the average global rate. Such regions include North Africa, Israel, Italy and Slovakia. The higher incidence relates to a raised number of genetic-type cases [9]. As with all prion disorders, the reported incidence of CJD is affected by how intensively cases are sought out and registered in different countries [5, 9].

64.3 Pathogenetic Basis

Prions are the infective agent in prion diseases. The prion itself (PrPSc) is a protein that can turn non-disease causing prion proteins (PrPc) into copies of the disease-causing version. It acts as its own catalyst in this process. The mechanism by which this occurs is described elsewhere [5].

Whilst it remains unknown exactly how PrPSc originates in sporadic cases of CJD, it is believed that they are not of extraneous origin. There are reports indicating that sCJD may occur in clusters of a few cases [17–19]. A study of cases of sCJD occurring in the UK between 1990 and 1998, which used a case–control design, found that the cases occurred in closer proximity than would be the case if no mechanism existed responsible for cluster formation. The evidence pointed to the existence of some external risk factor of an unknown type to which all the individuals in the cluster had been exposed [20]. Nonetheless, exactly what is signified by potential clustering has not yet been elucidated. According to one way of analysing the data [21], the apparent clustering may simply be a reflection of more intense disease surveillance within specific geographical areas [21].

Bovine forms of spongiform encephalopathy have been linked both to the prion agent responsible for new-variant CJD and some other potential agents [22–24]. One such prion, known as BASE, results in atypical deposition of amyloid on neuropathology. These appearances are not seen in classic bovine spongiform encephalopathy (BSE) [24]. The molecular form of this prion resembles that of a strain of prion causing sCJD, the MV2 subtype. It is not known what the similarity in molecular signature between BASE and MV2 signifies pathologically. It is possible that in sCJD cases where the MV2 prion protein is detected may reflect a role of BASE in the pathogenesis. The degree to which PrPSc undergoes glycosylation and movement within tissues may be an unreliable way to trace the original source of the prion. At present, whilst the research is unclear, the attribution of sporadic CJD cases to infection with BASE cannot be considered a proven fact [5, 25].

64.4 Clinical Characteristics

64.4.1 Frequently Occurring Presenting Features

Despite the considerable variation in how cases of CJD present to the clinician, all cases exhibit a deterioration in the neuropsychiatric condition of the patient which progresses rapidly and the occurrence of death in no more than a year after first presentation [26].

Neuropsychiatric symptomatology is invariable but may take various forms, such as irreversible, progressive cognitive decline, abnormal behaviour and cognitive deficits indicative of damage to higher cortical functioning, such as aphasia, apraxia or signs of frontal lobe disorders [27].

At an early stage, patients often exhibit reduced ability to concentrate, remember things or make correct judgements [28]. There may be affective problems, e.g.

feeling apathetic or depressed. Less commonly, the patient may be euphoric, with a labile mood, or excessively anxious [29]. The usual sleep pattern may be disrupted, with many patients sleeping more than usual, although the opposite in others, and this may be the first sign of the disorder [30, 31]. Psychosis occurs in some cases, with visual hallucination often prominent [32].

As the clinical condition deteriorates, in the majority of cases dementia becomes the main presenting feature. The decline may become very rapid [5].

Above 90% of cases feature myoclonus, particularly apparent when the patient is startled. This sign may appear at any stage of the disease, but may not be evident at the initial consultation, even if the patient is already profoundly cognitively impaired. Any patient who presents with dementia which is rapidly deteriorating and who presents with myoclonus should receive a differential diagnosis of sCJD [5].

Indications of cerebellar damage are evident in around 2 out of 3 cases. This may be evident as nystagmus or ataxia. In between 20 and 40% of cases, cerebellar signs are present at the first consultation [28]. The early predominance of cerebellar signs, with few other indicators, is especially characteristic of iatrogenic cases of CJD. This condition is usually the result of previous administration of human gonadotropin or growth hormone, or grafting of dura mater [33–35].

Between 2 and 4 out of every 5 cases of CJD feature corticospinal tract localising signs, manifesting as overly-brisk reflexes, extensor plantar response (i.e. the Babinski sign) and spastic rigidity [5].

There may also occur extrapyramidal signs. These include rigidity, abnormal muscular tone and hypokinesia or bradykinesia [5].

64.5 Subtypes within sCJD

There are several different subtypes within sCJD. These result in varying neurological abnormalities, depending on which area within the brain is most severely affected. The subtype which causes predominantly visual symptoms is known as the Heidenhain variant, whereas if cerebellar symptoms are the most prominent, the Oppenheimer–Brownell variant is diagnosed. In addition to these subtypes, there are also forms resulting in symptoms indicating involvement of the thalamus or striatum, as well as subtypes where cognitive or affective symptoms predominate [36, 37].

Current practice generally is to diagnose the subtype following death, based on genotyping the PRNP gene according to the amino acid encoded by codon 129, and by examining what type of PrPSc is present. Codon 129 may encode methionine or valine, thus the resulting genotype may be homozygous for either amino acid or heterozygous. The molecular character of PrPSc is ascertained by Western blotting, being assigned to either type 1 or 2 in the Parchi and Gambetti classification scheme according to how large the portion of the molecule resistant to protease degradation (PrPres) is and how it moves in an electrostatic field [38, 39].

The molecular characteristics of PrPres also correspond to six different clinical phenotypes for sCJD [39, 40]. These phenotypes were identified from the

observation of 300 European or American patients with sCJD [39], with a further 2451 cases examined from the point of view of results on diagnostic investigations [41]. The phenotypes are as follows [41]:

The MM1 and MV1 genotypes are found in around 70% of patients with CJD and represent the archetypal picture of CJD, in which symptoms begin in middle or old age, irreversible, progressive cognitive decline develops rapidly and myoclonus and ataxia are prominent at the early stage of the illness. The period between symptomatic onset and death is short, only 3.9 months on average.

Electroencephalographic studies of cases with the MM1 phenotype usually demonstrate periodic sharp wave complexes (PSWC) [5].

The VV2 phenotype is present in around 10% of patients and is also termed the ataxic variant. Ataxia is evident from the beginning of the illness, frequently without other manifestations of the disease. Dementia is a late-occurring feature. The time between symptomatic onset and death is somewhat longer than with the MM1 cases, lasting on average 7–9 months [42].

A further 10% of sCJD cases are attributable to the MV2 phenotype, also termed the kuru plaque variant. In these patients, the average length of illness is 17.1 months, and the key distinguishing characteristics are psychiatric disturbance and irreversible, progressive cognitive decline [43]. Electroencephalographic studies rarely reveal PSWC [41, 43–45].

The MM2 phenotype can affect mainly the thalamus or the cortex. A subgroup of cases are younger than expected when symptoms begin. According to one study, the median length of time between first symptoms and death was 14 months [46]. The rate of observation of PSWC on electroencephalographic studies in MM2 variant cases is generally lower than in either the MM or MV genotype [39, 41, 44–46]. Clinically, MM2 variant sCJD patients may appear similar to those with vCJD [5].

The MM2 variant, mainly affecting the thalamus, is also known as sporadic fatal insomnia. It is present in 2% of the total cases. On average, the illness lasts for 15.6 months. The clinical presentation is similar to that seen in cases of fatal familial insomnia, i.e. profound sleep disturbance, psychomotor agitation, ataxic features and decline in cognitive abilities [47].

The MM2 variant mainly affecting the cortex also represents 2% of overall cases, the illness lasting on average for 15.7 months. The most striking feature of the presentation is dementia, whereas indications of the cerebellum or visual tracts being involved seldom feature at the onset of the illness [48].

The VV1 phenotype is present in 1% of patients with sCJD. The associated illness has a mean duration of 15.3 months. Patients are relatively young and the cognitive decline predominates the presentation. One case series followed 9 individuals with the VV1 phenotype. The median length of illness in this group was 21 months [49]. Electroencephalographic studies failed to identify PSWC in any of these 9 patients. Magnetic resonance imaging studies revealed a higher frequency of cortical abnormality than an abnormality of the basal ganglia. In the majority of patients with the VV1 phenotype, the RT-QuIC (real-time quaking-induced conversion) test on cerebrospinal fluid is negative [50].

64.6 Research into CJD Biomarkers: State of Current Knowledge

Diagnostic confirmation of prion disorders can be achieved through the use of immunohistochemical stains for PrPSc [51, 52]. To achieve diagnostic certainty in a living patient, the central nervous system needs to be directly biopsied, however this procedure is not without difficulties. Besides the concerns arising with regard to infection control, there is a real possibility the tissue obtained may not contain typical pathological features and thus be interpreted incorrectly as indicating no prion disease. Such a situation may occur in sCJD or fatal familial insomnia (FFI) cases. The tissue obtained also needs to be of sufficient quality for processing. Furthermore, central nervous system biopsy is highly invasive. Accordingly, biopsying the brain is generally only undertaken if there is a high degree of diagnostic uncertainty and if another condition, for which treatment is available, may explain the presentation. Examples of conditions in this category include cerebral lymphoma or encephalitis. It may also be needed if there is a possibility of surgical contamination. It has proven possible to perform a less invasive procedure to diagnose new-variant CJD, i.e. biopsy of the tonsils or adenoids, but the other prion disorders cannot be diagnosed in this way [53]. ***It seems to be potentially possible to detect PrPSc in cases of sCJD using blood, urine or CSF, but one study that took this approach with urine samples found the method to detect only 40% of cases, i.e. it is poorly sensitive [54]. There is a need for the diagnostic criteria employed in cases of sCJD to be revised since direct detection of the prion or biopsy both have severe limitations. There is accumulating evidence to suggest an alternative in the form of novel PrPSc amplification or seeded aggregation assay. These newer investigations are outlined in the following sections, and the status of biomarkers, both those already in use and those being developed, is reviewed [51].

64.6.1 14-3-3 Proteins as Surrogate Markers. Detection in CSF

The brain expresses 14-3-3 proteins at a high level, but is not the only organ to do so. These molecules are found within the cytoplasm, bound to cellular membranes or within the intracellular organelles. It is evident that 14-3-3 proteins are of importance in cellular signalling, cell growth and programmed cell death, but the precise nature of their role is not yet clear [55]. There have been multiple studies investigating the use of Western blotting of 14-3-3 proteins as an aid in diagnosing sCJD. A meta-analysis dating from 2012 found the technique to be 92% sensitive and 80% specific [56], albeit less sensitive earlier on in the progression of the illness and with different degrees of sensitivity depending on molecular subtype. For example, the test was approximately 60% sensitive for the MV2 and 70% sensitive for the MM2 subtype of sCJD [45]. The highest rate of specificity was stated as 92% [57] and the lowest as 40% [58]. This large range for specificity may reflect the heterogeneity amongst the control groups used in each study. Recently, it has been reported that 14-3-3 proteins are highly specific for separating the diagnosis of sCJD from other

neurodegenerative dementias, including Alzheimer-type dementia, Lewy body dementia and frontotemporal lobe dementias [59, 60].

64.6.2 Imaging Investigations: MRI

Neuroimaging of cases of suspected sCJD is vital using MRI, since this investigation permits excluding competing diagnoses, e.g. ischaemic injury, encephalitis or a tumour, for which treatment may be available. When the WHO were gathering the criteria to recommend in diagnosing CJD in 2009, it was suggested that MRI appearances be included, namely the restriction of diffusion on diffusion-weighted imaging and hyperintensities seen on fluid attenuated inversion recovery (FLAIR) [4]. A different, frequently utilised set of recommendations for how to diagnose CJD proposes only employing diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps [61, 62]. The classic MRI appearances in CJD are of restricted diffusion within two or more areas of the cortex (termed "ribboning") with or without restriction of diffusion in the caudate nucleus and, to a lesser extent, in the putamen and thalamus. It is not possible to observe subcortical abnormalities using the visual modes (namely DWI, ADC and FLAIR) [61, 63], but it may be noted on quantitative diffusion tensor imaging [64]. Ribboning in the cortex and abnormality of the caudate nucleus (which may be uni- or bi-lateral, but seldom affects both sides to the same degree) is a very frequent finding in cases of the MM1 subtype, which accounts for the majority of cases. In the VV2 and MV2 subtypes, thalamic involvement (besides abnormality of the caudate nucleus and putamen) is noted with raised frequency [65]. On scans using the FLAIR and DWI modes, the presence of the pulvinar sign is very likely to be due to vCJD. The pulvinar sign refers to a brighter signal from the posterior thalamic region than from the anterior putamen [51, 53].

64.6.3 Genetic Markers

Around 10–15% of all cases of prion disorders occurring in humans are due to a mutation of the PRNP gene [1]. Some mutations are responsible for specific prion diseases, namely Gerstmann-Sträussler-Scheinker disease (GSS) and FFI, whilst the effect of other mutations is mimicry of the clinical features and biomarker properties of sCJD. An example of the latter is the E200K mutation [66]. The PRNP gene should therefore be sequenced to inform the differential diagnosis in cases of potential prion disorder, especially if the clinical and biomarker characteristics are not typical, there is a definite genetic component, or a possible genetic aspect to a rapidly progressive dementia in a family member. It has been noted that the indirect biomarkers are less sensitive in a number of subtypes of sCJD, notably the MV2 and MM2 phenotypes [45, 67]. Unfortunately, biopsy of the brain is needed to characterise the molecular nature of PrPSc. However, if codon 129 is known from PRNP sequencing, it may be more straightforward to interpret any results from investigation other biomarkers [68].

64.7 Diagnosis

Any patient who exhibits features of a rapid, progressive, irreversible cognitive decline and even more so when there are certain neurological abnormalities, namely myoclonus and ataxia, with or without abnormality of the visual system, should prompt a suspicion of CJD. It is vital that other competing diagnoses, for which treatment is potentially available, also be considered [5].

The diagnostic gold standard in prion disorders is still neuropathological examination of the brain aiming to identify the PrPres protein, i.e. the form of PrPSc which resists degradation by proteases. Biopsy of the brain is a potential method for providing material suitable for neuropathological examination, however, in many cases, this is not essential, as sCJD can be diagnosed to a sufficient level of confidence with non-invasive methods [5].

64.7.1 Diagnostic Criteria

There are some guidelines available on how to diagnose sCJD [7, 69–71]. If the clinical presentation and laboratory results are consistent with sCJD, this may be adequate for a working or probable diagnosis of sCJD, with the diagnosis later definitively established by postmortem neuropathological examination [72].

According to the CDC (US Centres for Disease Control and Prevention) the following criteria should be employed diagnostically in cases of suspected sCJD [5, 73]:

At least one of either:

- Neuropsychiatric abnormality accompanied by positivity of the RT-QuIC test
- or
- Progressive, irreversible cognitive decline

Plus a minimum of four out of the following potential clinical features:

- Myoclonus
- Abnormality of cerebellar or visual function
- Abnormal function of the pyramidal or extrapyramidal tracts
- Akinetic mutism

In addition, the following results of investigations support the diagnosis of sCJD:

- Characteristic electroencephalographic abnormalities (such as PSWC) lasting any length of time during the illness.
- Positivity of the 14-3-3 protein assay in CSF in a patient who dies no longer than 2 years after this occurs.

- MRI reveals hyperintensity affecting the caudate nucleus, putamen and two or more areas of the cortex, such as the temporal lobe, parietal lobe or occipital lobe. This hyperintensity should be observed using DWI or FLAIR.

Furthermore, non-specialised investigations should not point towards some other competing diagnosis.

64.8 Treatment

No efficacious therapy has yet been discovered for CJD. The outcome is invariably fatal. The duration of illness between the beginning of symptoms and mortality is generally less than 1 year, the median illness length being 6 months [26, 74, 75].

64.8.1 Palliative Support

Since no specific treatment for prion disorders in humans has yet been discovered and the outcome is invariably fatal [76], the aims of treatment are to alleviate symptoms and support the patient [5, 77]. The following are important considerations:

Engaging and communicating with the family at an early stage is vital. Sporadic CJD is generally poorly understood by most members of the general public and so providing good quality information is an especially valuable first step. There are some suitable materials published by the CJD Foundation [5].

Clinicians should also liaise with Social Services to ensure adequate care can be provided, a referral to a hospice made and counselling offered to the relatives or caregivers on what to expect as the disease progresses and what the financial implications are. This referral should be undertaken at the first meeting.

Cases of CJD tend to occur in adults of working age. These individuals may be entitled to receive some form of disability support. The US Government has instituted a procedure to fast track payments for CJD patients [5].

The patient's mental capacity should be assessed with regard to decisions about treatment and the management of his or her finances.

Symptoms of neuropsychiatric disturbance may frequently be treated if they cause distress or add to disability. Treatment encompasses both pharmacological and non-pharmacological strategies and is addressed elsewhere in the literature [5].

Benzodiazepines are sometimes helpful for treating myoclonus. Clonazepam falls into this category. Anti-epileptic agents, in particular valproate or levetiracetam, may also be used in this way. Details of dose schedule, etc. can be found elsewhere [5].

64.9 Conclusion

It is not likely that the dementia drugs of the cholinesterase inhibitor or NMDA-receptor antagonist types will be efficacious in sCJD and their use in this way is unusual, despite reports in the literature of benefit in terms of a reduction in psychosis in certain patients [32].

Advice on managing patients at the end stage of dementia is also covered in other sources [5].

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Part IX

Diseases of Unknown Etiology

Kawasaki Disease and Hearing Loss

65

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65.1 Introduction

Kawasaki disease (KD), previously called mucocutaneous lymph node syndrome, is one of the most common vasculitides of childhood, second only to immunoglobulin A (IgA) vasculitis. It is the leading cause of acquired heart disease in children in the developed world. In 1967, a Japanese pediatrician, Dr. Tomisaku Kawasaki, described 50 children presenting with fever and clinical findings suggestive of multisystem acute inflammation (rash, conjunctival injection, oral mucositis, extremity changes, and cervical lymphadenopathy). It is typically a self-limited condition; however, if left untreated, it may lead to coronary artery aneurysms in approximately 25% of cases. The risk of coronary artery involvement is higher in young infants younger than 6 months and children older than 8 years. Early diagnosis and timely initial treatment with intravenous immune globulin (IVIG) within the first 10 days of fever are key to preventing significant morbidity and mortality [1].

Besides coronary artery involvement, KD can cause damage to various organs, resulting in varying degrees of temporary or permanent loss of function.

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65.2 Epidemiology

Even though KD has a worldwide distribution, the incidence of KD is highest in Asian populations, especially in Japan and South Korea, followed by Taiwan and China. About 1.5% of children in Japan and 0.2% in South Korea develop KD by age 5. The usual annual rate in children younger than 5 years old in non-Asian populations is 10–20 cases per 100,000 [2]. Children with Asian ancestry living in the United States of America (USA) have a higher prevalence of KD than other ethnicities [3]. KD is more common in boys than in girls. The male-to-female ratio in KD is 1.5:1. Kawasaki disease most commonly affects children younger than 5 years, with an average of approximately 2 years [2]. The disease is rare in children under 6 months of age and adolescents; however, both age groups and the male gender have an increased risk of coronary artery involvement [4]. Studies regarding recurrence rates and familial occurrence of KD in Japan have reported that approximately 1% of patients with KD have a positive family history, and siblings of affected children have a ten-fold increased risk of KD compared with the general population [5]. The recurrence rate is around 3% [6].

65.3 Etiology

The cause of KD remains unknown. The epidemiologic characteristics of KD, such as its tendency to target young children, winter-spring seasonality, and geographic clustering, overlap with viral, primarily respiratory infections [6]. However, conventional microbiologic investigations have not yet determined an etiologic agent. Person-to-person spread has not been demonstrated. An intriguing study has stated that the large-scale tropospheric winds carry an unknown KD triggering agent from provinces in northeastern China to Japan, Hawaii, and Southern California, which serves as a source for the seasonal clustering and annual epidemics of KD [7]. Research has suggested that a possible superantigen triggering the excessive or uncontrolled immune response in susceptible hosts causes KD [8]. The known effect of race and family history on the incidence of KD implies that genetic factors may play a role in susceptibility. The influence of genetic variations on the progression of KD has been detected in different populations [8]. European KD patients with genetic variation in the transforming growth factor (TGF) pathway (TGFβ2, TGFβR2, and SMAD3) are more likely to have coronary artery involvements and aneurysms [8].

65.4 Pathophysiology and Pathology

Both innate and adaptive immune systems have an active role in acute KD. Neutrophils first invade the arterial wall, and mononuclear, and CD8 T cells appear in the vessel wall. As in other inflammatory diseases, proinflammatory cytokines, such as

interleukin (IL)-1, IL-6, IL-12, and interferon-gamma (IFN-γ), play an essential role in the course of KD [1].

A multisystemic vasculitis with fever is the dominant feature of the first 10 days in KD. Acute arteritis can proceed to extensive necrosis of all vessel wall layers. Destruction of internal and external lamina by neutrophil proteinases contributes to aneurysm formation [9].

The immune destruction in KD primarily affects small- and medium-sized, non-parenchymal muscular arteries, especially the coronaries. Destructive changes in coronary arteries due to vasculitis, the inflammation-induced hypercoagulable state, and thrombocytosis may lead to coronary aneurysms and stenosis, which can cause ischemic heart disease and myocardial infarction. The mortality rate reaches its highest point between 15 and 45 days after the beginning of the fever [1]. Myocardial infarction and death may occur months or even years later due to progressive coronary arterial stenosis [10]. Noncoronary arteries, such as the iliac, femoral, and renal, are less frequently involved [11]. Although the coronary arteries are the most seriously affected, the systemic inflammation in all medium-sized arteries of multiple organs and tissues during the acute febrile phase of KD results in diverse clinical findings [6].

65.5 Clinical and Laboratory Findings

The acute phase of KD often begins with sudden onset, persistent fever, though it, sometimes, is preceded by symptoms of an upper respiratory or gastrointestinal illness. Fever is frequently high (>39 °C to 40 °C) and lasts an average of 12 days without adequate treatment. It may not be responsive to antipyretic agents and tends to remain above 38.5 °C during most of the acute phase of the illness. The spontaneous remission of fever after 7 days cannot rule out the diagnosis of KD. Infants and young children are often excessively irritable during the acute febrile period. KD has no specific diagnostic test. Therefore, in a patient with a fever lasting for at least 5 days, which could not be explained by any other disease, the diagnosis of classic KD depends on the presence of at least four of the five principal clinical findings [6, 12]: (1) bilateral nonexudative conjunctivitis, (2) oropharyngeal changes, (3) skin rash, (4) extremity changes, and (5) cervical lymphadenopathy (Table 65.1).

Unfortunately, these principal criteria cannot determine all children with KD. Some children, particularly those <6 months of age, may not fulfill the 5 criteria and are referred to as having incomplete (atypical) KD (Fig. 65.1). Having subtle and transient signs, KD in this age group, can be a diagnostic challenge. Because of delayed diagnosis, these young infants may have an increased risk of developing coronary artery abnormalities [1, 2].

Table 65.1 Diagnosis of Kawasaki disease[a]

Classic KD is diagnosed in the presence of *fever for at least 5 days* together with *at least four of the five* following principal clinical features.
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oropharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Polymorphous rash (maculopapular, diffuse erythroderma, or erythema multiforme-like)
4. Erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
If ≥4 of the above criteria are present, a diagnosis of KD can be made on day 4 of the illness
Children who do not fulfill diagnostic criteria (have fever for 5 or more days and 2 or 3 compatible clinical criteria) or infants with fever for >7 days without other explanation may have incomplete or atypical KD (see Fig. 65.1)
Patients with fever of at least 5 days and < 4 principal criteria can be diagnosed with Kawasaki disease when positive echocardiographic findings are detected by 2-D echocardiography. Echocardiography is considered positive for purposes of this algorithm if any of three conditions are met: 1. Z score of left anterior descending coronary artery or right coronary artery ≥2.5 2. Coronary artery aneurysm is observed 3. Other ≥3 suggestive features exist; decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in the left anterior descending coronary artery or right coronary artery of 2–2.5

[a] Adopted and modified from Ref. [1, 2]

65.5.1 Bilateral Nonexudative Conjunctivitis

Conjunctivitis with limbal and palpebral sparing, characteristically bilateral and nonexudative, is seen during the acute febrile phase as one of the hallmarks of KD (Fig. 65.2). This is present in more than 90% of patients. Purulent discharge is unusual and suggests an alternate diagnosis.

65.5.2 Oropharyngeal Changes

Redness, dryness, fissuring, and cracking of the lips, strawberry tongue, erythema of the oral cavity, buccal mucosa, and posterior oropharynx are seen in up to 95% of patients with KD (Figs. 65.3 and 65.4). The redness of the lips may last for 2–3 weeks after the disappearance of other symptoms. Discrete oral lesions, such as vesicles or ulcers, and tonsillar exudate, suggest a disease process other than KD.

65.5.3 Skin Rash

The skin rash may occur in different forms although diffuse maculopapular, morbilliform, or targetoid skin lesions of the trunk and extremities are most characteristic. The rash usually begins on the trunk and perineal area in the acute phase of KD

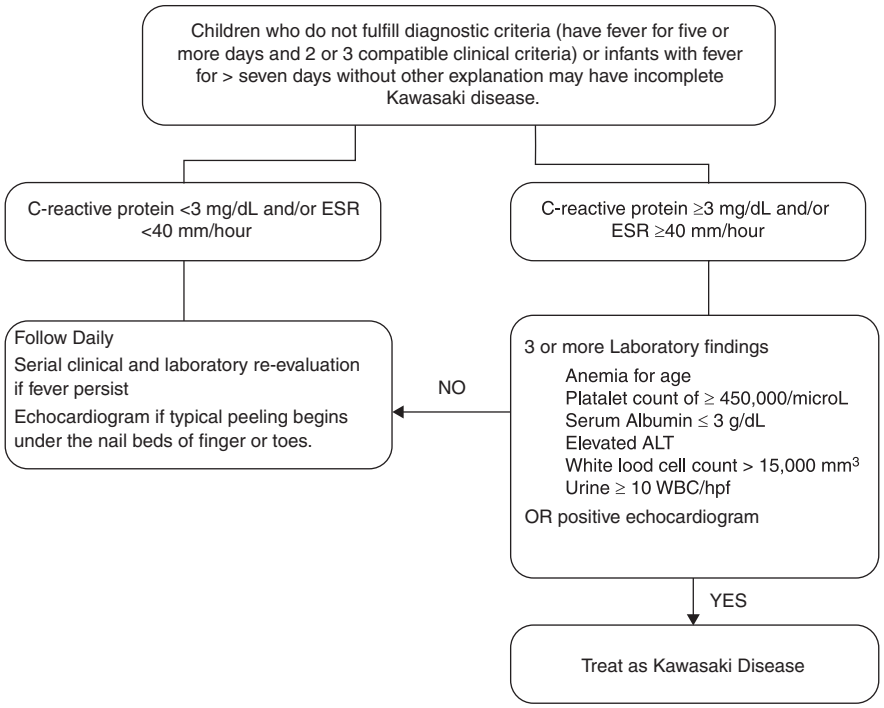

Fig. 65.1 Evaluation of suspected incomplete Kawasaki disease

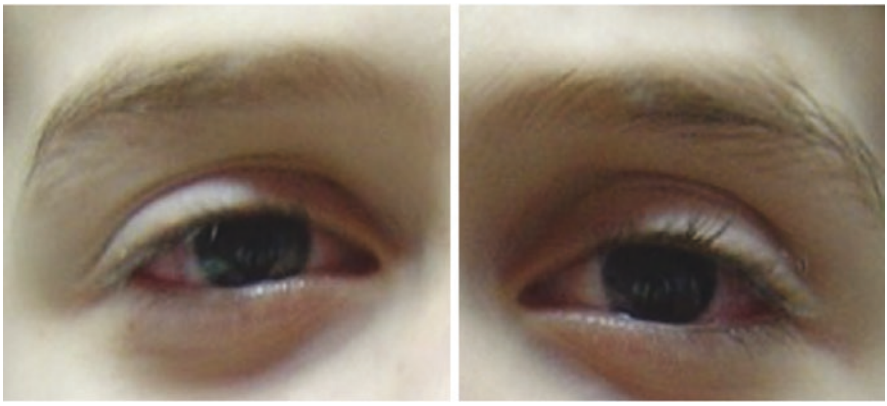

Fig. 65.2 Bilateral conjunctival injection without exudate in Kawasaki disease (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

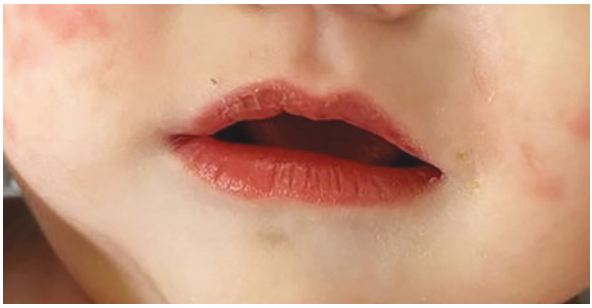

Fig. 65.3 Cracked red lips seen in Kawasaki disease (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

Fig. 65.4 Strawberry tongue in Kawasaki disease (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

(Fig. 65.5). An erythematous rash and subsequent desquamation in the perineal region are also notable features of KD. The rash is rarely pruritic. KD may also trigger a psoriasiform eruption in children without a known diagnosis of psoriasis. Vesicular, bullous, or petechial lesions are not observed in KD.

Although not included in the principal clinical findings, redness or crust formation erythema and induration at the site of Bacille Calmette–Guérin (BCG) inoculation is an important clinical sign seen in about half of KD patients during the acute phase [13].

65.5.4 Extremity Changes

Erythema, edema, and induration of the hands and feet with swelling of the fingers and toes are expected during the acute febrile period of KD and subside within a few days. It is usually the last manifestation to occur. During the subacute phase, about 2–3 weeks after the onset of illness, typical sheet-like desquamation on the fingers and toes begins from the periungual region and may involve the palms and soles

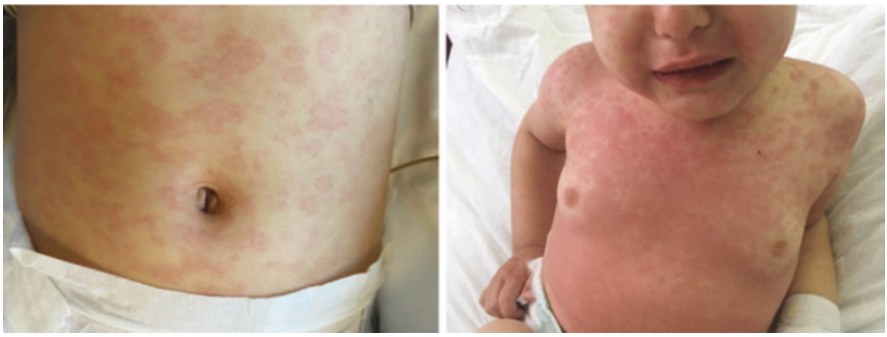

Fig. 65.5 Diffuse rash in a patient with Kawasaki disease. Rashes can be scarlatiniform, maculopapular, or erythema multiforme-like (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

Fig. 65.6 Changes in hands after 1–2 weeks; peeling of skin around fingernails in Kawasaki disease (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

(Fig. 65.6). Additionally, linear nail creases (Beau's lines) could be seen in the convalescent phase of KD (Fig. 65.7).

65.5.5 Cervical Lymphadenopathy

Nonsuppurative cervical lymphadenopathy, usually unilateral, with a diameter of >1.5 cm, is seen in approximately 60% of patients. Cervical adenopathy is the least consistent feature of KD. If present, it is the most prominent clinical sign of KD in some patients, emerging 1 day before or concurrently with fever. If bilateral adenopathy is present, it may be misdiagnosed as mumps. Diffuse lymphadenopathy or other signs of reticuloendothelial involvement (e.g., splenomegaly) could be an alternative diagnosis, such as Epstein–Barr virus (EBV) infection.

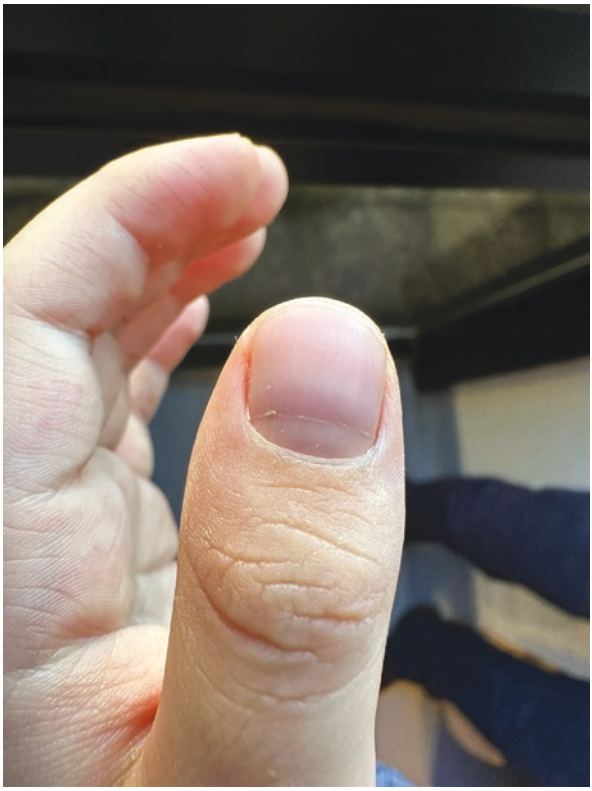

Fig. 65.7 Linear nail creases (Beau's lines) in the convalescent phase of Kawasaki disease (Courtesy Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Kocaeli University, Kocaeli, Türkiye)

65.5.6 Cardiovascular Problems

Cardiovascular problems are the primary cause of morbidity and mortality associated with KD during acute illness and the long-term course. Resting tachycardia disproportionate to fever, ST segment and T wave changes, abnormal Q waves, and low voltage on electrocardiograph (ECG) may reflect underlying myocarditis caused by KD. The endocardium, myocardium, and pericardium may be involved. Valvar, mostly mitral valve dysfunction, occurs in about 25% of patients, regardless of whether they have coronary artery involvement [6]. Gallium citrate Ga 67 scans and technetium Tc 99 m scans have shown that 50–70% of patients with KD have myocardial inflammation [14]. Myocardial inflammation without ischemic damage develops before coronary artery abnormalities [15]. Myocarditis in KD usually starts early, and acute left ventricle (LV) dysfunction, if any, is usually transient and responds well to anti-inflammatory drugs [16]. Coronary artery aneurysms, pericardial effusion, and mitral or aortic regurgitation may be seen in echocardiographic examinations of children with KD.

When considering a diagnosis of KD, echocardiography should be performed; however, unavailability or technical difficulties should not delay therapy. Neither

echocardiographic nor laboratory findings constitute the essential criteria for diagnosing KD [3].

65.5.7 Laboratory Findings

There are no laboratory tests among the diagnostic criteria for typical KD. However, some laboratory findings can help support the diagnosis of KD in patients with nonclassical clinical findings or incomplete cases. Systemic inflammation is seen in KD. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), neutrophilia, anemia, decreased serum albumin and sodium levels, elevated serum liver transaminases, and sterile pyuria can be utilized in supporting the diagnosis. Normochromic and normocytic anemia are common. During the resolution of inflammation, CRP returns to a normal level more quickly than ESR.

Furthermore, ESR should not be utilized to determine whether or not a patient has responded to IVIG treatment because IVIG therapy may increase the ESR level. In monitoring the treatment response, CRP level is a more helpful marker [6]. Thrombocytosis is a common feature of KD but is usually not seen until the second week [17]. It peaks in the third week (mean 700,000 per mm^3) and returns to normal 4–6 weeks after KD onset. Thrombocytopenia is rare but can occur in the first 1–2 weeks of illness. Thrombocytopenia can be a part of disseminated intravascular coagulation (DIC) and is associated with an increased risk of coronary artery disease [6].

In a suspected incomplete case with prolonged fever (≥5 days), high CRP and ESR levels, anemia, platelet count of ≥450.000/mm^3, albumin <3 g/dL, elevated liver enzymes, sterile pyuria, and leukocyte count of ≥15.000/mm^3 are supportive findings for the early diagnosis and treatment of incomplete cases [6]. The utility of elevated cardiac troponins for diagnosing acute KD is controversial [18]. Once coronary artery involvement is detected in a patient with prolonged fever, less than four principal findings are sufficient for diagnosing KD [19].

65.6 Differential Diagnosis

Clinical features of some bacterial and viral infections, rheumatologic diseases, and toxin-related syndromes may overlap with the symptoms of KD. Differential diagnosis of KD includes several clinical entities, such as measles, adenoviral infection, scarlet fever, toxic shock syndromes, juvenile idiopathic arthritis, drug hypersensitivity reactions, and Stevens–Johnson syndrome.

Multisystem inflammatory syndrome in children (MIS-C) associated with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been reported since 2020 during the coronavirus disease 2019 (COVID-19) pandemic. Some clinical and laboratory findings of MIS-C, such as prolonged fever, cardiovascular and mucocutaneous manifestations, highly elevated CRP and ESR levels, and other elevated inflammatory markers, overlap with KD. Intravenous immunoglobulin has

been successfully used in the treatment of both diseases. There is male preponderance in MIS-C, as in KD. However, there are notable differences between KD and MIS-C. Patients with MIS-C usually present older age (median at least 7 years) and have evidence of previous or current SARS-CoV-2 infection confirmed through polymerase chain reaction (PCR) or serologic tests. Gastrointestinal and neurological manifestations are much more common in patients with MIS-C [20, 21].

65.7 Treatment

Suppression of intense inflammation in KD reduces the likelihood of coronary aneurysmal formation. The mainstay of care for acute KD is a high dose (2 g/kg) IVIG together with acetylsalicylic acid (ASA; Aspirin®) unless it is contraindicated [22]. Intravenous immunoglobulin should be initiated within the first 10 days of the disease onset and administered slowly over 10–12 h as a single dose. Intravenous immunoglobulin should still be used in patients with persistent fever beyond the tenth day of illness. Intravenous immunoglobulin therapy reduces the incidence of coronary artery aneurysms from 25% to 5% if administered during the first 10 days of the disease [8]. The mechanism of action of IVIG in the treatment of KD is not clear to date yet.

Acetylsalicylic acid in a moderate to high dose (30–100 mg/kg/day, divided into 4 doses) is used for its anti-inflammatory effect during the acute phase of illness. The dose is reduced to a low dose (3–5 mg/kg/day) for its antiplatelet effect after the fever has resolved for 48 h [22]. Low-dose ASA is discontinued after 6–8 weeks of treatment if the patient has no coronary artery aneurysm, and acute phase reactants have normalized [7].

If the fever of a patient with KD recurs 36 h after completion of the first IVIG infusion, the patient is defined as an IVIG-resistant case (“refractory KD”). IVIG-resistant patients are at higher risk of developing coronary artery abnormalities. Treatment options for IVIG-resistant KD include a second dose of 2 g/kg IVIG, IVIG with steroid (prednisolone 2 mg/kg/day), or infliximab (5–10 mg/kg, intravenous single infusion) [6]. Glucocorticoids have been shown to decrease the rate of CA abnormalities in Japanese children with KD at high risk for IVIG resistance. It is recommended to add steroids in the high-risk group (e.g., age < 6 months old or CA z-score > =3. Cyclosporine, a calcineurin inhibitor, has shown some efficacy for refractory KD and initial therapy of KD in patients at high risk for IVIG resistance.

65.8 Complications of Kawasaki Disease

Due to the nature of KD causing multisystemic vasculitis, multiple organs and tissues can be involved in the acute uncontrolled inflammatory response. Various clinical signs may be seen during acute febrile illness or long-term follow-ups, such as

irritability, behavioral changes, vomiting, abdominal pain, diarrhea, gallbladder hydrops, pyuria, arthralgia, arthritis, peripheral gangrene, facial paralysis, ocular complications, ataxia, and sensorineural hearing loss (SNHL). Many noncoronary complications of acute KD are self-limiting [6, 23].

65.8.1 Ocular Complications of Kawasaki Disease

The most common ocular involvement in KD is non-purulent bilateral conjunctivitis with limbic sparing, one of the five principal diagnostic findings. The involvement of the anterior segment of the eye is much more common than the posterior segment involvement. Acute anterior uveitis is a frequent finding seen on ophthalmic examination of patients with KD, responds to topical anti-inflammatory therapy, and usually resolves within 2–8 weeks after disease onset without any sequelae [24]. More serious ocular complications, such as keratitis, involvement of retinal vessels and the optic disc, inflammation of the bilateral vitreous, and ophthalmic artery obstruction leading to blindness, have also been reported [25, 26].

65.8.2 Neurological Complications of Kawasaki Disease

Cerebral vasculitis and intracranial aneurysms, adverse events of IVIG therapy, the prothrombotic inflammatory state of the large vessels, and cardiogenic embolism induced by myocardial infarct are the possible causes of neurological manifestations of KD [27]. Neurological symptoms and signs, such as headache, extreme irritability, and convulsions, could be due to aseptic meningoencephalitis induced by IVIG treatment or caused by cerebral vascular involvement. The facial nerve is the most frequently affected cranial nerve in children with KD, with an incidence of 1% [23, 28]. The resultant facial palsy is usually left-sided and peripheral and resolves spontaneously within 3 months of follow-up. Ischemic or hemorrhagic strokes due to occlusion or rupture of cerebral arteries are infrequent complications [28]. Ataxia may occur in both acute and subacute phases of KD and is usually transient [23].

Additionally, behavioral sequelae, such as attention deficit, learning difficulty, and emotional effects, are commonly seen during the long-term follow-up of KD patients [28]. Alves et al. [23] evaluated 115 children with KD and reported that 23 patients experienced behavioral changes during their convalescence. All of them had irritability, nine had attention deficit, seven had learning difficulty, and two had antisocial behavior. Six patients had persistent aggressive behavior, three had persistent learning deficits, and five had persistent attention deficits 6 months after the acute period of the illness.

65.9 Kawasaki Disease and Hearing Loss

The first cases of SNHL in association with KD were reported by Suzuki et al. [29] in 1988. After that, more studies have revealed that SNHL is a possible complication of KD [30–34].

The pathogenesis of SNHL in patients with KD is not clear. Aspirin ototoxicity has been hypothesized to cause hearing loss (HL) [30, 32, 35]. Hypoalbuminemia seen in KD can lead to increased free circulating levels of ASA, contributing to ASA ototoxicity [30]. However, SNHL caused by ASA is known to cause mild HL on both sides and recovers within 72 h after stopping ASA intake [35]. Additionally, contrary to the ototoxicity hypothesis, moderate (41–55 dB) to severe (71–90 dB) SNHL has been reported before the administration of any doses of ASA in a 6-year-old girl with KD by Aggarwal et al. [32]. Furthermore, in Japan, even the children with KD not treated with aspirin because of the possible hepatotoxic effect of salicylates in that population have shown some degree of SNHL [30].

Another hypothesis has linked SNHL with the intense immune response observed in the acute phase of KD. This intense inflammatory process can damage the membranes of the labyrinth, the microvasculature of the inner ear, and the wall of the vasa nervorum, and alter the osmotic balance within the fluid compartments of the inner ear [30–32, 36, 37].

After the first published cases of SNHL associated with KD, Sundel et al. [33] reported a case series of 5 children with SNHL aged 7 months to 13 years who met the diagnostic criteria for KD. The patients had no associated neurologic abnormalities. Immunologic investigations and magnetic resonance imaging (MRI) failed to reveal a cause of SNHL. Treatment regimens differed among the children, but none had high salicylate levels (>20 mg/dL). All but one of the patients had bilateral HL with varying degrees from mild to profound. Sensorineural HL was detected in 4 patients during the acute phase of KD. In the remaining patient, HL was suspected by the mother after KD but was not clinically confirmed until approximately 2 years later. Despite being treated with IVIG, aspirin, and prednisone, the hearing recovered in only one patient. The remaining four patients had no significant improvement during follow-up. The authors concluded that SNHL of varying severities is a rare complication of KD, and salicylate toxicity is unlikely to cause SNHL in patients with KD [33].

The first multicenter prospective study evaluating KD and SNHL was published by Knott et al. [30]. Sixty-two patients diagnosed with KD were assessed by visual reinforcement, play audiometry, tympanometry, and brainstem auditory evoked response (BAER) testing within 30 days after the onset of fever. The hearing evaluation was inconclusive in 20 patients; 17 had normal hearing, 6 had HL associated with middle ear dysfunction, and 19 (30.6%) had SNHL. The patterns of HL in 4 patients differed from the pattern characteristic of ASA ototoxicity, and 15 had an HL pattern consistent with ASA ototoxicity. Thus, while the ASA toxicity might cause HL, it was detected that the relative risk of SNHL for patients on high-dose

ASA did not reach statistical significance. All but one of the patients had bilateral HL with varying degrees. The second audiologic assessment performed 41 days after disease onset showed that 2 patients had persistent HL [30].

In another prospective study by Magalhaes et al. [36] assessing 40 patients with KD, all patients underwent audiologic evaluation during the first 30 days, and 22 had SNHL, 12 of whom were bilateral, with varying severities from mild to moderate. The HL persisted in 12 patients on the second assessment performed 6 months later. In the study by Magalhaes et al. [36], 60% of patients with SNHL had received IVIG during the subacute phase of KD, and HL frequently persisted in patients, contrary to Knott et al. [30]. The authors concluded that the intense inflammatory process observed in the acute phase might be associated with SNHL in KD, and delays in IVIG therapy, high ESR (>50 mm/hr) during a prolonged period (>30 days), anemia, and thrombocytosis were risk factors for persistent SNHL [36]. Case reports regarding the effectiveness of steroid therapy for SNHL in patients with KD have shown different results ranging from complete recovery [38] and partial improvement [32, 39] to severe persistent HL requiring bilateral hearing aids [40].

The prospective cohort study by Alves et al. [23] evaluated 115 children with KD regarding complications seen in KD. The auditory evaluation was performed during the first 30 days of disease and 6 months later in patients having an HL initially. In the study, SNHL was the most frequent complication in patients with KD. As high as 33% of patients with KD were noted to have some degree of SNHL. Six months after the first assessment, SNHL persisted in nearly one-third of patients with SNHL persisting six months after the first audiologic assessment. These authors also, similar to the study by Magalhaes et al., reported that high and sustained inflammation, anemia, and thrombocytosis are predisposing factors to HL in KD [23].

A more recent prospective study published by Park et al. [34], including 59 children with KD, reported that 3 patients had mild bilateral SNHL on audiometric assessment. The patient was assessed at the acute phase and the eighth week after discharge. All three patients with hearing deficits showed a normal recovery pattern on follow-up tests at the 8-week outpatient visit. Contrary to the study by Magalhaes et al. [36], Park et al. [34] did not find a relationship between SNHL and a persistent inflammatory state, persistent fever, anemia, or thrombocytosis. The serum ASA level before the first hearing test in SNHL patients was significantly high. Hence, these authors indicated that the clinical manifestations of mild bilateral transient SNHL were similar to ASA toxicity [34].

In a cross-sectional study by Toomaj et al. [37], including 56 patients diagnosed with KD, only 1 patient had SNHL by audiologic evaluation performed 2 years after KD diagnosis. The patient received IVIG within the first 10 days of fever onset and had thrombocytosis, high ESR (>40/h), and coronary artery aneurysm [37]

Since the first description of the relationship between SNHL and KD, over the last 30 years, research on this relationship has continued, and the results of published studies have some inconsistencies.

65.10 Conclusion

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a small–medium size vasculitis of childhood affecting coronary arteries. KD rarely occurs in adults. It has a multifactorial etiology. The diagnosis of KD is clinical, with fever and accompanying findings that are often not present at the same time. No laboratory studies exist among the diagnostic criteria. It is typically a self-limited condition with fever lasting for an average of 12 days if left untreated. Early diagnosis and timely treatment are crucial for preventing CA aneurysms and better outcomes. It has been shown to decrease CA aneurysms from 25% to less than 5% with IVIG. Other KD complications include gastrointestinal, ophthalmologic, and neurological complications, arterial aneurysms outside the coronary artery, and behavioral changes.

Kawasaki disease is frequently associated with SNHL [31]. However, the factors predisposing to the development, severity, and persistence of SNHL in children with KD remain unexplained. Sensorineural HL associated with KD may resolve spontaneously or after systemic steroid therapy. Patients with persistent SNHL rarely need bilateral hearing aids. A hearing deficit persisting for months can lead to cognitive or speech disorders in infants or young children who might not report the deficit. Early diagnosis and intervention are essential in the re-acquisition of hearing, speech, and linguistic skills. It would seem advisable that primary care providers and parents of patients with KD be counseled regarding the possibility of SNHL after KD.

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Part X

Autoinflammatory Syndromes

Periodic Fever Syndromes in Children and Hearing Loss

66

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66.1 Introduction

Periodic fever syndromes (PFSs) are defined as three or more attacks of unprovoked fever in a six-month period, appearing at least 7 days apart and accompanied by varying clinical manifestations [1]. The underlying pathogenesis in PFSs is termed autoinflammation resulting in defects of the innate immune system without the presence of high-titer autoantibodies or antigen-specific T cells [2]. Periodic fever syndromes are a diagnostic spectrum including diseases of Mendelian inheritance and diseases of a complex mode of inheritance. Disease severity ranges from mild to life-threatening and may be complicated by AA amyloidosis. The inheritance pattern and main clinical findings of monogenic and polygenic PFSs are depicted in Tables 66.1 and 66.2.

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Table 66.1 Inheritance pattern of periodic fever syndromes

Diseases	Inheritance	Gene
Familial Mediterranean fever (FMF)	Autosomal recessive	*MEFV* 16p13.3
Tumor necrosis-associated periodic syndrome (TRAPS)	Autosomal dominant	*TNFRSF1A*
Mevalonate kinase deficiency (MKD)	Autosomal recessive	*MVK*
Cryopyrin-associated periodic syndromes (CAPS)	Autosomal dominant	*NLRP3*
Periodic fever, aphthous stomatitis, pharyngitis, lymphadenitis (PFAPA) syndrome	Polygenic inheritance	Not available

Table 66.2 Main clinical characteristics of periodic fever syndromes

	Familial Mediterranean fever (FMF)	Tumor necrosis-associated periodic syndrome (TRAPS)	Mevalonate kinase deficiency (MKD)	Cryopyrin-associated periodic syndromes (CAPS)	Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA)
Duration of attacks	1–3 days	>7 days	3–7 days	Variable	3 to 5 days
Mucocutaneous involvement	Erysipelas-like erythema	Migratory rash	Maculopapular rash, oral aphthous	Cold-induced urticarial-like rash	Oral aphthous
Musculoskeletal involvement	Acute monoarthritis, occasionally protracted arthritis in hip or knees	Arthralgia, arthritis, migratory myalgia	Arthralgia, arthritis	Arthralgia, arthritis and epiphyseal overgrowth, contractures	Arthralgia
Gastrointestinal involvement	Peritonitis, constipation, diarrhea	Peritonitis, constipation, diarrhea	Abdominal pain, vomiting, diarrhea	Rarely abdominal pain, nausea	Abdominal pain
Cardiopulmonary involvement	Pleuritis, pericarditis	Pleuritis, recurrent pericarditis	Rare	Rare	Unexpected
Renal involvement	Amyloidosis	Amyloidosis	Uncommon	Amyloidosis	Not reported
Ocular involvement	Uncommon	Periorbital edema, conjunctivitis	Uncommon	Conjunctivitis, uveitis, vision loss	Uncommon
Ear involvement	Uncommon	Uncommon	Uncommon	Hearing loss	Uncommon
Other findings	–	–	Cervical lymphadenopathy	Aseptic meningitis	–

66.2 Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is prototypic and most common monogenic hereditary PFSs. The disease results from the gain-of-function mutations on the *MEFV* (*Mediterranean FeVer*) gene. The *MEFV* gene encodes the protein pyrin, which acts part in activating the caspase-1 molecule and producing interleukin (IL)-1-β [3, 4]. Although considered an autosomal recessive disease, individuals

with only one mutation in the *MEFV* gene may display the FMF phenotype. The expression of disease phenotype in heterozygous people is linked to the penetrance of the gene, modifier genes, and/or environmental factors [5, 6].

66.2.1 Etiology and Pathogenesis

Familial Mediterranean fever has a high prevalence among Sephardic Jews, Armenians, Turks, and Arabs, with an estimated prevalence of 1–2:1000. Furthermore, the carrier frequency of *MEFV* variants is as high as roughly one in five among these populations [7–10]. However, apart from the Mediterranean basin, FMF cases are reported from all over the world. Nevertheless, why FMF is dominant in the Eastern Mediterranean region has been a matter of debate for decades. Recently, it was shown that pyrin mutations protect against the pandemic plague caused by *Yersinia pestis* [11]. In healthy individuals, Rho-GTPases activate serine–threonine kinases (PKN1 and PKN2), which phosphorylate pyrin. The phosphorylated pyrin becomes inactivated, and the inflammatory response is suppressed. Pyrin recognizes bacterial modifications in Rho-GTPases. Apart from other pathogenic bacteria, pathogenic Yersinia species (*Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica*) have a unique virulence factor called YopM [11, 12]. This virulence factor directly inactivates the pyrin inflammasome via phosphorylation. Mutations in the pyrin protein prevent interaction with YopM and the inactivation of the pyrin inflammasome. These findings confer resistance to plague in FMF patients.

66.2.2 Clinical Presentation

Fever is the predominant feature in FMF attacks. Febrile attacks are frequently accompanied by polyserositis and elevated acute phase reactants (APRs). Approximately 90% of patients experience their first attack before 20 years of age. The attacks are usually unprovoked, self-limiting, lasting between 12 h and 3 days. Menstruation or stress may trigger an attack. Abdominal pain ranging from mild discomfort to severe pain mimicking appendicitis is observed in up to 95% of patients during the attacks. Constipation or diarrhea may also be present. About one-third of patients present with unilateral chest pain caused by pleuritis. Albeit rare, recurrent pericarditis may be observed in 0.5% of patients.

Most patients appear clinically well during attack-free periods, while in some, elevated APRs may be detected even between the attacks. Joint involvement is another common characteristic (33–70%), usually presenting with the acute, nonerosive monoarthritis of large joints such as the knee, ankles, and wrist, while chronic arthritis affecting hips or knees may be seen in 5–10% of patients. Exertional leg pain may be seen in 20% of FMF patients. Protracted febrile myalgia is a rare but severe presentation of FMF. Patients with protracted febrile myalgia present with paralyzing myalgia and high fever requiring corticosteroids. High fever, elevated APRs, and normal serum creatine kinase levels are typical findings of protracted febrile myalgia.

Erysipelas-like erythema is the pathognomonic skin rash of FMF, which usually appears on the extensor surface of lower extremities resembling cellulitis. Furthermore, FMF patients are at increased risk for other rheumatologic diseases such as vasculitis (polyarteritis nodosa, immunoglobulin A vasculitis/Henoch Schönlein purpura, and Behçet's disease), inflammatory bowel diseases, and chronic arthritis [13–15]. There are no diagnostic biomarkers for FMF patients, whereas leukocytosis and elevated APRs may be observed during the attacks.

66.2.3 Diagnosis

The diagnosis of FMF depends on clinical findings. Genetic analysis is performed to support the diagnosis. Recently, a new set of classification criteria (Eurofever/PRINTO) has been introduced. These new criteria set combine clinical manifestations with genotype for the first time [16]. According to the Eurofever/PRINTO classification criteria, patients may be classified as having FMF in the presence of confirmatory *MEFV* mutations and the presence of at least one of the following findings: (1) duration of episodes between 1 day and 3 days, (2) arthritis, (3) chest pain, and (4) abdominal pain [16]. In the absence of confirmatory *MEFV* mutations, at least two clinical findings are required to classify a patient as having FMF [16]. More than 300 *MEFV* sequence variants have been introduced (*http://fmf.igh.cnrs.fr/infevers/*). The most prevalently detected pathogenic variants, such as M694V, M694I, M680I, V726A, R761H, and A744S, are all located in exon 10. M694V is the most frequently seen pathogenic variant related to a severe phenotype. According to the consensus guideline for the genetic diagnostic testing of hereditary recurrent fevers, a total of 14 variants (nine variants defined as clearly pathogenic, M694V, M694I, M680I, V726A, R761H, A744S, E167D, T267, and I692del, and five variants defined as unknown significance, K695R, E148Q, P369S, F479L, and I591T) are recommended to be tested [17]. Without the presence of clinical findings, genetic screening of siblings or parents is not recommended [18].

66.2.4 Treatment

The mainstay treatment of FMF is colchicine. In addition to suppressing inflammation, colchicine also prevents amyloidosis. Colchicine shows its effects via binding to tubulin and depolymerizing the microtubules. It is a safe and well-tolerated drug, while 5–10% of the patients suffer side effects at the recommended doses. The recommended dose of colchicine is as follows: for children <5 years of age; a starting dose of ≤0.5 mg/day (≤0.6 mg/day in case tablets contain 0.6 mg), for children 5–10 years of age; 0.5–1.0 mg/day (1.2 mg/day in case tablets contain 0.6 mg), for children >10 years of age; and 1.0–1.5 mg/day (1.8 mg/day in case tablets contain 0.6 mg). In the presence of amyloidosis or high disease activity, the colchicine dose may be gradually increased up to a daily dose of 2 mg in children [18]. The most common side effects are gastrointestinal symptoms such as

nausea, vomiting, transient elevation of transaminases, and especially diarrhea. As colchicine is metabolized by CYP3A4, drug interactions and toxicity may occur when using drugs (such as macrolides, cyclosporine, and cimetidine) metabolized by the same enzyme [18]. Despite an adequate colchicine dose, 5–10% of FMF patients are unresponsive to colchicine therapy. If a patient suffers from an attack for at least a month or has persistent APRs during attack-free periods, this patient should be considered unresponsive. Anti-interleukin (IL)-1 therapy, anakinra, canakinumab, and rilonacept emerge as alternative agents for colchicine-resistant FMF patients [18].

Disease severity may vary based on the genotype. Previous studies have shown that M694V homozygosity increases the risk of severe phenotype and early disease onset. As patients have an increased risk of secondary amyloidosis, performing urinalysis periodically to detect proteinuria is highly recommended [18]. A positive family history of amyloidosis, the male sex, M694V homozygosity, and the SAA1.1a/a genotype are predisposing factors associated with an increased risk of developing amyloidosis.

66.2.5 Hearing Loss in Familial Mediterranean Fever

Due to the multisystemic effects of FMF, it raises curiosity about whether FMF affects the ear. However, conflicting results have been published concerning high-frequency audiometry and otoacoustic emission (OAE) testing in FMF patients. Uysal et al. [19] compared cochlear function between FMF patients and healthy controls and reported that the FMF patients had similar transient-evoked otoacoustic emission (TEOAE) parameters to the healthy controls. Somuk et al. [20] demonstrated similar vestibular-evoked myogenic potential (VEMP) alterations in FMF patients compared to healthy volunteers. Keskindemirci et al. [21] confirmed no significant differences in the hearing levels of FMF patients, and disease severity did not influence cochlear functions. In contrast to these studies, Salimov et al. [22] demonstrated cochlear involvement in FMF patients. In the distortion product otoacoustic emission (DPOAE) (1, 1.4, 2, 2.8, 4 kHz) test, the hearing thresholds of FMF patients increased at most frequencies in comparison with the control group, while Lordoglu et al. [23] showed the deterioration of cochlear functions, particularly at high frequencies. Albeit not evaluated, differences between studies were attributed to the genetic heterogeneity of FMF. Most recently, Çetin et al. [24] assessed the effects of FMF on both the inner ear and the middle ear. They did not demonstrate any significant inner ear alterations in FMF patients, similar to most studies on FMF patients [19–21, 24, 25] but in contrast to the studies by Salimov [22] and Lordoglu [23]. They found that contralateral acoustic stapedial reflex thresholds were significantly higher in the FMF patients, and the ambient and peak pressure absorbance values of wide-band tympanometry were affected by disease severity and duration at 2000 and 4000 Hz. They concluded that FMF affects the middle ear and suggested that structural alterations of the joints between the middle ear ossicles may result in middle ear involvement [24].

66.3 Tumor Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS)

Originally called familial Hibernian fever, the autosomal dominant inherited disease was renamed as tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) in 1999 after the discovery of mutations in the TNF receptor superfamily member 1A (*TNFRSF1A*) [26]. The disease was first described in 1982 in a family with distinctive localized myalgia and painful erythema, in addition to clinical findings like FMF disease such as fever, abdominal pain, and serositis attacks, but with family tree characteristics suggesting an autosomal dominant inheritance pattern [27].

66.3.1 Etiology and Pathogenesis

Tumor necrosis factor is a type II transmembrane protein that has roles in many important pathways such as apoptosis, cell proliferation, immune modulation, inflammation, T-cell activation, and B-cell homeostasis [28]. This molecule has two receptors called TNFRSF1A and TNFRSF1B [29]. The gene that causes TRAPS, *TNFRSF1A*, is located on the short arm (12p13) of chromosome 12 [30]. Mutations in this region are usually localized to exons 2, 3, 4, and 6, and the vast majority are single nucleotide missense mutations [31, 32]. Most of these mutations affect the first two N-terminal cysteine-rich domains (cysteine-rich domains 1 and 2; CRD1–2) [33]. Two of the most common mutation sites in patients with TRAPS are T50M and T50K, associated with the CRD1 region, and affect hydrogen bonds, closely related to the structure of this region [34]. Nonstructural mutations usually lead to a milder clinical picture [35]. R92Q (new nomenclature R121Q) and P46L (new nomenclature P75L) mutations, nonstructural mutations, are also seen frequently in healthy individuals; therefore, their pathogenic significance is still controversial [34].

66.3.2 Clinical Presentation

The TRAPS may present with attacks quite like FMF. The median age at presentation is 7 years, and the attacks are characteristically different in children than adults [36]. Unlike adults, attacks in children can last longer, even for several weeks. Most patients experience recurrent episodes of fever with serositis presenting as abdominal and/or chest pain, myalgia with or without the typical migratory rash, arthralgia, and arthritis [28]. Frequent findings were reported to include fever (88%), abdominal pain (74%), rash (63%), ocular findings (43%), pleuritic pain (32%), headache (28%), and lymphadenopathy (14%) [37]. Most attacks can last from less than a week to 3 weeks, but a minority of patients may have a continuous illness with exacerbations. Attacks can be triggered by stress, menstrual

cycle, fatigue, infections, exercise, and vaccinations in approximately one-quarter of patients.

The clinical examinations and diagnosis of TRAPS patients are like any other autoinflammatory disease. More common conditions, such as infections and malignancy, need to be excluded in a new patient with no known family history. Although routine laboratory tests are not usually diagnostic, it is important to test high acute phase response proteins during attacks. Attacks are typically associated with elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (SAA) levels, as well as the presence of neutrophilia and thrombocytosis [38].

66.3.3 Diagnosis

There are no definitive clinical diagnostic criteria for TRAPS. The genetic analysis of the *TNFRSF1A* gene is required to confirm the diagnosis. Recently, the Eurofever/PRINTO classification criteria have been proposed to classify autoinflammatory diseases, including TRAPS [16]. The most crucial difference in these new classification criteria from the previous ones is that the genotypes of patients were also included in the evaluation. Patients can be classified as TRAPS patients in the presence of confirmatory mutations of *TNFRSF1A* and at least one of the following criteria: attacks lasting 7 days or longer, myalgia, migratory rash, ocular edema, and family history.

66.3.4 Treatment

The main aim of treatment is to control disease activity as early and quickly as possible and prevent disease- and treatment-related damage. Untreated TRAPS cases are at risk of AA amyloidosis and were demonstrated in 18% of adult patients in a recent series [39]. Although most patients benefit symptomatically from nonsteroidal anti-inflammatory drugs (NSAIDs), they are often unsuccessful in the cessation of attacks [40]. They generally end the attacks when corticosteroids are used at a dose of 0.5–1 mg/kg. However, the effectiveness decreases over time in most patients, and the long-term use of corticosteroids is not recommended due to serious side effects [41]. The effectiveness of colchicine treatment in TRAPS patients is low. Patients with low penetrance mutations might respond to colchicine. In a study evaluating the treatment responses of patients registered in the Eurofever database, it was reported that only three patients diagnosed with TRAPS achieved complete remission [42]. In a prospective study, etanercept was shown to significantly improve symptoms and inflammatory parameters; however, most patients discontinue the drug due to its diminished efficacy [43]. Interleukin (IL)-1 blockade with anakinra is highly effective [44]. Another anti-IL-1 agent, canakinumab, was also shown to terminate and prevent attacks effectively [45].

66.3.5 Hearing Loss in Tumor Necrosis Factor Receptor-Associated Periodic Syndrome

Tumor necrosis factor receptor-associated periodic syndrome-related hearing loss (HL) has not been reported.

66.4 Cryopyrin-Associated Periodic Syndromes

Cryopyrin-associated periodic syndrome (CAPS) is an autosomal dominant autoinflammatory disease with fever, urticarial rash, and musculoskeletal and central nervous system (CNS) findings. Three different disease subtypes have been defined under the name of CAPS: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystemic inflammatory disease (NOMID) or chronic infantile neurological cutaneous articular syndrome (CINCA) [46]. These are now recognized as a spectrum of severity rather than separate diseases.

66.4.1 Etiology and Pathogenesis

The disease results from functional mutations in the nucleotide-binding and oligomerization domain, leucine-rich repeat, and pyrin 3 (*NLRP3*) gene on the long arm of chromosome 1, encoding the protein cryopyrin [47]. Interleukin (IL)-1 production increases due to functional mutations in the NLRP3 inflammasome complex [48]. The NLRP3 inflammasome can be activated by a few factors, including potassium, mitochondrial reactive oxygen species, changes in extracellular calcium levels, the lysosomal release of cathepsin B, and crystals such as uric acid. Most disease-causing mutations are found in exon 3 of the *NLRP3* gene, which encodes the NACT domain, but mutations can also be detected in other exons. While different mutations are seen in severe disease, in mild-spectrum disease, more than half of reported patients are heterozygous for one of the three common mutations: R260W, T348M, or A439V [49]. Although the disease is classically inherited in an autosomal dominant pattern, somatic mutations have been detected in a significant proportion of patients with clinical features of CAPS. Somatic mutations have been reported in up to 50% of cases with severe disease and 10% of the much more typical intermediate-spectrum disease [49].

66.4.2 Clinical Presentation

Increased IL-1 production causes chronic inflammation presenting from birth as fever, characteristic urticarial rash, and red eyes. Irreversible damage may include childhood-onset sensorineural HL (SNHL), vision loss due to inflammation affecting any eye level from the cornea to the optic nerve, skeletal deformities, cognitive

impairment, and systemic AA amyloidosis [47–49]. Skin findings are usually the first and most noticeable findings of the disease. Although the typical skin finding described in the disease is urticaria-like rash, erythematous, edematous papules or plaque-like rashes may also be observed. Biopsy of skin lesions reveals neutrophil and lymphocyte infiltration [50]. The musculoskeletal system is another important site of involvement in the disease. Extremity pain, myalgia, and arthralgia are reported in FCAS. Arthritis is mainly detected in MWS and CINCA/NOMID patients. Polyarticular involvement that causes deformity may be seen in patients diagnosed with CINCA/NOMID [48–50]. Skeletal deformities are also more common in patients with a diagnosis of CINCA/NOMID. Frontal bossing, osteopenia, and nasal bone flattening may be seen [48, 50]. Progressive HL is one of the main findings in patients diagnosed with MWS and CINCA/NOMID. Hearing loss is thought to be caused by degeneration in the organ of Corti. It has been reported that HL can be stopped and even partially regressed with timely treatment [40, 50]. The most common ocular findings in CAPS patients are conjunctivitis and keratitis. Uveitis, papilledema, and optic atrophy have been reported in CINCA/NOMID and rarely in MWS. Visual acuity may decrease due to optic nerve involvement [40, 51, 52]. The most common CNS involvement finding is headache, which can be seen in all disease subtypes. Aseptic meningitis and increased intracranial pressure are neurological findings to be considered in patients diagnosed with CINCA/NOMID [50].

Chronic leptomeningeal inflammation may cause adhesions, and hydrocephalus may develop [47, 51]. Growth retardation, seizures, stroke, and vascular occlusion are other CNS findings of the disease [50]. The clinical findings of CAPS patients are summarized in Table 66.3.

Abnormal laboratory findings detected in CAPS include neutrophilia, thrombocytosis, and anemia. The neutrophil count may be high between attacks, but it

Table 66.3 Clinical findings of patients with cryopyrin-associated periodic syndrome (CAPS)

	FCAS	MWS	CINCA/NOMID
Attack duration	<1 day	1–3 days	1–3 days of exacerbation; persistent course
Systemic findings	Fever, malaise	Fever, malaise	Fever, malaise
Cutaneous	Urticarial rash	Urticarial rash	Urticarial rash
Musculoskeletal	Arthralgia, myalgia	Arthralgia, myalgia, arthritis	Arthralgia, myalgia, arthritis, bone overgrowth, chronic deformities
Ocular	Conjunctivitis, keratitis	Conjunctivitis, keratitis, uveitis	Conjunctivitis, keratitis, uveitis, papilledema, optic atrophy
Neurological	Headache	Headache	Headache, increased intracranial pressure, aseptic meningitis, seizure
Hearing loss	–	Sensorineural	Sensorineural

CINCA chronic infantile neurological cutaneous articular syndrome, *FCAS* familial cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *NOMID* neonatal-onset multisystemic inflammatory disease

usually increases significantly during an exacerbation. Diffuse inflammation in CAPS is manifested by elevation in acute phase markers such as ESR, CRP, and SAA. The phagocyte-specific S100 proteins S100 A12 and MRP 8/14 are novel biomarkers that can be used to detect inflammation. By measuring these markers, potentially subclinical disease activity can be detected [48].

66.4.3 Diagnosis

CAPS symptoms are sufficiently characteristic in that validated diagnostic criteria have been developed. In addition to increased inflammatory markers, two or more of the six typical symptoms diagnose CAPS with 94% specificity and 81% sensitivity [53]. In 2019, new Eurofever/PRINTO classification criteria were proposed to classify autoinflammatory diseases [16]. The presence of a confirmatory mutation of NLRP3 and the presence of at least one of the following criteria may be classified as CAPS: urticaria, red eye (conjunctivitis, episcleritis, uveitis), and SNHL.

66.4.4 Treatment

The cryopyrin-associated periodic syndrome has been successfully treated since the early 2000s, with the recognition of the role of IL-1 blocking agents [54]. Currently, three different anti-IL-1 treatments for CAPS, anakinra (recombinant IL-1 receptor antagonist), rilonacept (recombinant fusion protein), and canakinumab (a fully human monoclonal antibody with high specificity for IL-1b), are approved [55–57]. All three treatments have shown remarkable efficacy in completely resolving CAPS-related symptoms, normalizing the acute phase response, and dramatically improving quality of life. A recent study reported that 64% of patients using anakinra had complete and 34% had partial responses, whereas 75% of patients using canakinumab had complete, and 25% had partial remissions [42]. No evidence suggests that therapies involving other disease-modifying drugs may be effective in patients with CAPS [41, 50].

66.4.5 Hearing Loss in Cryopyrin-Associated Periodic Syndromes

Progressive SNHL is a significant symptom in MWS and NOMID patients. High frequencies (4–10 kHz) are primarily affected [58], but lower frequencies are also affected, and progressive worsening throughout the course of the disease and with age has also been reported [59]. Unlike more common diseases that cause HL, the pathogenesis is due to ongoing cochlear inflammation leading to the degeneration of sensory structures in the organ of Corti. Therefore, a reversal or halt in the progression of HL can be achieved with the timely initiation of targeted anti-inflammatory therapy.

66.5 Mevalonate Kinase Deficiency

Mevalonate kinase deficiency (MKD) is a periodic fever known as hyperimmunoglobulin D syndrome (HIDS). It is a disease that causes a severe form called mevalonic aciduria in the absence of the relevant enzyme. It also draws attention because it is a congenital metabolic disease and is included in the classification of periodic fevers due to its clinical features [60].

66.5.1 Etiology and Pathogenesis

Loss-of-function mutations in the mevalonate kinase (*MVK*) gene located on the long arm of the 12th chromosome (12q24) lead to a decrease in the biosynthetic functions of the MVK enzyme [61]. Two clinical phenotypes are known, determined by the activity of intracellular enzymes. In autoinflammatory disease, residual enzyme activity is about 10%, while in the inherited metabolic disorder mevalonic aciduria, there is almost no detectable enzyme activity. More than 170 mutations thought to be associated with the disease have been reported, two of which are the most common. The V377I mutation was detected in 84% of the patients in the largest series. The second most common mutation is I268T, demonstrated in 25% of patients, although none were homozygous [62].

Mevalonate kinase plays a role in the sterol and isoprenoid biosynthetic pathway that converts mevalonic acid to mevalonate-5-phosphate. The pathological mechanisms of autoinflammation in MKD are not fully understood, but the reduced synthesis of isoprenoid lipids, particularly geranyl-geranyl diphosphate, is thought to play a central role [63]. Isoprenyl groups are essential for proteins' function and intracellular location, such as the small GTPase Ras, Rac, and RhoA [62]. A deficiency of geranyl-geranylated RhoA leads to pyrin inflammasome coupling and hence the proteolytic activation of IL-1β [12]. Another mechanism is NF-κB activation caused by the defective isoprenylation of GTPase [12].

66.5.2 Clinical Presentation

The most common phenotype, also called the HIDS phenotype, is characterized by the onset of 3- to 7-day recurrent episodes of fever during the first six months of life [62]. In almost 50% of cases, fever attacks are triggered by vaccination, stress, or infection. Symptoms and signs accompanying the attack include painful cervical lymphadenopathy, abdominal pain, vomiting, and diarrhea [41]. Arthritis or arthralgia of large joints can be observed in most patients. Oral or genital ulcers may develop. Skin lesions may be seen in the forms of erythema, papules, purpura, or urticaria-like rashes. Although rare, findings such as pericarditis, macrophage activation syndrome, erythema nodosum, uveitis, and prolonged fever may be observed in an attack [64]. Patients with mevalonic aciduria with very low enzyme activity

(<0.5%) experience severe inflammatory attacks, as in MKD. Additionally, facial dysmorphia, growth retardation, developmental delay, seizures, and liver involvement are frequently observed in these patients [64]. MKD-related HL has not been reported so far.

Inflammatory episodes are characterized by increases in APRs such as CRP, ESR, and SAA. Leukocytosis with prominent neutrophils is also observed. Although the acute phase response and leukocyte count return to normal between attacks, sometimes, subclinical inflammation may be observed during these periods. During an attack, mevalonic acid can be detected in the urine [65]. Persistent hematological abnormalities (e.g., anemia, leukocytosis, thrombocytopenia, and atypical cells) and liver dysfunction may be observed in mevalonic aciduria [66]. Albeit not all patients, most have elevated immunoglobulin (Ig) D and/or IgA levels [67, 68].

66.5.3 Diagnosis

The diagnosis is based on a detailed medical history and evaluation of the patient during an attack. Periodic fever, aphthous stomatitis, pharyngitis, cervical lymphadenitis (PFAPA) syndrome, other autoinflammatory diseases, and viral infections are included in the differential diagnosis of the HIDS phenotype in young children. Other metabolic diseases should be considered in the differential diagnosis of mevalonic aciduria. The patient can be classified as MKD if at least three of the six signs are present: age at onset younger than 1 year, gastrointestinal symptoms, painful lymph nodes, aphthous stomatitis, triggers, and maculopapular rash [16].

66.5.4 Treatment

Nonsteroidal drugs relieve symptoms during an attack but do not shorten the duration of the attack [41]. Corticosteroids and colchicine may often be ineffective, but long-term colchicine may benefit those with mild disease. In severe diseases, IL-1 blockade appears to be the most promising treatment [62]. Therapeutic success is generally moderate, with only 30% complete remission and 70% partial remission in patients treated daily with anakinra. Canakinumab, a monoclonal antibody against IL-1β, appears to have superior efficacy over anakinra, with more than half of patients achieving a complete response [69]. The blockade of the IL-6 receptor with tocilizumab has been shown to be highly effective in very few patients who have been proven resistant to other treatments [70].

Mevalonic aciduria has a poor prognosis because of early mortality and severe developmental delay. Early stem cell transplantation seems to be a rational option. Patients with the HIDS phenotype have a better prognosis. In many patients, the frequency and severity of inflammatory attacks decrease in adulthood. AA-type amyloidosis is seen as a long-term complication. The prevalence of AA amyloidosis in MKD is approximately 4–5%, lower than some other hereditary autoinflammatory syndromes [62].

66.5.5 Hearing Loss in Mevalonate Kinase Deficiency

There is no information yet about the development of HL in mevalonate kinase deficiency.

66.6 Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Lymphadenitis (PFAPA) Syndrome

Periodic fever, aphthous stomatitis, pharyngitis, and cervical lymphadenitis (PFAPA) syndrome is the most common cause of recurrent fever in childhood. It was first described by Marshall et al. [71] in 1987. Attacks recur at regular intervals of three to eight weeks, and fever lasting 3–6 days is accompanied by signs of aphthous stomatitis, cervical lymphadenitis, and pharyngitis. The disease often begins before the age of 5 years and usually regresses in adolescence. The general condition, growth, and development of patients are normal between episodes.

66.6.1 Etiology and Pathogenesis

Although the pathogenesis of the condition is not precisely known, it is evaluated in autoinflammatory syndromes. Studies have shown that the pro-inflammatory cytokines IL-1β, IL-18, TNF-α, and interferon (IFN)-γ increase rapidly in the early phase of the fever attack, and IL-6 increases similarly in the late phase. Dysregulation in the immune system and a high rate of improvement in clinical findings after tonsillectomy bring tonsil tissue to the center of the event in PFAPA [72]. A previous study examining tonsillectomy specimens suggested that microbiota may play a role, although it failed to identify the mechanism [73].

66.6.2 Clinical Presentation

Attacks recur at regular intervals of 3–8 weeks, and fever lasting 3–6 days is accompanied by signs of aphthous stomatitis, cervical lymphadenitis, and pharyngitis. The disease often begins before the age of 5 years and usually regresses in adolescence. Characteristically, the attacks are so regular that sometimes parents can predict the time [74].

Clinical improvement, normal growth, and development are important parameters in the period between attacks. In most children, the disease is resolved within a few years or during adolescence, but the attacks severely impact the quality of life of the child and family.

There is no diagnostic laboratory test. Patients can be diagnosed with tonsillitis or viral infection. Group A streptococcus can be detected in the throat culture in 9.8% of cases [75]. Nevertheless, PFAPA attacks do not respond to antibiotic treatment. During the attack, neutrophilia, lymphopenia, and monocytosis may be

present. C-reactive protein is detected high at the beginning of the attack, and ESR may be normal, but it can elevate after a few days [76]. Serum amyloid A, S100A8/A9, and S100A12 levels may be high during the attack period [77]. Procalcitonin is not elevated like other AFRs [78]. Serum immunoglobulin levels are normal, while IgD is normal or slightly increased [76, 79]. All inflammatory parameters return to normal levels between attacks [72, 76].

66.6.3 Diagnosis

Although the diagnosis of the condition had been made with the modified Marshall criteria, new diagnostic criteria were developed in 2018, as these criteria have low specificity despite their high sensitivity [80]. According to these criteria, a diagnosis can be made if at least two of the symptoms of oral aphthae, cervical lymphadenitis, and pharyngitis are accompanied by fever attacks that start before the age of 6 years and last for 2–7 days at intervals of less than 2 months.

66.6.4 Treatment

There is no particular treatment modality yet since PFAPA syndrome is a self-limiting and benign disease. Considering the potential side effects of treatments and social problems, such as the inability of the child and family to go to work and school in this febrile period, the family and the doctor should decide on the treatment together [81].

Clinical experience has demonstrated that antipyretics partially affect the treatment of PFAPA syndrome. The effects of NSAIDs on fever are slightly more prominent than those of paracetamol. However, they cannot control other symptoms except fever [82].

Administration of 1–2 mg/kg prednisolone at the onset of fever controls the signs of fever and pharyngitis but has no effect on aphthous stomatitis and adenitis. This rapid response also has diagnostic characteristics that help differentiate PFAPA syndrome from other periodic fever syndromes [76, 83]. Moreover, glucocorticoids can shorten the time between attacks in 25–50% of patients [82].

Colchicine has also been tried in patients with PFAPA, based on many years of experience in FMF patients. However, there is no standardized treatment protocol for colchicine in PFAPA patients. Recent studies have shown that colchicine reduces the number of attacks and disease duration in patients with PFAPA who are heterozygous MEFV carriers [84–86]. Most recently, consensus treatment plans for PFAPA were announced by the childhood arthritis and rheumatology research alliance (CARRA). According to CARRA protocol, colchicine prophylaxis (0.5–1.25 mg/day) may be prescribed to patients whose attack intervals are less than 21 days despite 2 mg/kg prednisolone in attacks [87]. Due to the role of IL-1 in the pathogenesis of PFAPA, anakinra was tested to be used in a small group of patients,

and a dramatic improvement was observed [88]. The use of anakinra in PFAPA is still limited due to the lack of randomized controlled trials on the drug [82].

While deciding on the surgical treatment option, the decision should be made according to the patient's age, the frequency and duration of the attacks, the patient's response to other treatment options, and the loss of workforce of the family and the child. Before surgical treatment, a specialist in autoinflammatory diseases should evaluate the patient [81]. A meta-analysis reported remission in 92% of 555 patients treated with adenotonsillectomy [89].

66.6.5 Hearing Loss in PFAPA

There is no evidence suggesting that PFAPA causes HL.

66.7 Conclusion

In conclusion, hereditary fever syndromes are among the common diseases of childhood. It is essential to raise awareness because they have a broad spectrum of differential diagnoses such as infection, metabolic diseases, and malignancy. Hearing loss is frequently seen in this disease group, especially in the MWS and CINCA/NOMID forms of CAPS. It should be kept in mind that these conditions can be prevented with early diagnosis and treatment.

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Part XI

Vaccines

Vaccines and Hearing Loss

67

Makbule Özlem Akbay, Edhem Unver, and Osman Gül

67.1 Introduction

Vaccination has proven to be among the greatest advances in medicine within the modern era. The majority of diseases for which vaccination offers protection have become rare, and thus, most parents are unaware of their potentially devastating impact on their children. Vaccine hesitancy is increasing since parents do not fully appreciate the need for vaccination and focus on the possible complications and side effects instead. General practitioners need to understand both the benefits and risks of immunising children according to the recommendations. At present, the compound thimerosal is added to vials of influenza vaccine as a preservative. There have been concerns about this compound, but research indicates that exposure to thimerosal via vaccination does not cause any harm to the nervous system. Despite some claims to the contrary, the measles, mumps and rubella vaccine does not have any association with autistic spectrum disorders. Genuine risks include a local reaction at the site of injection, leading to redness and discomfort and a very slight increase in the incidence of intestinal intussusception following the administration

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of the rotavirus vaccination. Immunisation with various vaccinations may cause a syncopal episode. However, other side effects are very rare. Sadly, whilst the recommendation is for children of both sexes to be vaccinated against the human papillomavirus (HPV), the number of children immunised remains low [1].

Immunisation offers children a direct benefit through immunity to disease whilst also providing an indirect benefit to other children by reducing the number of potentially infective individuals to below a critical level, known as herd (i.e. community) immunity. When community immunity is established, the transmissibility of pathogens falls to a low level [2, 3]. The indirect benefits conferred by community immunity are important for those children below the recommended age for vaccination and those in whom immunisation is contraindicated. For community immunity to exist, however, most of the individuals living in an area must accept the offer of vaccination according to the recommended immunisation schedule [4].

67.2 Side Effects of Vaccination

Discomfort, oedema and redness frequently occur in the area where the vaccine was initially injected. It is also possible for a systemic reaction to be observed, such as pyrexia or increased irritability. The child may become drowsy or an exanthem may appear [5]. Immunisations administered more deeply (with a needle of length 25 mm rather than 16 mm) are less liable to provoke a local reaction [6]. The frequency of pyrexia and localised reactions in children receiving the fourth instalment of the diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine is higher than for the initial injection, in a quarter of cases [5]. Following the fourth or fifth dose, there is oedema affecting the whole thigh or upper arm in 1 in 30 vaccinated children, and this may last up to a week [5]. Syncopal episodes are also a potential complication shortly after administering certain vaccines, particularly to adolescent patients. This applies to the HPV, quadrivalent meningococcal conjugate (MCV4), tetanus toxoid and DTaP vaccines [7]. As a precaution, observation of adolescent patients should continue for 15 minutes following the administration of the vaccine [5, 8]. Whilst paracetamol given at the time of injection or soon after does have some benefit in terms of reduced side effects, the use of antipyretic agents may reduce the expression of immunoglobulins in response to the vaccine [9]. Accordingly, the US Centres for Disease Control and Prevention (CDC) have ceased to advise the use of antipyretics prophylactically when immunisation is undertaken. Furthermore, antipyretics do not effectively protect against the occurrence of a febrile convulsion [1, 10].

67.3 Allergenic Compounds Included in Vaccine Preparations

There are very low levels of certain antibiotics in three commonly used vaccines, namely varicella, MMR and inactivated poliovirus vaccines. Neomycin is one of the antibiotics involved. If a patient has previously suffered anaphylaxis in response to

any of the antibiotics involved, this counts as a contraindication to the use of the vaccine [11, 12]. Likewise, gelatine is a potential ingredient in vaccine preparations containing live viruses, especially varicella and MMR vaccines, and thus, these vaccines should not be administered to patients with a previous anaphylactic reaction to gelatine [11]. Although the MMR vaccine is grown in tissue cultures containing chick embryonic fibroblasts, patients with an allergy to egg can still be administered this vaccine [12]. However, if there is a history of anaphylactic reaction to the protein contained in egg, inactivated influenza vaccine is contraindicated. The trivalent inactivated influenza vaccine does not contain egg protein and is therefore an appropriate substitute [13]. There is a comprehensive listing of vaccine excipients and other possibly allergenic compounds contained in vaccines produced by the US CDC [11, 14]. The frequency of anaphylaxis following vaccine administration is around 1 in one million doses [15]. In cases where this occurs, the patients need to be tested using a skin prick allergen challenge, which can establish whether anaphylaxis occurred via the action of immunoglobulin E and, if so, which component of the vaccine the immunoglobulin targets. Where skin testing fails to identify any culprit, it is reasonable to give the vaccine a second time, provided facilities for anaphylactic resuscitation (including adrenaline-loaded syringes) are available and it is possible to observe the patient after the vaccine has been administered [1, 13, 15].

67.4 Immunisation Against Meningococcus

The recommendation for all adolescents to receive the MCV4 vaccine has been in place since 2005. The first dose should be given to patients at the age of either 11 or 12 years, with a further booster when the child turns 16. The vaccine offers protection against the Meningococcal serotypes A, C, Y and W135. Although there initially appeared to be an association between Guillain–Barré syndrome and MCV4, this has now been demonstrated not to exist [16]. The side effects occurring with the highest frequency are pyrexia, headache, redness in the area of injection and vertigo. There is a progressive decrease in immunity, which occurs even following the booster [16]. Since 2015 two vaccines offering protection against *Neisseria meningitidis* of serotype B have been licensed by the USA FDA. Patients tolerate both types well, in contrast to earlier vaccines against the same pathogen, which caused cross-reactions with antigens normally found within the central nervous system [17]. Since disease caused by the B serotype pathogen is relatively rare, it is usually suggested that these vaccines only be administered to patients who are at raised risk, or where an outbreak occurs [18]. The two serotype B vaccines cannot be used interchangeably [18].

The consequences of infection with *N. meningitidis* are generally highly severe. The disease typically affects young patients without a history of previous medical problems. The infection may cause mortality within hours. Furthermore, even where patients do not die, there may be complications in the longer term, such as amputation of limbs, deafness and cognitive or neurological abnormalities [1].

Currently, there are two types of vaccine formulated to protect against *N. meningitidis*, namely MCV4 (which protects against serotypes A, C, Y and W135, i.e. it is polyvalent) and those which protect against the B serotype (i.e. monovalent vaccines). All meningococcal vaccines currently in use are of the inactivated type [19].

The immunisation strategy to employ is dictated by the local prevalence of the different meningococcal serotypes, in addition to the age of the patient and their risk factors for infection with *N. meningitidis*. Both monovalent vaccines and the polyvalent vaccine currently available stimulate adequate immunity and rarely result in side effects of more than mild severity [19].

67.4.1 Side Effects

In adolescent and adult recipients of the MCV4 vaccine, the side effects that are reported with the highest frequency are localised redness and oedema, muscular pain, pyrexia, fatigue and headache [19]. Other than injection site complications, the adverse effects in infants and children generally consist of the child exhibiting drowsiness and increased irritability [19].

Postmarketing pharmacovigilance data for the quadrivalent vaccines Menactra and Menveo indicate that syncopal episodes occur, which may result in severe injuries [20]. The occurrence of syncope is always possible following vaccination, with the peak frequency in adolescence [21].

67.5 COVID-19 Immunisation and Auditory Loss

COVID-19 was a new infection, which caused a global pandemic, beginning in 2019. This led to efforts to mass-immunise entire countries. Although vaccination has only rarely resulted in adverse effects of high severity, there are reports indicating the occurrence of Guillain–Barré syndrome, thrombus formation and low platelets and inflammation of the myocardium associated with vaccination. There have also been reports indicating adverse ENT-related events in some individuals following vaccination for COVID-19. In a number of individuals, sudden sensorineural hearing loss (SSNHL) has been noted [22]. A case series of three patients reported by Jeong et al. noted the occurrence of SSNHL some 3 days after administration of the COVID-19 vaccine. These researchers felt that the association between immunisation and SSNHL was possible but unproven, given that viral infections in themselves are known causes of SSNHL. Viral infections causing sudden deafness should be treated as an emergency necessitating the use of corticosteroid treatment [22].

There have been some reports of serious complications arising from the use of particular COVID-19 vaccines. The vaccine produced by Janssen utilises an adenovirus vector. It has been associated with Guillain–Barré syndrome, as well as thrombotic events with thrombocytopenia [23]. Myocardial inflammation has been reported with the mRNA vaccines developed by Pfizer-BioNTech and Moderna [23]. Pharmacovigilance data gathered using the VAERS (Vaccine Adverse Events Reporting System) operated by the US CDC provide a signal for various ENT-related issues, including SSNHL [22, 24].

An article by Formeister et al. concludes that neither of the two mRNA vaccines for COVID-19 (as mentioned above) is associated with SSNHL [24]. In any case, where vaccines have been potentially implicated in SSNHL, there has been unclarity about the exact cause of hearing loss. One possible pathogenetic mechanism for vaccination causing deafness is via the production of immunoglobulins and cytokines triggered by the vaccine. If immune complexes form, these may result in an autoimmune response directed against the cochlea [25]. The cochlea may become the site of vasculitis and sustain ischaemic injury. Although vaccination may conceivably trigger this sequence of pathological events, other events, such as viral infections, may equally be responsible. If hearing loss occurs within a short period of vaccination (i.e. 3 days), this may, however, count as evidence for a vaccine as the aetiology behind SSNHL [22].

For SSNHL to be diagnosed, there must be a loss of at least 30 dB affecting three adjacent frequencies and developing in a 72-hour period [25–27]. This type of deafness generally cannot be ascribed definitely to a particular cause, although likely aetiologies include a viral infection, vasculitis, neoplasia or an autoimmune disorder [26, 28, 29].

67.5.1 Management of SSNHL

For cases of SSNHL occurring following the administration of a COVID-19 vaccine, the management is the same as when other causes are implicated. According to the published guidelines, the first-line treatment is to begin steroid therapy in the first 14 days after deafness begins [26]. The rapid administration of corticosteroids systemically may prevent the expression of immunoglobulins reacting to the antigenic challenge of the vaccine. Although this is current practice, there have been no studies, which have examined in detail how corticosteroid therapy affects the disease progression. It is known that a number of pharmacological agents can suppress the expression of immunoglobulins, namely steroids and immunosuppressants. Disorders resulting in immunosuppression alter antibody expression. One potential strategy is to deliver corticosteroids directly to the inner ear as a way to suppress the immune attack locally without preventing the development of systemic immunity [30]. For patients who do receive corticosteroid treatments at high doses whilst undergoing vaccination, there may be a need to perform serological quantification of the immunoglobulin response in order to see how effective vaccination has been [22].

67.6 Immunisation Against Influenza, Tetanus, Diphtheria and Rabies

There was a 1 in 100,000 risk of Guillain–Barré syndrome following vaccination with the swine influenza vaccine, introduced in 1976. This was between four and eight times the baseline frequency [31, 32]. The influenza vaccine developed in 2009 was, however, demonstrated not to be associated with any such risk [33]. There is a lack of consensus in the medical literature concerning the likelihood of developing

Guillain–Barré syndrome following influenza vaccination. It seems reasonable to conclude that any increase in risk is only slight, possibly 1 case in 1,250,000 vaccinations, resulting in one patient being hospitalised for every million patients immunised [31, 32, 34]. The research appears to confirm that Guillain–Barré syndrome is more strongly associated with influenza itself than with any vaccine, which would mean that the vaccination in fact lowers the risk [31, 32].

There are a number of case reports in which SSNHL has been linked to immunisation. The vaccines in question were those for influenza [27, 28, 35], tetanus, diphtheria and rabies [25, 30], as well as one targeting polysaccharides attached to the meningococcus [29]. The precise cause of SSNHL following immunisation has not been established [29]. A study involving large numbers of participants undertaken by Baxter et al. [28] found that SSNHL and previous immunisation were not connected, especially the use of the trivalent influenza vaccine of inactivated type and certain other vaccines [24, 28].

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Part XII

Cochlear Implants

Cochlear Implant Infections in Children

68

Erdem Gönüllü and Armagan İncesulu

68.1 Introduction

Hearing loss is a common problem in childhood and can have developmental, educational, and cognitive consequences in language development without early hearing rehabilitation [1]. One in every 1000 children in the United States of America (USA) is diagnosed with profound bilateral sensorineural hearing loss (SNHL) with the aid of universal newborn hearing screening [2]. Cochlear implants (CIs) are increasingly used to treat hearing loss (HL). The documented benefits of early placement of the CI on speech and language skills have reduced the age at which authorities approve these devices from 24 months to 9 months [1]. Nine months is also the earliest Food and Drug Administration (FDA) of USA-approved age for an implant procedure in children's bilateral profound SNHL [3, 4]. According to the National Institute on Deafness and Other Communication Disorders, 736,900 registered devices have been implanted worldwide: in the USA, 118,100 in adults and 65,000 in children, as of December 2019 [5].

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68.2 Cochlear Implant Device

A CI is an implanted electronic hearing device designed to produce helpful hearing sensations for a person who has a profoundly lost sense of hearing by electrically stimulating nerves inside the inner ear, bypassing the damaged hairy cells within the organ of the Corti [6, 7]. The implant consists of an extracorporeal part usually sitting behind the ear and a surgically placed inner part extending to the cochlea and electronically stimulating the cochlear nerve (Fig. 68.1).

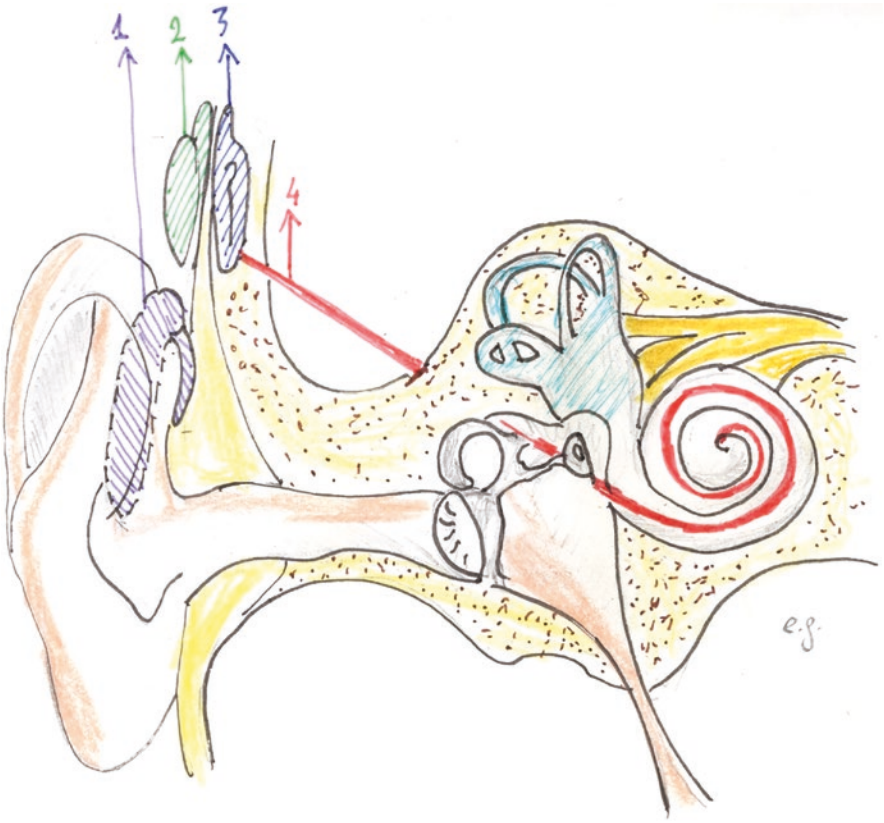

Fig. 68.1 Parts of the cochlear implant device**.** (1) Microphone and speech processor, (2) transmitter, (3) receiver, (4) electrode array (Courtesy Erdem Gönüllü, MD)

68.3 Infectious Complications at the Cochlear Implant Site After Placing

Infection-related complications after CI placing are mainly local infections such as superficial skin and deep soft tissue or device-related infections. There is a possibility that otitis media attacks after the intervention may progress to inner ear infection and rarely feared complications such as mastoiditis and meningitis [8, 9].

Superficial and deep wound infections associated with the internal part of the implant device are considered surgical site infections. The FDA recommended prophylactic perioperative antibiotic treatment in CI recipient children in 2006; this recommendation was withdrawn when using positioner-containing devices was discontinued [10].

Surgical wound infection rates have decreased as surgical techniques have improved toward fewer incisions and more optimal skin flap design [9, 11]. Although surgical wound infection rates decrease due to the improvement of the surgical incision technique and the reduction in the incision, significant complications that require device removal are observed more frequently in children than in adults [9].

A systematic review showed that surgical site infection rates vary from 1% to 13% [12]. In a large pediatric CI cohort including 475 pediatric cases ages 5 months to 18 years between 2010 and 2012, the postoperative surgical infection rate was 6.1%, and device infections were found at a rate of 2.7%, respectively [13].

Although staphylococci spp., including methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* and *Staphylococcus epidermidis* strains, and *Pseudomonas aeruginosa* were the significantly identified microorganisms [13], *Escherichia coli*, *Klebsiella pneumoniae*, *Achromobacter xylosoxidans*, and *Candida albicans* were also reported as other causes of surgical site infections [9].

The culture taken from the wound sample may not always give a positive result. In this case, molecular tests, such as microbial gene sequencing, may be helpful. It should be kept in mind that these tests may occasionally show colonization rather than existing infection. The biofilm formed by bacteria, such as *S. aureus*, on foreign surfaces is a structure that protects microorganisms in their depths from phagocytes. Also, biofilms significantly contribute to delayed or repeated wound infections [13]. *Pseudomonas* spp., on the other hand, forms a "pseudocapsule" that prevents blood circulation around the device and reaches a sufficient concentration of antibiotics following soft tissue swelling [14].

68.3.1 Clinical Manifestations

When planning the treatment and predicting the prognosis, it is essential to determine whether the surgical wound infection is superficial or deep. Superficial infections tend to occur in the first weeks after the operation, while deep infections arise after months or even years later. One or more signs of inflammation may be detected around the electrode array. Pain, or sometimes painless swelling at the incision site, may be the only finding that develops without other inflammatory findings.

Fever, pain, erythema, swelling, and granulation tissue around the electrode array can also be found. Sometimes only pain around the receiver or stimulator or crusting of the skin is the sole symptom without other elements of inflammation.

68.3.2 Laboratory Workup and Radiological Approach

Although complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are required to evaluate infection, their clinical utility is limited.

Head and temporal bone computed tomography (CT) imaging is appropriate to assess for implant infection, and gallium single-photon emission CT imaging is appropriate for patients with suspected implant infection without evidence [15].

68.3.3 Management

Management of superficial wound infections contains local antiseptic care of the surgical incision site and an appropriate antibiotic regimen (Table 68.1).

Management of deep infections includes the culture of drainage material, appropriate systemic antibiotic administration for MRSA, surgical debridement, and consideration of device removal. The therapy interval must be tailored according to the

Table 68.1 Empiric antibiotic therapy for superficial *Staphylococcus aureus* or beta-hemolytic *Streptococcus* skin and soft tissue infection in children >28 days[a]

Desired spectrum	First-line therapy	Second-line therapy
MRSA	Clindamycin	Vancomycin (intravenous)
	Trimethoprim–sulfometaxazole (TMP-SMX)	Ceftaroline (intravenous)
	Doxycycline	Linezolid (oral or intravenous)
		Daptomycin (intravenous)
		Tedizolid (in children over 12 years; oral or intravenous)

[a] Adopted and modified from Ref. [9, 16]
MRSA methicillin-resistant *Staphylococcus aureus*

Table 68.2 Empiric antibiotic therapy for deep implant infection in children with or without methicillin-resistant *Staphylococcus aureus* > 28 days after cochlear implant surgery[a]

Desired spectrum	Antibiotic	Dose
Methicillin-resistant *S. aureus* (MRSA) *Staphylococcus epidermidis*	Vancomycin	15 mg/kg/dose every 6 h
Methicillin-susceptible *S. aureus* (MSSA)	Nafcillin	150–200 mg/kg/day in 4–6 divided doses (maximum dose 12 g/day)
	Oxacillin	150–200 mg/kg/day in 4–6 divided doses (maximum dose 12 g/day)
	Cefazolin	100–150 mg/kg/day in 3 divided doses (maximum dose 12 g/day)
MRSA or MSSA and retained device	Rifampin as adjunctive	10–20 mg/kg/day in 2 divided doses, maximum 600 mg/dose

[a] Adopted and modified from Ref. [9, 16]

patient's age, clinical status, infectious agent, and host response to treatment. Appropriate antibiotics and doses are listed in Table 68.2. Device removal should be considered in progressive infectious symptoms despite proper antibiotic therapy and surgical debridement.

68.4 Infections of the Middle Ear and Associated Tissues Related to Cochlear Implant

The risk of otitis media with effusion increases slightly after CI placement. Although the opening created in the cochlear wall or round window between the middle and inner ear during electrode placement is usually closed with fascia or other material, it remains a potential route for acute otitis media (AOM) that causes bacteria from the middle ear to spread to the inner ear [8].

Infectious agents that can reach the inner ear can cause HL through damage to auditory primary afferent neurons, implant infection, inner ear infection, and meningitis.

68.4.1 Acute Otitis Media in Cochlear Implant Recipient Children

Prospective studies in the epidemiology of AOM in children with CIs are rare. A prospective study of 60 children who had CIs has been published. Tympanic tube (TT) replacement was performed in 34 children prone to otitis media before the implant operation. All group members had normal tympanic membranes; no drainage from the TT was observed 2 weeks before implantation. Despite these interventions, AOM occurred following cochlear implantation in 44% of cases; otitis media happened within the first month following implantation in 36%. In contrast, among 26 children not prone to otitis media who underwent cochlear implantation, the rate of otitis media was 8% during the mean follow-up period of 20 months [17].

Bacterial agents in the etiology of otitis media consist primarily of *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* identified as the dominant causative agent in tympanocentesis after using 13-valent pneumococcal conjugate vaccines. Forty-five percent of causative agents are also beta-lactamase-positive [18].

68.4.1.1 Clinical Manifestations

Otitis media is a clinical diagnosis. Bulging of the hyperemic or normal tympanic membrane and pain in the ear suggest otitis media. Additional symptoms suggesting otitis media in CI recipient children are postauricular fold swelling and auricular proptosis. Postauricular swelling indicates tympanic membrane bulging and otitis media rather than mastoiditis in CI recipient children [9].

68.4.1.2 Microbiological Workup

In children with a toxic appearance, sending the fluid obtained by tympanocentesis to culture before antibiotic treatment may help diagnosis, but this procedure should not delay the treatment.

68.4.1.3 Radiological Assessment

Contrast CT imaging of temporal bone and surrounding tissue may help assess the spreading of infection for sigmoid sinus (sinus thrombophlebitis), epidural or intradural area (empyema), or brain tissue (brain abscess).

68.4.1.4 Management

An appropriate and adequate antibiotic therapy must be started at the initial diagnosis of AOM. Considering the complications like meningitis and explantation of the implant, "wait and watch" is not a logical option for CI-induced otitis media in children.

Oral antibiotic therapy is indicated in non-toxic children without signs of mastoiditis or meningitis only if the child had no inner ear dysplasia such as Mondini malformation and if the implant operation was at least 2 months since the diagnosis. Some implant models with "positioners" produced and available between 1999 and 2002 were recalled because of the increased risk of meningitis.

A first-line oral antibiotic for oral therapy targeting non-typeable *H. influenzae* is amoxicillin–clavulanate (80–90 mg/kg/day amoxicillin, divided into two doses). If there is beta-lactam hypersensitivity, oral treatment choices include cefdinir or cefpodoxime. Although levofloxacin is not indicated in children with AOM, the American Academy of Pediatrics (AAP) reserved the agent for *P. aeruginosa*-associated chronic suppurative otitis media [19].

If the patient does not meet the criteria for oral therapy, appropriate antibiotic treatment should be given intravenously. If the child appears toxic or a discharge is present, a sample should be obtained and sent for culture from tympanocentesis or TT without delay. The parenteral drug choices for children are listed in Table 68.3. The desired treatment interval is no shorter than 10 days and usually completed in 2 weeks. Oral amoxicillin–clavulanate may be used after the first afebrile 24 h, with clinical improvement and the disappearance of the toxic state.

Table 68.3 Empiric parenteral antibiotic therapy for otitis media in children with a cochlear implant[a]

Desired spectrum	Therapy	Dose
Streptococcus pneumoniae Non-typeable *Haemophilus influenzae*	*Ceftriaxone*	50–75 mg/kg/day, divided two doses, maximum 2 g/day
	Cefotaxime	150 mg/kg/day, divided three doses, maximum dose 2 g/day
Toxic appearance (penicillin-resistant *pneumococcus*)	Vancomycin	15 mg/kg/dose, every 6 h

[a] Adopted and modified from Ref. [8, 9]

A proper antibiotic regimen can be designed after an antibiogram of the tympanostomy fluid sample.

Suppose toxic appearance or fever is not resolved, and no clinical improvement is observed. In that case, a myringotomy should be done, and a CT imaging should be planned for complications if it is not done at the decision of intravenous antibiotics. Also, consultation with an otolaryngologist is advised [8].

68.4.1.5 Prevention

Most otolaryngologists advise TT insertion for the presence of fluid in the middle ear space before cochlear implantation [20]. Therefore, emptying the middle ear space is advocated. After drainage, most pediatric otolaryngologists preferred removing the TT and repairing the tympanic membrane before CI implantation [9].

This application depends on avoiding an entryway through which bacterial agents can reach the inner ear. In a study conducted on children receiving CI, although there was no significant relationship between the presence of a TT and the incidence of infectious complications after CI, the frequency of meningitis increased in the presence of TT [21].

68.4.1.6 Education

The symptoms of middle ear infection and meningitis should be explained to patients and their families, and it is vital to seek medical advice and start treatment without delay in cases of earache, fever, displacement, deformation of the auricle, swelling or pain, nausea, vomiting, neck stiffness, and changes in consciousness.

68.5 Meningitis and Mastoiditis Related to Cochlear Implant

68.5.1 Meningitis

Acute bacterial meningitis and mastoiditis can complicate otitis media in CI recipient children. In 2003, *S. pneumoniae* meningitis incidence in CI recipient children was 30-fold higher than in a cohort of healthy children [22]. Despite improved PCV vaccination and surgical technique, meningitis in children with CI is still a concern. The incidence of acute bacterial meningitis is 11–14/100,000 patient-years and 9,66/100,000 patient-years in the period of 2006–2010 [23].

The risk factors for developing meningitis in children with CI are [9, 25] as follows:

1. A current or recent episode of otitis media: AOM is the most common antibiotic prescribed for upper respiratory tract infection in childhood. Its incidence peaks between 3 and 18 months [25, 26].
2. Children under 5 years old are at increased risk for infectious complications. However, there is no evidence that the risk of meningitis increases with decreased age in children under 5 years old, according to a large cohort [26].
3. Preimplantation meningitis was an independent risk factor for postimplant meningitis in a survey based on CI recipients [26].
4. Impaired immune status [9].
5. Incomplete series of vaccination, *H. influenzae* type b and 13-valent pneumococcal conjugate vaccine (PCV-13) [24].
6. Congenital and acquired access route for bacteria to reach the inner ear and central nervous system (congenital ear dysplasia such as a Mondini malformation, inadequate sealing of regular or wide cochleostomy, presence of ventriculoperitoneal shunt, cerebrospinal fluid leak [26–28]).
7. Hematogenous seeding of pneumococcal bacteremia [25, 26].

After recalling specific models of CIs containing spacers, the incidence of postcochlear implantation bacterial meningitis in children has been reduced [25]. In a study conducted after introducing PCV vaccines (PCV13) to the vaccine schedule in the USA, only one of 173 pediatric bacterial meningitis cases had a CI [29]. Also, after introducing the PCV-13 vaccine, the annual incidence of bacterial meningitis was reported as 11–40 per 100,000 CI recipient children [29].

The incidence of bacterial meningitis may increase up to 10 times in CI recipient children who do not receive conjugated pneumococcal vaccine [30].

In the perioperative period, within 30 days following the implant operation, the meningitis agent is primarily *S. pneumoniae*, then in descending order *Acinetobacter baumannii, H. influenzae* type b, and *E. coli*. After 30 days following the implant operation, *S. pneumoniae* is noteworthy, followed by non-typeable *H. influenzae* [21]. Acute otitis media has been reported to cause half of the meningitis cases 30 days after the operation [22]. Although *S. epidermidis* is frequently found to cause wound infection, it is not an expected cause of bacterial meningitis [8]. Meningococcus species do not pose a greater risk of meningitis in children with intact immune responses than in the average population [22, 24].

68.5.1.1 Clinical Manifestations

Although bacterial meningitis can occur at any time, it is more likely to occur within 2 months of implant surgery; postimplant meningitis can rarely be expected after 24 months [9].

Signs of meningeal irritation, such as nuchal rigidity, photophobia, headache, and symptoms, suggest meningitis with fever in older children. Most of these findings may not be detected in the clinic in children younger than 24 months. Instead, irritability, feeding difficulties, vomiting, bulging fontanel, and high-pitched cry should be among the findings that raise suspicion of meningitis in young children [31]. Recognizing that even small clinical clues are valuable, families of young children who have undergone implant surgery should be educated about the findings suggestive of meningitis.

68.5.1.2 Laboratory and Microbiological Workup

A lumbar puncture (LP) should promptly be performed when meningitis is suspected. Suppose the child has a medical condition, such as increased intracranial pressure, coagulopathy, hemodynamic or respiratory instability, or skin infection over the LP site. In that case, the procedure is contraindicated, but contraindications for performing an LP should not delay empiric antibiotic treatment.

A tympanocentesis sample should be sent for aerobic culture, if possible. CSF should be sent for aerobic culture, Gram stain, cell count, and biochemical parameters. The criteria for community-acquired meningitis are used to diagnose meningitis in children with CIs (Table 68.4).

68.5.1.3 Radiological Assessment

Contrast CT imaging of temporal bone and surrounding tissue may help assess the spreading of infection for sigmoid sinus (sinus thrombophlebitis), epidural or intradural area (empyema), or brain tissue (brain abscess).

68.5.1.4 Management

Empirical antibiotic therapy for perioperative onset meningitis should cover MRSA, and sporadic (postoperative 30 or more days) meningitis therapy should cover *S. pneumoniae*. Antibiotic regimens with doses are listed in Table 68.5. Routine use of corticosteroids is not recommended unless CSF culture revealed positive for *H. influenzae* type b.

Table 68.4 Cerebrospinal fluid findings in bacterial meningitis[a]

	CSF WBC count (cells/mm$^{3)}$	Neutrophils	CSF protein concentration (mg/dL)	CSF glucose concentration (mg/dL)
Healthy children (Normal)	<6	None	20–40	40–80
Bacterial	>1000	85–90%	100–150	<1/2 serum
Viral	<1000	20–50%	40- <100	>1/2 serum

[a] Adopted and modified from Ref. [32–34]
CSF cerebrospinal fluid, *WBC* white blood cell

Table 68.5 Empiric parenteral antibiotic therapy for meningitis in children with a cochlear implant[a]

Period	Desired spectrum	Therapy	Dose	Duration
Perioperative and early postoperative period (≤2 months to prior operation)	Gram-negative bacilli and methicillin-resistant Staphylococcus aureus (MRSA)	Vancomycin	15 mg/kg/dose, every 6 h	Minimum 21 days or 14 days after first repeated negative CSF culture for gram-negative bacilli. Minimum 14 days for MRSA
		AND		
		Ceftazidime	150 mg /kg/dose, divided three doses, maximum dose 2 g/day	
			OR	
		Cefepime	150 mg /kg/day, divided three doses, maximum dose 2 g/day	
Sporadic meningitis (>2 months after operation)	Penicillin-resistant *Streptococcus pneumoniae* [#] *Haemophilus influenzae*[##] *Neisseria meningitidis*[###]	Vancomycin	15 mg/kg/dose every 6 h	[#] Minimum 14 days [##] Minimum 7 days [###]Minimum 14 days
			AND	
		Ceftriaxone	100 mg /kg/day, divided two doses, maximum dose 2 g/day	
			OR	
		Cefotaxime	300 mg /kg/dose, divided 3–4 doses, maximum dose 2 g/day	

[a] Adopted and modified from Ref. [8, 9, 32]

68.5.2 Mastoiditis

Mastoiditis can occur in almost any otitis attack of children with CIs due to the routinely performed cortical mastoidectomy during implantation. The most common organisms causing mastoiditis in an extensive series of cochlear-implanted children were *S. pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Pseudomonas* spp., and *H. influenzae* [35].

Clinical signs include fever, auricle protrusion, postauricular swelling, hyperemia, and otalgia. An inflamed, protracted, sometimes disrupted tympanic membrane would be expected to accompany the findings. In the context of cochlear-implanted children, an intact tympanic membrane without signs of inflammation mostly rules out mastoiditis [9].

Acute mastoiditis complications include spreading the infection to the surrounding subperiosteal, epidural, subdural regions, brain and cerebellar tissue, and sternocleidomastoid muscle [36].

68.5.2.1 Laboratory and Radiological Workup

A sample should be taken from the middle ear for aerobic culture by myringotomy before starting empirical antibiotic therapy at the time of diagnosis. Computed tomography imaging of the mastoid area is advocated if there is concern about central nervous system (CNS) complications or failure of empirical antibiotic therapy [36].

68.5.2.2 Management

Empirical parenteral antibiotic therapy should start after myringotomy. Initial empiric therapy should cover penicillin-resistant *S. pneumoniae*, *S. aureus*, and *H. influenzae*. Therapy should rearrange due to the results [36]. Empirical antimicrobial agents to be selected for initial mastoiditis therapy are listed in Table 68.6.

Table 68.6 Empiric parenteral antibiotic therapy for mastoiditis in children with a cochlear implant[a]

Desired spectrum	Therapy	Dose	Duration
Streptococcus pneumoniae *Streptococcus pyogenes* *Staphylococcus aureus* *Haemophilus influenzae*	Vancomycin	15 mg/kg/dose, every 6 h	Minimum 14 days
		AND	
	Ceftriaxone	100 mg /kg/day, divided two doses, maximum dose 2 g/day	
		OR	
	Cefotaxime	300 mg/kg/dose, divided 3–4 doses, maximum dose 2 g/day	
Pseudomonas spp. (chronic suppurative otitis media OR cholesteatoma)	Vancomycin	15 mg/kg/dose every 6 h	Minimum 14 days
		AND	
	Ceftazidime	150 mg /kg/dose, divided three doses, max. dose 2 g/day	
		OR	
	Cefepime	150 mg /kg/day, divided three doses, max. dose 2 g/day	

[a] Adopted and modified from Ref. [9, 36]

Surgical drainage is indicated if the subperiosteal abscess is present. Explantation is almost unnecessary with adequate therapy because mastoiditis is not as equal to CI infection.

68.6 Preventive Measures

The Centers for Diseases and Prevention (CDC) of the USA recommends pneumococcal vaccination for all children, including those with CIs. According to the routine immunization schedule, children younger than 2 years old with CIs should receive PCV-13 in four doses at 2, 4, 6, and 12–15 months [36]. Children should get all recommended pneumococcal vaccines at least 2 weeks before CI surgery, but no further doses are required. Those who have had pneumococcal meningitis should also be vaccinated with pneumococcal vaccines.

All children, including CI recipient children, should be vaccinated against *H. influenzae* type b [36]. If the Hib vaccine status is unknown or the child has received fewer than two doses, the *H. influenzae* type b vaccine scheme should be completed before surgery. *H. influenzae* type b vaccines are generally not recommended for children after 60 months of age. Cochlear implant recipients are not at increased risk for meningococcal meningitis. Therefore, the CDC does not recommend meningococcal vaccination specifically for younger children and adults with CIs [37].

68.7 Conclusion

Although CIs allow children to hear again, maximum attention should be paid to recognizing infections such as otitis media and accompanying mastoiditis, common in childhood. Rapid recognition and proper management of these infections are critical to prevent complications like bacterial meningitis. Early recognition and appropriate and timely management of CI infections and complications will protect children's health and device function and avoid explantation.

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Part XIII

Therapeutic Agents

Antibacterial Agents for Pediatric Infections, and Hearing Loss

69

Özlem Özgür Gündeşlioğlu, Derya Alabaz, and Grant T. Stimes

69.1 Introduction

Antibiotics, widely used in childhood due to frequent infectious diseases, are one of the most important inventions that prolong human life. In addition to the benefits of these drugs, there are many reported side effects, and one of them is hearing loss (HL), reported for many antibiotics. Hearing loss and loss of balance may occur due to the damage (ototoxicity) caused by antibiotics in the inner structure of the ear.

Hearing loss is difficult to detect in children, especially those unable to express themselves, so the true incidence of ototoxicity of antibiotics is not known precisely. The risks of ototoxic side effects of antibiotics are even higher, especially in the elderly, premature infants, and patients with underlying diseases, such as chronic kidney failure and chronic liver disease. In addition, a critical fact is that using more than one ototoxic drug together increases the ototoxic effect even more. For this reason, it is essential to know the ototoxic effects of antibiotics during use in pediatric practice and not to ignore these in terms of protecting children's cognitive functions and quality of life.

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In this section, in light of the literature, information is summarized about the antibiotics used in childhood, those that cause hearing-related side effects, and the type of effect, duration of action, and permanent damage caused.

69.2 Ear Anatomy and Hearing Physiology

The human ear can be divided into three sections: external, middle, and inner.

(a) The *external ear* consists of the auricle, external auditory canal, and tympanic membrane (TM). In this section, the sound coming from the outside is transmitted to the TM, and sound localization is provided.
(b) The *middle ear* section consists of the middle ear cavity, the mastoid cavity, and the Eustachian tube. It connects the TM to the inner ear through the oval window via the middle ear ossicles, malleus, incus, and stapes. The energy of the incoming sound transfers from the air to the fluid medium in the cochlea via the TM and middle ear ossicles. Although 99.9% of the sound energy passes into the liquid medium and is lost by around 30 decibels (dB), this is replaced by the hydraulic and leverage effect created by the middle ear structures.
(c) The *inner ear* consists of the vestibule, cochlea, and semicircular canals. In this section, the incoming mechanical energy is converted into electrical energy, and hearing is provided. The part of the inner ear that plays a role in auditory function is the part of the cochlea. The cochlea is located within the petrosae of the temporal bone. The cochlea is a spiral bone system that decreases in diameter after 3 rotations around its axis and ends blindly, covered with a thin layer of laminar bone. The organ of Corti is a receptor organ located on the scala media surface of the basilar membrane in the cochlea, consisting of sensory (hair) and support cells. The hair cells in the organ of Corti are in contact with a structure called the "tectorial membrane" from their upper parts. When the sound energy coming to the labyrinth moves the basilar membrane, the ciliated cells hit the tectorial membrane. In this way, the mechanical energy is converted into electrochemical energy. It is carried to the Heschel gray in the cortex by the vestibulocochlear nerve (auditory vestibular nerve), known as the eighth cranial nerve, where it is perceived as sound [1–3]. The ear's anatomy is shown in Fig. 69.1, and the cross section of the cochlear canal is shown in Fig. 69.2.

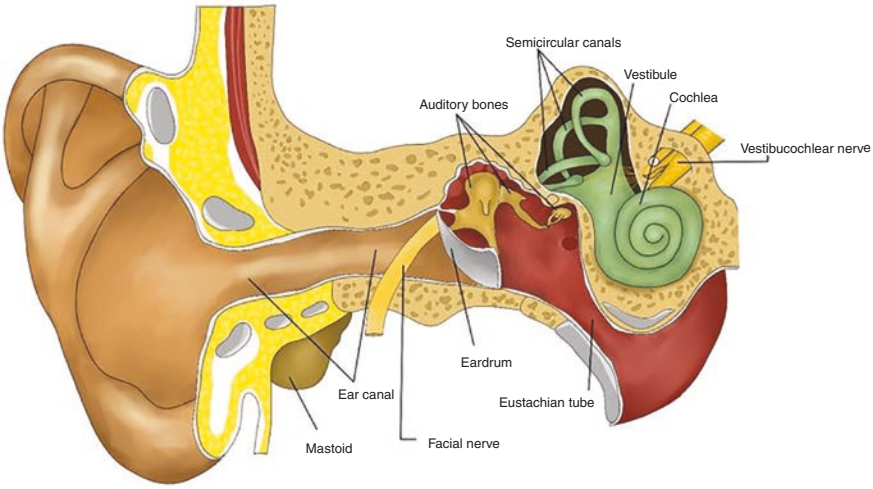

Fig. 69.1 Gross ear anatomy (Courtesy Mehmet Meriç Horoz)

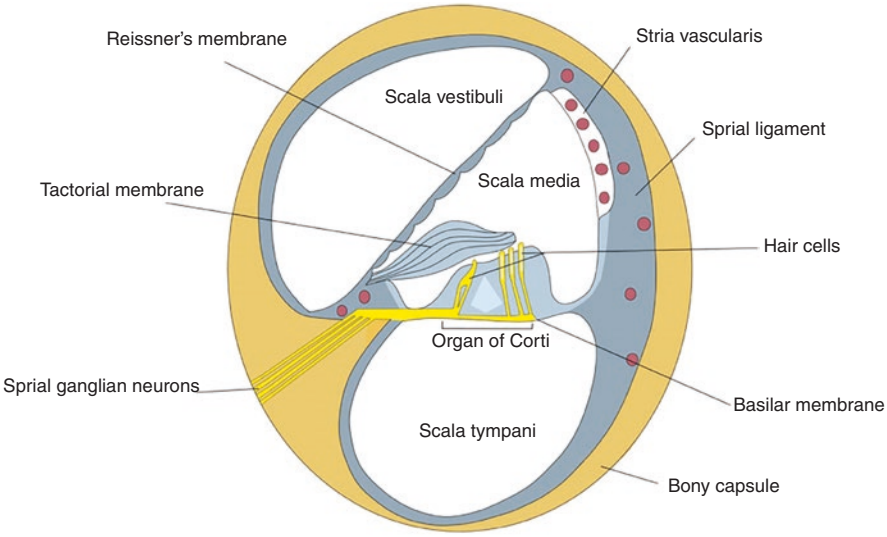

Fig. 69.2 Transverse section of the cochlear duct (Courtesy Mehmet Meriç Horoz)

69.3 Ototoxicity

Ototoxicity is defined as the structural or functional deterioration of the parts of the cochlea or vestibule in the inner ear due to a drug or chemical substance. Damage occurs in the outer hair cells in the organ of Corti and type 1 hair cells in the vestibular system. Ototoxicity is one of the frequently reported drug side effects that significantly affect the quality of life [4]. Ototoxicity began to be defined with the introduction of streptomycin in the 1940s, and it has been reported that aminoglycosides, macrolides, and antimalarial drugs are the most common causes [4, 5].

Antibiotics may affect the cochlear and/or vestibular system in the inner ear. In the case of cochleotoxicity, HL and tinnitus symptoms are usually observed, while in vestibulotoxicity, symptoms such as dizziness and vertigo occur [4]. Antibiotics-caused ototoxicity and the areas affected in the inner ear are summarized in Table 69.1.

Table 69.1 Ototoxic effects of antibiotics[a]

	Cochleotoxicity		Vestibulotoxicity		
Antibiotics	Available	Reversible	Available	Reversible	Hearing Loss
Amikacin	Y	N	N	N	Y
Ampicillin	Y	NK	N	–	Y
Azithromycin	Y	Y	Y	–	Y
Aztreonam	Y	Y	N	–	Y
Ciprofloxacin	Y	NK	N	–	Y
Chloramphenicol	Y	NK	N	–	–
Clarithromycin	Y	Y	N	–	Y
Clindamycin	Y	Y	NK	–	Y
Colistin	Y	N	NK	–	Y
Doxycycline	N	–	Y	–	–
Erythromycin	Y	NK	NK	–	Y
Gentamicin	Y	Y	Y	N	Y
Metronidazole	Y	Y	Y	Y	Y
Minocycline	Y	NK	Y	Y	–
Moxifloxacin	Y	NK	Y	NK	–
Neomycin	Y	N	Y	N	–
Norfloxacin	Y	Y	Y	NK	Y
Plazomicin	Y	N	Y	Y	–
Polymyxin B	Y	NK	Y	Y	–
Streptomycin	Y	N	Y	Y	Y
Sulfamethoxazole	Y	NK	Y	NK	–
Teicoplanin	Y	NK	Y	NK	Y
Tetracycline	Y	NK	Y	NK	–
Tobramycin	Y	Y	Y	NK	Y
Vancomycin	Y	Y/N	Y	NK	Y

[a]Adopted and modified from Ref. [3–5]
N indicates no, *NK* not known, *Y* yes

69.4 Antibiotics and Hearing Loss

69.4.1 Aminoglycosides and Hearing Loss

With the discovery of streptomycin for the first time in 1944 and other aminoglycosides, including neomycin, kanamycin, gentamicin, tobramycin, and amikacin, this class of antibiotics has been used mainly in the treatment of gram-negative infections. In addition, aminoglycosides are among the essential agents used in treating intracellular microorganisms, *such as Mycobacterium* species. Today, 9 aminoglycosides have been approved for use by the Federal Drug Administration (FDA), of which amikacin, gentamicin, and tobramycin are the most commonly used in childhood [3].

Hearing loss has been reported with a rate of 1–33% due to aminoglycoside antibiotics, and it has been reported that it is usually permanent [6]. Studies have reported that vestibulotoxicity or cochleotoxicity side effects develop at a rate of 20% due to intravenous (IV) use of aminoglycosides for more than a few days [7, 8]. The risk of ototoxicity is even higher in premature neonates [9]. While the cochleotoxic side effects of aminoglycoside agents such as amikacin, kanamycin, and neomycin are more dominant, streptomycin and gentamicin have more vestibulotoxic side effects. On the other hand, ototoxic and vestibulotoxic side effects of tobramycin can occur at equal rates [10].

Although aminoglycosides enter the cochlea shortly after systemic administration, the toxicities are not correlated with the distribution of the drugs in the cochlea or vestibular system. Aminoglycosides can persist in the inner ear for as long as ≥6 months [11]. In the body, aminoglycosides enter many cells, and these cells clear the aminoglycosides in their cytoplasm by mechanisms that are not yet known. Aminoglycosides accumulate longer in inner ear hair cells and renal proximal tubule cells. This situation clarifies why patients who have received aminoglycosides are more prone to ototoxicity [5, 12, 13]. Prolonged use of aminoglycosides may result in the death of outer hair cells in the Corti organ and type 1 hair cells in the vestibule, resulting in permanent ototoxicity. The auditory nerve is damaged next. Because there are fewer hair cells in the inner ear in older adults, the ototoxic effect of aminoglycosides occurs more frequently in this patient population [6]. Keene et al. [14] reported that after gentamicin injection in guinea pigs, bilateral sensorineural HL (SNHL) occurred at high frequencies, decreasing basal fold outer hair cells of the cochlea and some loss in spiral ganglion cells.

Administration of other ototoxic agents, such as diuretics, may increase ototoxicity. Patients with renal insufficiency are at an even greater risk of ototoxicity, as aminoglycosides can have higher serum levels and longer half-lives in this population due to reduced excretion [10]. Therapeutic drug monitoring of aminoglycosides in patients with renal insufficiency is necessary.

Mutations in the mitochondrial 12S ribosomal ribonucleic acid (rRNA) make patients highly susceptible to aminoglycoside ototoxicity [15]. A study showed that the nuclear transcription factor (NF)-Kb has a protective effect on kanamycin-related ototoxicity [16].

Aminoglycosides can also react with the element iron to form a reactive oxygen metabolite. According to one animal study, chelators such as deferoxamine may reduce the ototoxic effect of aminoglycosides [17]. These chelating agents do not affect the antibacterial activity of aminoglycosides, though these agents are not commonly used clinically for this purpose. In animal experiments, some antioxidant agents, such as lipoic acid, d-methionine, salicylates, and dihydroxybenzoate, were shown to provide protective activity against the ototoxic effects of aminoglycosides [6, 18]. A double-blind, randomized study showed that aspirin/sodium salicylate was protective against gentamicin-induced ototoxicity; HL was 13% and 3% in the groups receiving gentamicin plus placebo and gentamicin plus aspirin, respectively [6]. Aspirin also is not commonly used for this indication. Recent studies on developing agents with less ototoxicity risk, such as gentamicin C1a and apramycin, seem promising [19].

Aminoglycosides can cause ototoxicity both acutely after one course and more chronically after past exposure(s). Generally, a basic audiological evaluation should be performed within 72 h after aminoglycoside use. Patients treated with aminoglycosides should undergo audiological follow-up 1 month after the last treatment and every 3 months for 1 year [20].

69.4.2 Macrolides and Hearing Loss

After erythromycin was first used in 1952, roxithromycin, clarithromycin, and azithromycin came into use as second-generation macrolide derivatives in the 1980s. Macrolides are used to treat and prevent a wide variety of infectious diseases. Macrolide antibiotics are mainly used in respiratory and gastrointestinal tract infections, sexually transmitted diseases, and non-tuberculous mycobacterial infections. Moreover, they are used in non-infectious etiologies due to their anti-inflammatory action. Macrolides may cause ototoxicity by several mechanisms. Sensorineural HL may develop due to the involvement of the auditory nerve, cochlear nucleus, and superior olivary complex and to edema of the stria vascularis.

Although a generally transient ototoxic effect with erythromycin use occurs, persistent ototoxicity was reported in case reports [21]. Erythromycin ototoxicity is dose-dependent; female gender, advanced age, kidney failure, and liver dysfunction may also be other risk factors [22, 23]. Animal experiments showed that also azithromycin is ototoxic. After azithromycin dripped into the middle ear, inner and outer hair cells were lost dose-dependent [24, 25]. In patients with chronic lung disease, SNHL develops at a rate of more than 25% with long-term use of azithromycin [26]. Many case reports also highlighted HL with short-term use of azithromycin [27, 28]. Although this situation is problematic, other factors that may cause HL were not evaluated in these studies, and there is no clear data on the short-term use of azithromycin causing hearing loss [27, 28].

Hearing loss due to clarithromycin is usually reversible; however, permanent HL has also been reported [24, 25]. The literature shows that clarithromycin-related HL is less common than other macrolides [29, 30]. A meta-analysis of 183 studies

involving 252,886 participants reported that macrolide ototoxicity as SNHL was more common than in the placebo group [31]. On the other hand, in another study in which 9 studies were evaluated, SNHL developed more frequently in the macrolide-used group; however, this result was not statistically significant when compared with the placebo group [23, 31]. As these studies were not controlled randomized trials, more research is needed to determine the significance of this effect.

69.4.3 Beta-Lactams and Hearing Loss

Ototoxicity side effects of beta-lactam antibiotics are not common. Among beta-lactam antibiotics, ampicillin and aztreonam are more ototoxic. While ampicillin causes HL with a cochleotoxic effect, aztreonam may cause both HL and tinnitus with a cochleotoxic effect. The ototoxic effect of aztreonam is reversible [4, 32] and has also been shown in animal experiments [33]. In a randomized, double-blind study conducted in nonneutropenic patients, aztreonam was found to cause less ototoxicity than amikacin (7% vs. 11%) [34]. This difference is not statistically significant likely due to the low rate of occurrence in both treatment arms of this subgroup analysis (61 of 184 patients).

69.4.4 Tetracyclines and Hearing Loss

Tetracyclines are a broad-spectrum bacteriostatic antibiotic group effective against intracellular microorganisms such as chlamydia, mycoplasma, rickettsia, protozoa, and gram-positive and gram-negative bacteria. After the production of chlortetracycline, the first member of this group, in 1948, the second-generation, long-acting compounds doxycycline (1966) and minocycline (1967) came into use as semisynthetic tetracyclines in the late 1960s. In the early 1990s, third-generation tetracyclines were developed.

Tigecycline is a long-acting 9-t-butyl glycyl amido 119 derivative of minocycline and is used in clinical practice [35]. Minocycline can cross the blood–brain barrier and protect neurons against antioxidants; this feature reduces the ototoxic effects of gentamicin, neomycin, and cisplatin in animal studies [36–39]. There are no data in human trials demonstrating this protective effect of minocycline.

Tetracyclines have been reported to cause both cochleotoxicity and vestibulotoxicity, but these data are limited [4]. More research is needed to determine the degree of ototoxicity caused by tetracyclines.

69.4.5 Fluoroquinolones and Hearing Loss

Although side effects of fluoroquinolones on the central nervous system are common, limited literature data show systemic use causes HL [40]. Ciprofloxacin and

moxifloxacin may cause tinnitus, and HL, with cochleotoxic effects [4]. Moxifloxacin has also been reported to cause some vestibulotoxicity. Limited data exist describing systemically administered quinolones and the development of ototoxicity.

69.4.6 Glycopeptides and Hearing Loss

Vancomycin, a glycopeptide, came into use in 1954 and is mainly used in the treatment of gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Although ototoxicity is not a frequently reported side effect of vancomycin, HL and tinnitus due to vestibular and cochlear involvement were reported. Vancomycin causes more ototoxicity when used with other ototoxic agents, as in the use of aminoglycosides. However, reports suggest that vancomycin alone may be ototoxic [22]. Forouzesh et al. [41] reported 12% high-frequency HL in patients receiving vancomycin. Ototoxicity has generally been reported after intravenous vancomycin use but was also reported after oral use for *Clostridium difficile* infection. Reversible HL was also reported after intrathecal therapy [42, 43].

Vancomycin has a longer half-life in neonates. A 5-year study in New Zealand evaluated HL with otoacoustic emission (OAE) testing in 2347 newborns treated with vancomycin. Failure of OAE testing occurred in 22% and 7% of newborns treated with vancomycin and not receiving vancomycin or aminoglycosides, respectively [44]. In contrast, HL was not demonstrated in infants of pregnant women who received vancomycin therapy during pregnancy [22].

It has been observed that vancomycin ototoxicity is generally reversible, except in a few cases. In the case of concomitant use of vancomycin with other ototoxic drugs, caution is recommended regarding ototoxic effects [45]. While ototoxicity can occur in longer-term use, such as 4–5 weeks, ototoxicity findings were also reported in cases with short-term use, such as 2 weeks [45]. Humphrey et al. [46] found ototoxicity developed in 8% of patients receiving vancomycin for longer than 14 days though there was no control group.

69.4.7 Polymyxins and Hearing Loss

Polymyxins are classified into five groups from A to E. Of these, polymyxin B and polymyxin E are forms used for treatment. Colistin, first obtained from *Paenibacillus polymyxa* in 1947, has been used to treat gram-negative infections since 1959. Although the use of colistin has decreased due to its nephrotoxic side effects, it maintains its importance as a last-line antibiotic, given the increase in resistant gram-negative infections in recent years [47]. The rate of colistin-related neurotoxicity has been reported as 0–7% [48]. Although polymyxin B and colistin were reported to be ototoxic, there is no clear data on the frequency of ototoxicity in the literature [4]. Sarıca et al. [49] reported that 2 of 30 premature infants who received

colistin had unilateral HL, and one had bilateral HL. It was recommended to monitor the hearing of infants given colistin.

69.4.8 Topical Antibiotics and Hearing Loss

In topical treatment, agents can be used in drops, ointments, and intratympanic injections. Aminoglycosides have been used intratympanically in treating Meniere's disease since the 1950s. While streptomycin was used intratympanically in the first years, it was replaced by gentamicin later on. While these agents take advantage of their vestibulotoxic effects, unfortunately, it has been observed that they also cause HL with varying degrees of cochleotoxic effect [50].

Topical drops containing polymyxin B, gentamicin, and hydrocortisone effectively treat otitis externa and chronic suppurative otitis media. Consecutive use of these drugs for more than 10 days increases the risk of ototoxicity per the package insert. In cases where the tympanic membrane is not intact, topical medications are not recommended.

Ciprofloxacin and ofloxacin from quinolone group antibiotics are used topically in patients with intact TMs [51]. There are no data on the topical ototoxicity of fluoroquinolones in clinical use; ciprofloxacin and ofloxacin were shown to be non-ototoxic in animal experiments. However, there are few studies reporting that moxifloxacin, one of the quinolone antibiotics, is ototoxic [4, 52]. Moxifloxacin is among the most commonly used topical antibiotics in treating otitis media in humans. When used topically, its ototoxic effect was demonstrated in animal experiments [52]. Also, intermittent low-frequency HL has been reported with eye drops containing moxifloxacin [53].

69.5 Genetic Susceptibility to Ototoxicity

The same drug and treatment dose do not show similar effects in every patient; some may develop ototoxicity, while others do not. More recently, data have been reported that individual differences are associated with a genetic predisposition. Genetic differences in the drug uptake, intracellular effects, and tissue response of drugs have been reported. Ototoxicity due to aminoglycosides and cisplatin, a chemotherapeutic agent, is reported more frequently in the literature.

Through sequencing analysis of the mitochondrial genome, the researchers discovered mutations in human 12S rRNA associated with aminoglycoside-induced ototoxicity and established a genetic basis for aminoglycoside-induced HL. Nguyen T et al. [54], in the literature review between 1993 and 2017, detected mitochondrial mutations in 220 patients with SNHL due to aminoglycosides in 25 studies. Knowing the genetic predisposition to HL choosing non-ototoxic drugs and providing closer audiological follow-up when ototoxic drugs are required will be essential steps in preventing ototoxicity [54].

69.6 Diagnosis and Monitoring of Hearing Loss

The primary test to evaluate hearing is pure tone audiometry, which determines the minimum hearing levels in both ears at all frequencies. The normally accepted value is ≤20 decibels. The patient's hearing is evaluated in a wide frequency range (usually 125–8000 Hertz) by giving different frequencies and intensities with headphones in a soundproof room. In SNHL, the loss typically begins at high frequencies, and if exposure to the toxic agent continues, the losses decrease to lower frequencies, making the HL more severe. Speech tests assess the patient's ability to hear and understand speech.

Non-invasive evaluation can be performed without requiring the child's active participation by using the OAE test, which tests the inner ear function, in hearing screenings of babies who cannot respond to auditory stimuli. High-frequency audiometry (HFA) is the most critical test in the ototoxicity monitoring program in audiology. This test should be performed during the patient's initial evaluation and subsequent follow-ups. Ototoxic drugs tend to exert their initial effects on the outer hair cells in the basal part of the cochlea. HFA allows ototoxic losses to be identified before HL becomes evident in conventional audiometry. In addition, a tympanometry test should be applied to evaluate whether a problem exists in outer and middle ear functions and conduction. Ototoxicity should be evaluated simultaneously in the vestibular system. Caloric, rotation, vestibular evoked myogenic potential, and computerized dynamic posturography tests can be used as vestibular tests.

The frequency of performing the hearing test varies depending on the patient's age, the presence of risk factors that may lead to ototoxicity, and the drugs used. Initial audiological evaluation for aminoglycoside antibiotics before starting treatment and within the first 24 and 72 h allows the hearing assessment before and after the treatment. Pediatricians, audiologists, and psychiatrists should cooperate in following up on children with HL. Assistive hearing aids and cochlear implants can be used [6, 55].

Antibiotics with ototoxic effects, especially aminoglycosides, are frequently used in neonatal infections. Clear recommendations and protocols cannot be presented for the follow-up of ototoxicity in newborns. There are several vital steps to prevent or reduce ototoxicity in infants hospitalized in the neonatal intensive care unit:

1. Avoid the use of potentially ototoxic antibiotics or other ototoxic drugs. The treatment duration should be kept as short as possible if it needs to be used.
2. The sound level of the environment in the neonatal intensive care units should be monitored; the sound level should be reduced if determined to exceed the set threshold.
3. Genetic risk factors associated with HL may be tested during pregnancy.
4. Parents and neonatal intensive care unit personnel should be educated about the risks of progressive or late-onset HL, the importance of continuous screening, and the preservation of hearing in newborns [56].

69.7 Conclusion

With the discovery of important revolutionary antibiotics in the fight against infections, the human lifespan is extended, while undesirable adverse effects are also observed. Ototoxicity should be kept in mind in the long-term use of antibiotics known to be ototoxic in children. Also, providers and patients should follow-up on the development of ototoxicity after patients are exposed to ototoxic antibiotics. Studies suggest that it would be more accurate to self-assess individuals for susceptibility to ototoxicity and to plan individual antibiotic treatment regimens.

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Antituberculous Agents for Pediatric Mycobacterial Diseases, and Hearing Loss

70

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70.1 Introduction

More than 1.5 billion people worldwide live with hearing loss (HL), and 34 million children need rehabilitation due to disabling HL [1]. Every year, March 3 is held as World Hearing Day, established by the World Health Organization (WHO) to raise attention to deafness and HL [2].

The most common causes of HL can be prevented with effective strategies, such as not using ototoxic drugs and rational antibiotic use. Aminoglycosides have taken an important place in treating tuberculosis in various fields of use, but the adverse effect of these drugs that should be emphasized the most is HL. In the following, antituberculous drugs and related HL will be discussed in the order of discovery of the drugs, with more emphasis on aminoglycosides, mainly streptomycin and amikacin.

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70.2 Aminoglycoside Antituberculous Drugs and Hearing Loss

Among the aminoglycoside antibiotics, streptomycin has been covered in more detail because of its prolonged use as a primary drug in treating tuberculosis and due to the large body of data, including historical experience.

70.2.1 Streptomycin

70.2.1.1 Discovery and Pharmacological Properties

The mortality rate of tuberculosis, which had a more heavy disease burden before its treatment was found, decreased from 80 to 100% [3, 4] to around 15% with the introduction of effective antituberculous drugs [5–7]. As the first discovered antituberculous drug, streptomycin alone reduced mortality in half [8, 9].

The in vitro inhibitory effect of streptomycin against *Mycobacterium tuberculosis* was first published in 1944 [10]. Streptomycin was obtained from *Actinomyces griseus* [10]. Farber and Eagle [11] reported that streptomycin has a bacteriostatic effect on the tuberculosis bacillus.

Streptomycin is detected in many body fluids after parenteral administration, but its penetration into the cerebrospinal fluid (CSF) is not good in the absence of inflammation [12]. Streptomycin crosses the placenta, and the amount passing varies with the frequency of administration and dose [13]. It was found in cord blood and appeared in amniotic fluid when given intravenously to a pregnant woman in labor [12]. Streptomycin can reach amounts close to maternal blood in cord blood [13]. Topical, intrabronchial, and aerosol spray solutions of streptomycin were also applied. In the case of tuberculous meningitis, streptomycin was intrathecally administered with lumbar or cisternal puncture [8]. Streptomycin reaches very high amounts in the CSF following the intrathecal route [14].

70.2.1.2 Early Experiences in Tuberculosis Treatment with Streptomycin

After the discovery of streptomycin in 1944, a chance of recovery from tuberculosis appeared, for which there was little possibility of spontaneous recovery in severe forms such as meningitis [14]. In the first years after the discovery of streptomycin, it could only be used in terminally ill children with tuberculous meningitis or acute miliary tuberculosis [14]. The first experience with streptomycin was in a child with tuberculous meningitis, reported by Cooke et al. [15] in 1946. Streptomycin was used for the first time intramuscularly and intraventricularly in a 1-year-old baby who had no previous symptoms and signs and presented with high fever and unstoppable convulsions. The child had a favorable disease modification, but permanent bilateral deafness developed. The authors commented that this might be drug-related or a sequela of the disease.

After the discovery of streptomycin, a medical committee decided to plan which type of tuberculosis treatment it would be used since its availability was not

sufficient initially, and the amount of the drug expected to be available for the trials was limited [14]. The first case series comprising 100 patients with various types of tuberculosis treated with streptomycin was published 2 years after the drug's discovery [8]. Here, it was mentioned that deafness in patients with tuberculous meningitis might be due to streptomycin. Streptomycin was prescribed to the patients as a deep subcutaneous or intramuscular route, 1 to 3 g/day, divided into 4–6 doses [8]. In other early reports, administration of streptomycin was also done by daily intrathecal in addition to intramuscular injection up to four times a day [14]. Streptomycin was used intramuscularly, intrathecally, and intraventricularly in tuberculous meningitis [16].

70.2.1.3 Adverse Effects of Streptomycin

Four forms of systemic toxic reactions of streptomycin have been observed: 1) histamine reaction (flushing, headache, and sudden drop in arterial pressure), 2) hypersensitivity reaction (including anaphylaxis), 3) neurological damage (vestibular dysfunction and deafness, dizziness, tinnitus), and 4) kidney damage (cylindiruria, albuminuria, increased blood urea nitrogen [BUN]) [17].

Pain and swelling after intramuscular administration of streptomycin may exist, pain in the sacral region due to intrathecal route, eosinophilia, and dermatitis at the injection site [11, 18, 19]. In kidney disease, the excretion of the drug is reduced and may contribute to toxicity [9, 19]. Long-term use of streptomycin was identified as causing drug resistance within a few years of its introduction [11].

70.2.1.4 Streptomycin and Early Experiences on Hearing Loss

The first notable and most frequently observed undesirable effect was ear-related disorders during the initial use of streptomycin [8, 17, 20]. Streptomycin is toxic to the cochlea, vestibule apparatus, or both [21, 22]. Streptomycin treatment can cause HL at all ages [23]. However, ototoxicity does not develop at the same severity in every individual. Deafness due to streptomycin was reported to develop in three conditions [18]: 1) due to use at extraordinarily high doses, 2) in renal failure, and 3) intrathecal use. Deafness may develop without damage to the labyrinth [24].

The potential for streptomycin sulfate to cause ototoxicity was described by Hinshaw et al. [8] in 1946, even in its first clinical trial. Its universal use was avoided in all tuberculosis cases due to its undesirable toxic effects shortly after its discovery. A recommendation was made not to use it in diseases such as minimal pulmonary tuberculosis with a good prognosis [18]. When other effective antituberculous drugs were not yet discovered, the primary treatment modalities included bed rest, good dietary support, adequate nursing care, collapse procedure if necessary, and symptomatic drugs [11]. When only streptomycin was available as an antituberculous drug, it was used only as an adjunct to treating tuberculosis. Indications for streptomycin therapy were the following conditions: miliary tuberculosis, tuberculous meningitis, laryngeal and endobronchial tuberculosis, osseous tuberculosis, tuberculous lymphadenitis, sinuses and fistulae, and exudative tuberculous pulmonary lesions not responsive to conservative therapy [11]. It was not recommended to be used before birth if the disease process could be controlled with other

interventions [11]. Only 12% of children with tuberculous meningitis under 3 years and 36% of older children (>3 years) and adults made good progress [14].

Ranta [25] has extensively studied the acoustic and vestibular dysfunctions associated with streptomycin therapy in children with various forms of tuberculosis. Children were more affected by streptomycin ototoxicity than adults [26]. Prazić and Salaj [26] reported that after using streptomycin, ototoxic lesions were observed in 36% of 975 children hospitalized with the diagnosis of pulmonary tuberculosis (involvement in the organ of Corti in 1/3 of cases).

Streptomycin ototoxicity was also reported in both different forms of tuberculosis and nontuberculous (e.g., angina and pneumonia) treatments [21]. Although it has no place today, streptomycin could also be used in treating throat infections in those years. Toxic effects were reported that can occur even with just a few injections in some patients [21].

Hearing loss related to streptomycin can range from moderate to complete deafness [9, 18], may be unilateral or bilateral, but is usually bilateral [16, 25]; it may develop at 5 weeks of treatment [23, 27], 2–3 months [28], or even 12 months [25] and is very likely irreversible [18, 23, 25]. Toxic findings are unrelated to the amount of streptomycin used [23, 26]. Some patients may complain of tinnitus before developing HL [18, 28, 29], but HL may progress without prior warning symptoms [23, 26]. Even if time has passed after streptomycin treatment has been discontinued, HL that has not been apparent during the treatment process can be seen later and is irreversible [25, 30, 31].

Experience in the treatment of tuberculosis during the 35 years after the discovery of streptomycin was analyzed from 55 reports [9]. It was reported that in 271 patients who developed hearing problems, a mild or moderate decrease in hearing and mostly high-frequency loss occurred, and hearing improved in only one patient. Vertigo can also coexist in people with significant HL [9].

Deafness may develop in patients with tuberculous meningitis, both due to the disease, that is, due to cortical damage, and the streptomycin use [16, 27]. Hearing loss can occur in tuberculous meningitis of any severity [16, 32]. One hundred ninety-four pediatric patients with tuberculous meningitis treated with streptomycin, isoniazid, and/or para-aminosalicylic acid were followed for 11 years [16]. The audiogram test performed on 65 survivors was abnormal in 25% of the patients, and the severity of ear involvement increased as the severity of meningitis worsened (the audiogram was more abnormal). Hearing function was assessed in another more recent retrospective cohort study in children with tuberculous meningitis, treated with 4-drug combination therapy of isoniazid, rifampin, pyrazinamide, and streptomycin [32]. Of 139 children (the mean age 44 months; range 7–162), 28 were available for evaluation with the brainstem auditory-evoked response (BAER) test. Hearing loss was identified in 11 patients; most suffered from delayed neurological and mental development: The more severe meningitis, the greater the hearing loss.

70.2.1.5 Streptomycin Use During Pregnancy

Streptomycin is present in the fetal blood circulation at a level close to 50% of that in the maternal blood [33]. Using streptomycin in pregnant women with tuberculous

may cause mild or severe disability and HL in the fetus [33, 34]. Hearing loss can be unilateral or bilateral [35]. It is predicted that unborn children will be more susceptible to streptomycin than adults [33]. Ototoxicity has been reported primarily after streptomycin use in the first trimester [35] but may develop throughout pregnancy [34, 36]. In a series of 17 children aged 6–13 years whose mothers had used streptomycin during pregnancy, eight patients had abnormal eighth nerve function, and four had abnormal audiograms [24].

According to the literature review by Snider et al. [36] on the use of antituberculous therapy in pregnancy, 203 women used streptomycin in 206 pregnancies, 35 infants were reported as abnormal, and all but one had eighth nerve damage, auditory involvement ranged from mild to severe. Streptomycin should be avoided during the first 3 months of pregnancy [35]. One in six infants exposed to streptomycin in utero developed some HL or vestibule defect [36].

Using streptomycin during pregnancy has lost its importance with the introduction of effective oral antituberculous drugs suitable for short-term use [35]. The use of streptomycin during pregnancy is not recommended due to the risk of fetal ototoxicity [37]. If it is necessary, it is recommended that the use of streptomycin should be postponed to the second trimester as much as possible and should not be used in the presence of renal dysfunction [35, 38].

70.2.1.6 Dihydrostreptomycin

Dihydrostreptomycin was discovered in 1946 [39] and has been shown to be effective against tuberculosis disease [40, 41]. Although dihydrostreptomycin was thought to be less toxic than streptomycin, it was just as toxic as streptomycin; auditory disturbance due to dihydrostreptomycin was more frequent [21, 25, 42–44]. Hearing loss induced by dihydrostreptomycin may not be apparent for several weeks to several months after the use of the drug [45], while it can develop even at highly rapidly as 4 days [46] or in extremely low doses [44]. Hearing loss associated with dihydrostreptomycin is more burdensome in children than adults and can range from mild HL to complete deafness [43].

In 102 children with pulmonary and bone–joint tuberculosis, mild HL was recorded in 18% by audiometric tests after dihydrostreptomycin treatment for an average of 3 years (ranging between 3 weeks and 6 years) [47]. In another group of 101 children with tuberculous meningitis treated with intramuscular dihydrostreptomycin and intrathecal streptomycin, 68% of patients developed HL (15% had severe HL with speech hearing <2 m); in some (26%), the loss was detected only by audiometric measurement [48]. In these patients, increased intracranial pressure was not found to be associated with the development of HL. Dihydrostreptomycin use for tuberculous meningitis in children was associated with higher survival, but deafness occurred significantly more than streptomycin. In studies between 1950 and 1956, when tuberculous meningitis could only be treated with streptomycin or dihydrostreptomycin, the highest HL was observed with intramuscular and intrathecal administration of dihydrostreptomycin [47].

The incidence of HL in non-meningitis tuberculosis cases treated with dihydrostreptomycin has been reported between 0 and 33% [25]. Hearing impairment may

develop even months after dihydrostreptomycin treatment is finished [9, 19]. Dihydrostreptomycin causes more HL, while streptomycin disrupts the vestibule system more [9, 16]. It is not recommended to be used because it has been shown that dihydrostreptomycin is not superior to streptomycin in terms of toxicity [45]. Due to its ototoxicity, the United States of America (USA) Federal Drug Administration (FDA) banned dihydrostreptomycin in children in 1960, and streptomycin was recommended for the treatment of children [21, 49].

70.2.1.7 Combined Streptomycin Formulas

Ambistryn® (Squibb and Sons®) [50] and streptoduocin [51–55], a mixture of streptomycin and dihydrostreptomycin, consisting of a combination of half the therapeutic doses, have been produced and existed for a while in clinical use. In the two groups of 20 patients, more hearing impairment was reported with Ambistryn® than with streptomycin alone [50]. In another study, streptomycin, dihydrostreptomycin, and streptoduocin treatment were used in addition to isoniazid and/or para-aminosalicylic acid in 272 patients with moderate-to-severe tuberculosis, and the lack of toxic effects with streptoduocin was encouraging for its use [51]. In another study using audiometric tests for adverse effects evaluation, streptoduocin was found to be more ototoxic than streptomycin alone [52]. Streptoduocin is slightly superior to streptomycin in terms of allergic reactions [53]. According to literature support, before the discovery of highly effective antituberculous drugs, researchers suggested that streptomycin should be preferred between the two preparations, but it was recommended that streptoduocin should be used instead of streptomycin if vestibular symptoms are prominent [54].

Since dihydrostreptomycin is no longer used in humans [49], combined streptomycin–dihydrostreptomycin formulas are not used in current tuberculosis therapy. However, dihydrostreptomycin is usually used in veterinary medicine to treat bacterial diseases in livestock [56, 57].

70.2.2 Viomycin

Viomycin is a tuberactinomycin antibiotic first isolated from *Streptomyces puniceus* in 1951 [58]. It is the third antituberculous antibiotic discovered after streptomycin and para-aminosalicylic acid. Viomycin differs from most antibiotics because it is more active against *Mycobacteria* than other Gram-positive or Gram-negative bacteria groups [59, 60]. Viomycin acts by blocking bacterial ribosomal translocation by binding to the interface between the 30S and 50S subunits of the bacterial ribosome [61]. As with streptomycin, ototoxicity is a known adverse effect of viomycin [62], and drug–drug interactions increase the potential for this side effect [63].

Viomycin was used to treat *M. tuberculosis* until the less toxic capreomycin replaced it [61]. It is now only used in extreme cases of drug resistance, with a daily dose of 15 mg/kg by intramuscular route [64]. Viomycin has potential antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the experimental setting [65].

70.2.3 Capreomycin

Capreomycin, discovered in 1960, is a peptide antibiotic synthesized by *Streptomyces capreolus* possessing antituberculous activity [66, 67]. Capreomycin belongs to the tuberactinomycin antibiotic group and is structurally similar to viomycin. It inhibits protein synthesis [68]. Unlike aminoglycosides, it can also act under anaerobic conditions and non-replicating *M. tuberculosis* [69].

It has had much less toxic effects in mice than other antituberculous drugs [66]. Side effects, mainly on the ear and kidney, have been reported associated with the use of capreomycin in treating tuberculosis disease in humans [70]. It was used in combination with ethambutol in one study, and relatively severe toxic effects were not observed [71]. Side effects on hearing increase when capreomycin is used together with amikacin [72]. In 25 patients with advanced pulmonary tuberculosis, capreomycin nephrotoxicity developed in all patients, while vertigo was noted less frequently; the hearing was not affected [62]. A decreased hearing was observed in only three of 294 patients of all ages (0– > 80 years) with advanced tuberculosis treated with capreomycin [73]. No worsening of HL was observed after discontinuation of the drug.

The reported incidence of HL from capreomycin ranges from 0.7% to 25% [74] and may be permanent [63, 75]. The mechanism of ototoxicity is unknown, but toxic effects are thought to occur with similar pathogenesis as seen with aminoglycosides [74]. Regular monitoring of liver and kidney function tests is required in patients using this drug [71]. Capreomycin, available in vial formulation, is administered at 15–20 mg/kg once a day [76]. Capreomycin is not recommended in current multidrug-resistant tuberculosis (MDR-TB, resistance at least to both isoniazid and rifampin) treatment guidelines [77–79].

There may be cross-resistance among amikacin, kanamycin, capreomycin, and viomycin due to the genotypic overlap of resistance-producing mutations to these antituberculous agents, which is commonly observed [80].

Despite being an antibacterial agent, capreomycin binds with high affinity to and shows good activity against the SARS-CoV-2 spike protein [81]. Although it may seem outdated in treating tuberculosis, it may regain importance with emerging infections.

70.2.4 Kanamycin

Kanamycin (kanamycin A) is a natural aminoglycoside antibiotic obtained from *Streptomyces kanamyceticus* in 1957 and inhibits ribosome/protein synthesis [82, 83]. It is effective against aerobic Gram-negative bacteria, some Gram-positive bacteria, and *M. tuberculosis* [84]. It was one of the drugs used to treat streptomycin-resistant tuberculosis in the 1950s. Kanamycin, available as an injectable vial formulation, is given at a dose of 15–30 mg/kg once daily [76]. Kanamycin is excreted poorly in breast milk.

The main toxic effects of kanamycin are on the eighth nerve and renal tubules, similar to other aminoglycosides [84]. Ototoxicity is a significant side effect of

kanamycin [63]. The drug accumulates in the endolymph and perilymph of the inner ear, causing partially reversible or irreversible bilateral HL in the hair cells of the cochlea. Kanamycin ototoxicity is increased in renal dysfunction and when other ototoxic drugs (e.g., streptomycin) are used [85]. The risk of ototoxicity is also most significant in patients receiving high-dose or long-term therapy, renal impairment (including in the past), or dehydration [84]. Verbal communication may be preserved if there is damage to the hearing of high-frequency sounds and if the drug is discontinued early. Unless regular monitoring is done, HL occurs, and unfortunately, communication problems develop [76].

Since kanamycin has been associated with adverse outcomes, it is recommended not to treat MDR-TB patients with kanamycin on prolonged regimen therapy, instead to use new and more effective antituberculous drugs [77, 78].

70.2.5 Amikacin

Amikacin is a semisynthetic aminoglycoside introduced into medical use in 1972 as a derivative of kanamycin [86]. It is more effective than kanamycin against many Gram-negative and Gram-positive bacteria. Moreover, it is the most active aminoglycoside against nontuberculous mycobacteria (*Mycobacterium fortuitum, Mycobacterium abscessus,* and *Mycobacterium chelonae*) [87]. Amikacin is more active than kanamycin and capreomycin against susceptible and resistant *M. tuberculosis* strains if evaluated by the absolute concentration method [88]. Amikacin is available in a vial formulation and is administered at a dose of 15–25 mg/kg once a day [76].

Amikacin, kanamycin, and capreomycin use in MDR-TB patients may lead to persistent HL in almost one in five patients, even after 1 year [75].

In the 2016 WHO guideline, second-line injectable drugs in the treatment of MDR-TB (i.e., amikacin, capreomycin, kanamycin, and streptomycin, if none of the other three agents are available and the strain is not resistant) were included as part of the adult treatment regimens [89]. However, injectable agents were recommended to be excluded from pediatric mild tuberculosis patients, as the harms of these drugs in children may outweigh the potential benefits [89]. The current WHO MDR-TB treatment guideline offers amikacin as a component of long-regimen therapy for patients aged 18 years and over if the microorganism is susceptible, provided the side effects can be monitored [77]. This group of agents should be monitored for undesirable effects; HL and nephrotoxicity are the most serious side effects [89]. The toxicity of MDR-TB long-term amikacin therapy should be watched using therapeutic drug monitoring [90]. Regular audiometry should be performed if amikacin or streptomycin is mandatory in children [77].

Among injectable drugs, streptomycin and amikacin were associated with more treatment success, as 7–10 and 6–9 per 100 patients, respectively, according to a meta-analysis from treatment follow-ups of 12,030 adult pulmonary MDR-TB

patients in 25 countries [78]. The authors recommend that streptomycin or amikacin should be preferred first, not kanamycin or capreomycin if injectable antituberculous drugs should be included in the treatment of MDR-TB, and their use is supported in drug susceptibility tests (if the agent is susceptible).

As published in "rapid communication" by WHO in 2022, all-oral drug treatment regimens containing oral bedaquiline for 6–9 months for MDR-TB patients, including the pediatric age group, other than severe lung and disseminated disease eliminated the need for an injectable agent [91, 92]. However, an individualized regimen containing amikacin/streptomycin may be considered for patients with severe or extensively drug-resistant forms of tuberculosis (XDR-TB), according to the revised WHO definition of XDR-TB [93], unresponsive to an all-oral MDR-TB regimen.

70.2.6 Injectable Aminoglycoside-Induced Auriculo-Pathological Changes and Pathogenesis

Streptomycin has been shown to cause marked changes in animals' ampullar cristae and the otolithic maculae sensory epithelium [31, 94, 95]. Liquefaction necrosis in the central cochlear nucleus was found in the postmortem examination of patients who developed deafness [96]. Complete loss of cochlear hair cells and the organ of Corti was also noticed in the postmortem evaluation of patients who used aminoglycosides for a long time [97]. Cochlea cells cannot regenerate and, when destroyed, result in permanent deafness.

A comprehensive review was written by Xie et al. [98] detailing the physiological and molecular pathology of HL in organotypic culture. Histopathological studies performed in patients with aminoglycoside ototoxicity revealed that the loss of hair cells in the organ of Corti progresses from the base of the cochlea to the top (base-to-apex progression) and from the outer to the inner hair cells [98]. In animal experiments, aminoglycosides accumulate in hair cells by entering in one direction in relation to plasma concentration, and ototoxicity develops when a particular threshold value is reached [99]. Shortly after the aminoglycoside is administered, the drug enters the cochlear hair cell through a unidirectional membrane channel [100]. The drug can remain there for more than 30 days without being metabolized, so the drug accumulates and, as a result, explains the occurrence of HL even when the drug is discontinued [101].

After aminoglycoside treatment, reactive oxygen species (ROS) appears in vivo in hair cells or the organ of Corti of the inner ear. Hair cells are very sensitive to ROS, and ROS generation is considered the first step in a series of reactions that will subsequently result in cell death [102]. Hearing loss occurs due to cochlea damage. The degeneration of hair cells begins at the basal coil and progresses to the apex. During early ototoxicity, damage to high frequencies occurs, and speech hearing is not impaired. Over time, hearing deteriorates at low frequencies as well [103].

70.2.7 Injectable Aminoglycosides Used as a Component of Modern Combination Antituberculous Therapy Including Multidrug-Resistant Tuberculosis and Hearing Loss

There is no unity in the definition of ototoxicity in the medical literature. In some publications, the "ototoxicity" term is used as similar to hearing loss, while in others, as similar to hearing loss (used as equal to cochleatoxicity) plus tinnitus plus vestibulotoxicity [104, 105].

In 1149 patients (7.3% aged 13–19 years) who received tuberculosis treatment, ototoxicity occurred only in those receiving streptomycin, seen in 3.2% of them [106]. Ototoxicity was evident on the mean 25th day of treatment and was most common in those aged 20–39 years. Ototoxicity was the third after hepatotoxicity and hyperuricemia, but it was the most severe of all serious adverse events [106].

Aminoglycoside ototoxicity does not change with the frequency of administration (daily or three times a week); however, it is associated with advanced age, prolonged treatment duration, and higher total dose received [104]. The higher the total dose of aminoglycoside, the higher the risk of ototoxicity [107]. Ototoxicity is not associated with nephrotoxicity and vestibulotoxicity. Streptomycin is less ototoxic than kanamycin and amikacin [104, 108]. Ototoxicity seems to be a more serious problem than nephrotoxicity in patients taking aminoglycosides for a long time [103]. For this reason, patients using streptomycin should undergo regular audiometric examination, and HL should be detected early [23, 35].

After the widespread use of modern antituberculous drugs, MDR-TB began to be detected with increasing frequency [109]. Aminoglycosides were among the MDR-TB treatment recommendations in previous times [89, 110]. Antituberculous drugs such as streptomycin, kanamycin, and capreomycin, whose use has been pushed to the background due to their toxicity, have become the leading drugs in the treatment of emerging MDR-TB. Below are the data on the frequency of ototoxicity with aminoglycosides in treating MDR-TB from various countries.

In the Netherlands, at least 18% HL occurred in patients using aminoglycosides, amikacin, kanamycin, and streptomycin, for at least 14 days for the treatment of MDR-TB [103]. None of the criteria such as gender, age, therapy duration, total aminoglycoside dose, and initial creatinine concentration were associated with the development of HL in these patients. In a Turkish study, ototoxicity, including HL, tinnitus, and disequilibrium, was reported at 41.8% in 263 adults due to aminoglycosides, most frequently amikacin, in 79.8% of patients, for the treatment of MDR-TB [105]. The high rate of ototoxicity was attributed to the cumulative effect associated with the previous use of streptomycin in a significant proportion (40.3%) of patients.

In a retrospective United Kingdom (UK) study using injectable antimicrobials to treat MDR-TB, 18% of 50 patients developed HL [72]. Advanced age, renal dysfunction, use of amikacin, and combination of amikacin plus capreomycin were significantly associated with ototoxicity (58% used amikacin, 22% capreomycin, and 20% streptomycin or a combination). Treatment was terminated due to HL in

40% of 85 adult patients diagnosed with MDR-TB in another trial from the UK, treated with amikacin and capreomycin [111]. Compared to capreomycin, ototoxicity due to amikacin use was five times, and HL was 14 times higher.

Of the 153 patients with MDR-TB who participated in a prospective cohort study in South Africa, 96% were treated with the combination regimen using kanamycin, as 87% had previously received streptomycin [112]. Although HL was observed in 57% of the patients, the authors emphasized that the frequency of HL could increase if more sensitive hearing tests were performed and followed up after the treatment. In a series of MDR-TB adult patients in Namibia, amikacin and kanamycin-related cumulative HL was 58% [113]. In Ethiopia, ototoxicity was 4.8% in MDR-TB patients; capreomycin was used most frequently [114]. The authors emphasized that the low rate may have been seen because the audiometry was not performed. Ototoxicity due to kanamycin was 17.5% in pediatric and adult patients who received short-term (9 months) MDR-TB treatment in Niger [115]. In Nigeria, kanamycin and capreomycin were used in treating adults with MDR-TB, and varying degrees of HL were found with a frequency of 54.6% [116]. In another trial from Nigeria, 7.5% of MDR-TB patients using kanamycin developed ototoxicity within 2 weeks of treatment [117].

In Bhutan, 45% of the patients who used kanamycin to treat MDR-TB and regular audiological testing showed varying degrees of HL [118]. Multidrug-resistant tuberculosis treatment-related HL was the most common of all adverse events in 70% of adult patients in Zimbabwe [119]. In Pakistan, streptomycin and amikacin were used to treat adult MDR-TB, and ototoxicity was found in 24% of patients, followed by audiometry [120]. The prevalence of HL was 20% in patients receiving tuberculosis treatment in Ghana, and the effect was varying degrees [121].

Hearing loss is most common in young people among healthy individuals [118]. Male gender, low baseline body weight [113], advanced age, and pre-existing HL [122] bring a high risk for developing HL. As the cumulative aminoglycoside dose increases, the probability of HL also increases [122]. Hearing loss occurs on the median 90th day of treatment [123]. Hearing loss is primarily bilateral, with about one-third unilateral [118]. Tinnitus may also be seen in some patients [105, 118]. Hearing loss associated with ototoxic antituberculous drugs is more common in high-income countries, maybe the higher income provides a chance to be diagnosed with HL, thanks to the availability of auditory equipment [124].

No clear linear relationship exists between the duration of aminoglycoside use and the timing for developing HL. In the literature, sudden HL developed within minutes after drug administration in a patient treated with kanamycin for more than 100 days [125]. Conflicting results have been reported regarding the development of HL after administering aminoglycosides by checking the drug level. In one study, although 15 mg/kg of amikacin was administered and serum trough concentration was checked, as in the WHO recommendation, HL happened and progressed even after discontinuation of the drug [126]. Another recent study noted fewer side effects when amikacin was administered at a dose of 8–10 mg/kg with dose adjustment based on therapeutic drug monitoring instead of 15 mg/kg [127].

The pathogenesis of HL is progressive even after the drug is discontinued, which may be linked to auditory hair cell loss due to accumulation and long half-life of aminoglycoside sequestered in the endolymph of cochlear canals [113].

70.2.8 Exclusive Pediatric Studies on Drug-Resistant Tuberculosis and Aminoglycoside-Related Hearing Loss

Pediatric tuberculosis accounts for 11% of all tuberculosis cases worldwide. Unfortunately, only 15% of the cumulative number of children with MDR-TB were reported to be enrolled in therapy [7]. Little is known about the optimal treatment for these children [128]. Hearing loss due to the use of aminoglycosides in the treatment of MDR-TB in children has been reported with a variable frequency from 0.33% to over 50% [129–136]. The reason for this difference is that the studies were not in a standard design, the doses and durations of the drugs used were not adequately documented, the treatment received before, comorbid conditions, and it is not possible to conduct a healthy meta-analysis due to the variability in the test methods [130]. After the influence develops, the burden becomes profound and impairs the quality of life.

In eight retrospective studies conducted on children receiving MDR-TB treatment with streptomycin, kanamycin, and amikacin, HL was 6.7–10.0% in 315 patients [129]. Hearing loss was less than 10% in most of the 35 studies of children with MDR-TB and, in some, about 50% or more [130]. Hearing loss was found in 16.7% [132], 24.5% [131], and 48% [133] of children who received MDR-TB treatment in various trials. The serious side effects in 599 children who received tuberculosis treatment and followed up for 5 years were evaluated [134]. Auditory involvement occurred in only two patients (0.33%) who used streptomycin; hearing returned to normal after streptomycin was discontinued. Hearing screening with close monitoring is required. Hearing loss was 31% in children with MDR-TB using amikacin and kanamycin, seen after a mean duration of 5.9 months [136].

Children have a greater clearance capacity of aminoglycosides and seem less at risk, as cumulative drug exposure is the most critical risk determinant in children. On the other hand, infants under 6 months may experience lower clearance capacity and higher ototoxicity than older children [137]. Experiencing damage in the neurodevelopmental period is more critical, especially in young children, as it causes profound effects on hearing development in the future. In a recently published prospective study in children with MDR-TB, HL developed in 8.5% [138].

More and faster research on new and fit-for-purpose tuberculosis drugs and regimens in children should be advocated [139].

70.2.9 Tuberculosis and Human Immunodeficiency Virus Coinfection and Aminoglycoside-Related Hearing Loss

Human immunodeficiency virus-infected patients are more disadvantaged than non-HIV-infected individuals regarding the risk of HL and ototoxicity caused by aminoglycosides [112, 113, 140]. If HIV-infected individuals developed MDR-TB

before the era of all-oral antituberculous regimens, they had to be exposed to ototoxic aminoglycosides for the treatment. In this population, the incidence of ototoxicity may increase up to three times due to aminoglycoside treatment [112]; amikacin caused higher HL than kanamycin (75% vs. 56%) in this group of patients [113]. Hearing loss may develop more frequently in HIV-positive children receiving antituberculous treatment than in HIV-negative children, as in adults [135]. Another study concluded that hearing was affected by audiometric examination in treating MDR-TB in children; however, there was no statistically significant difference between the HIV-infected and non-HIV-infected groups [131].

The primary mechanism of increased HL in tuberculosis and HIV coinfection is unknown. It is thought that chronic immune activation in HIV infection triggers intense ROS formation. It has been suggested that HIV-infected individuals who have not received antiretroviral therapy (ART) before may be more vulnerable to aminoglycoside ototoxicity [141]. Hearing loss can be detected in HIV-infected individuals, regardless of ART and the severity of the disease [142, 143]. Auditory monitoring should be an integral part of follow-up in HIV-positive MDR-TB patients [112, 113].

70.2.10 Current Tuberculosis Treatment Guidelines and Aminoglycoside-Related Hearing Loss

All-oral drugs such as bedaquiline, delamanid, para-aminosalicylic acid, and linezolid have an important place in the updated treatment regimen of MDR-TB. Injectable aminoglycosides are recommended to treat MDR-TB only if test results confirm susceptibility and audiometric monitoring for HL is possible [77, 144, 145]. Audiometry performed at baseline and follow-up should be compared. If HL develops, it is appropriate to decrease the daily dose or frequency, discontinue the agent, or switch to another aminoglycoside. Cross-resistance between streptomycin and other second-line injectable antituberculous drugs (kanamycin, capreomycin, amikacin) is rare [87, 146, 147]. If amikacin can not be used due to resistance, streptomycin may be considered only if susceptibility has been documented. Kanamycin and capreomycin are not included in the treatment of MDR-TB [144]. The recommended use of streptomycin and amikacin for children is the same [146].

Amikacin and streptomycin should not be used in the absence of conditions where high-quality audiometry for HL can be performed [77]. Amikacin is recommended only in patients whose hearing can be monitored monthly [145]. A baseline audiogram and a monthly repeat are recommended in adult patients [148]. Otoacoustic emission (OAE) testing in children younger than 5 years and pure tone audiometry in those 5 years and older can be performed for hearing assessment [145].

Knowledge of the classification and management of HL in drug-resistant tuberculosis (DR-TB) guidelines is lacking, and no consensus exists [130]. The injectable drug should be discontinued and replaced with an alternative one, such as delamanid when HL is grade 1, >26 decibels (dB) [145].

70.2.11 Genetic Susceptibility to Aminoglycoside-Related Hearing Loss

Familial HL and hereditary weakness of cochlea cases due to streptomycin use were defined [149]. In the audiological examination of 3000 patients who received streptomycin, wide individual differences in susceptibility to streptomycin toxicity were detected [21]. In other words, familial susceptibility to streptomycin toxicity exists [21]. Mothers and children in eight families who developed HL after receiving streptomycin treatment were identified [29]. Based on the observation that it occurs in relatives of the same family, susceptibility to streptomycin was previously thought to be inherited in an autosomal dominant manner [28].

In subsequent studies, analysis of 36 pedigrees that used aminoglycosides for various infections, including pulmonary tuberculosis, showed that susceptibility to aminoglycoside ototoxicity was only female-transmitted and mitochondrially inherited [150]. The duration of aminoglycoside use was generally less than 30 days in families with HL, and HL developed in two cases after 1 day of streptomycin administration. The authors warned that if ototoxicity developed after using aminoglycosides in maternal relatives, care should be taken regarding familial aminoglycoside ototoxicity in these individuals [150].

In a region in China, the prevalence of aminoglycoside-related deafness was reported as 0.035%, and aminoglycoside-related HL was 21.9% of all "deaf-mute" people [150]. Hearing loss mostly developed in the form of severe or complete deafness.

The association of mitochondrial 1555A > G (A1555G) point mutation with aminoglycoside-associated deafness was first described in 1993 by Prezant et al. [151] and Hutchin et al. [152]. Mitochondrial ribosomal ribonucleic acid (rRNA) mutation causes antibiotic-associated ototoxicity when nucleotide 1555A > G substitution is present in the mitochondrial deoxyribonucleic acid (mtDNA)-encoded 12S mitochondrial rRNA gene. Ototoxicity develops by the activation of aminoglycosides in this region [151]. The common features of aminoglycoside-induced HL associated with the mitochondrial mutation are bilateral and symmetrical sensorineural HL (SNHL). Individual audiograms may vary, but high-frequency disturbance is present in all cases [153]. Most patients with the 1555A > G mutation have HL, which may be progressive [153]. Hearing loss can also occur years after using aminoglycosides in people carrying this mutation [154]. Although 3243A > G and 7445A > G mitochondrial point mutations also cause genetic HL, the 1555A > G mutation was found to be primarily associated with HL after aminoglycoside use [155].

Some genetic mutations associated with ototoxicity have been described after using aminoglycosides but are relatively rare in the general population and were detected in 0–1.8% of populations representing a wide geographic distribution [137]. No specific populations with an exceptionally high prevalence of these mutations have been identified. The mitochondrial 1555A > G mutation incidence in Japan is 0.08–0.7% [156].

The frequency of mitochondrial 1555A > G mutation and the relationship between aminoglycoside use and HL were investigated in different ethnic groups. The role of aminoglycosides in the development of HL in people carrying the 1555A > G mutation is estimated to be 20% or less when a large number of patients and families are studied [151, 152, 154, 157–159]. The frequency of adult-onset, non-syndromic aminoglycoside-related familial sensorineural deafness has been identified as 0.5–2.4% in Europe and 3% in Japan [159–162]. The 1555A > G mutation in the USA was found in 17% of 41 people with HL who had used aminoglycosides [154]. In a Japanese series, 1555A > G mitochondrial gene mutation frequency was found to be 33% in patients with SNHL and using aminoglycosides and 59% in patients with cochlear implantation with aminoglycoside-induced HL [155]. In a Spanish study, the 1555A > G mutation was found in 15% of those in a cohort of 443 unrelated families with hearing impairment, and 22% of deaf patients with this mutation had taken aminoglycosides [159]. In Mexican individuals with HL using aminoglycosides, no 1555A > G mutation was found [163].

The mutation at position 1555 of the human mitochondrial DNA makes the human mitochondrial ribosome even more similar to the bacterial one, facilitating aminoglycoside binding [164, 165]. After binding, aminoglycosides have a long half-life (several months) in the inner ear hair cells, increasing the risk of ototoxicity.

A rapid screening method and careful counseling should be established to prevent aminoglycoside-induced HL [153]. Genetic screening of patients who will use aminoglycosides repeatedly is recommended [164]. Genetic assays should be tests that can be obtained quickly. Although genetic screening is costly, it will reduce unit costs with more testing [164]. A fast, reliable, and easy-to-use diagnostic method has been developed for the mitochondrial 1555A > G mutation and will be helpful in patients who will receive aminoglycosides [166].

70.3 Non-Aminoglycoside Antituberculous Drugs and Hearing Loss

Regarding HL caused by non-aminoglycoside antituberculous drugs, information for isoniazid, ethambutol, and thiacetazone exists in the literature. Hearing damage due to antituberculous other medicines, including rifampin and pyrazinamide, has not been reported.

70.3.1 Isoniazid

The successful use of isoniazid in treating tuberculosis was first reported in 1952, thus breaking new ground in the treatment of tuberculosis [167]. Isoniazid is the safest and most widely used drug for treating and preventing all types of tuberculosis diseases caused by isoniazid-susceptible *M. tuberculosis* strains [168]. It is a

particular agent, ineffective against other microorganisms. The most commonly known side effects of isoniazid are acute hepatitis, peripheral neuropathy, and hematological problems [169].

Unlike neurotoxicity as a well-known side effect, ototoxicity is an unusual adverse effect of isoniazid. Ototoxicity developed after using isoniazid to treat tuberculosis in adult hemodialysis patients with end-stage renal disease who received drug combinations, not including streptomycin [170]. The repeated audiometric examination was resolved after isoniazid was discontinued. Since many drugs are used in these patients, drug interactions are expected; but according to the authors' comment, isoniazid, in particular, was responsible for ear damage. It should be considered that isoniazid probably has an ototoxic effect, and audiometric testing should be performed before starting and at regular intervals during treatment [170].

70.3.2 Ethambutol

Ethambutol is a synthetic compound with a bacteriostatic effect against *M. tuberculosis*, first announced in an article in 1961 [171]. It is effective in the synthesis of the mycobacterial cell wall. Ethambutol has no cross-resistance with capreomycin, streptomycin, other aminoglycosides, and isoniazid [171, 172]. Ethambutol monotherapy is not recommended as this may result in the rapid development of resistance [173]. The most serious side effect is optic neuritis, which can be unilateral or bilateral and is usually reversible, though irreversible cases have been reported. In addition, pruritus, dermatitis, and peripheral neuritis have been described [173].

Hearing loss due to ethambutol use was reported in one case in the literature, but the causality–effect relationship has not been definitively proven [174]. The presented 52-year-old male patient received isoniazid, streptomycin, and ethambutol for pulmonary tuberculosis and developed peripheral neuropathy, visual impairment, SNHL, and rarely tinnitus 18 months after the treatment started. Streptomycin was discontinued 5 months before those symptoms appeared, and isoniazid was terminated, while the patient was given vitamins B1, B2, B6, and B12, with no substantial improvement recorded. Since the patient's tuberculosis disease was inactive, his other complaints, including HL, disappeared 3 months after ethambutol was discontinued.

Using the Italian spontaneous reporting database, 652 of at least one ototoxic adverse drug reaction were made out of 325,980 adverse event reports from 2001 to 2017 [175]. Among antituberculous drugs, the adjusted reporting odds ratio for tinnitus associated with ethambutol use was statistically significant.

70.3.3 Thiacetazone

Thiacetazone was synthesized in 1946 but was not used long to treat tuberculosis due to its kidney and liver toxicity [176]. Thiacetazone increases the ototoxicity of streptomycin. While ototoxic symptoms were 9.7% when used with isoniazid, it increased to 82.9% when streptomycin was added to combination therapy [176].

70.3.4 Macrolides

Erythromycin, the primary drug of the macrolide antibiotics class, is gradually losing its usage area, leaving its place to azithromycin, the new azalide antibiotic member of this class, clarithromycin, the semisynthetic macrolide antibiotic member. Today, clarithromycin and azithromycin have come to the fore in pediatrics and treating mycobacterial infections.

Adult patients treated for various indications using macrolides have an increased risk of HL [74, 175, 177, 178]. Clarithromycin is a component of the combination antibacterial therapy of nontuberculous mycobacteria (NTM) [179]. Hearing impairment has been reported rarely after treatment with clarithromycin in adults with/without acquired immunodeficiency syndrome (AIDS) who have a lung infection with *Mycobacterium avium–intracellulare* complex or disseminated disease [180–182].

Clarithromycin-related HL has also been described in children during the treatment of mycobacterial infections. Hearing loss was reported in 7% of 47 pediatric patients treated for NTM lymphadenitis after an average of 3 months of use of clarithromycin [183]. Of the 51,216 adverse event reporting records made to the French PharmacoVigilance Database system between 1985 and 2019, 70 were related to HL in children under 18 years of age [184]. One of the four children with clarithromycin-related HL was a 12-year-old girl who used clarithromycin, ethambutol, moxifloxacin, and rifabutin for mycobacterial infection.

Hearing loss that develops after clarithromycin therapy used for NTM lymphadenitis in children may improve weeks after the drug is discontinued [185]. Temporary HL can also be observed at high doses [186]. A systematic review of 44 publications evaluating macrolide-related SNHL showed that a decrease in hearing might be reversible or irreversible with oral and intravenous administration of standard and high doses of macrolides [187].

A meta-analysis of six randomized controlled trials examining the adverse effects of long-term use of azithromycin in patients with chronic lung disease reported that HL in children with cystic fibrosis and adults with chronic obstructive lung disease develops with long-term use of azithromycin [188]. Azithromycin has led to the development of HL in treating NTM infections in HIV-negative [189, 190] and HIV-positive [190–192] adults. Reducing the dose of azithromycin may reduce HL [189, 190]. It is recommended to monitor HL by audiogram in patients receiving macrolides to treat NTM infections [193].

70.4 Systematic Review and Meta-Analyses on Multidrug-Resistant Tuberculosis Treatment and Hearing Loss

The treatment outcomes in 975 children aged <15 years (median age 7.1 years, 75% bacteriologically confirmed) treated for MDR-TB were evaluated by a systematic review and meta-analysis of 33 studies from 18 countries, aiming to provide information on the pediatric characteristics of WHO MDR-TB treatment guidelines

[128]. Second-line injectable agents were not used in children with non-severe MDR-TB, and 78% of patients were successfully treated. According to the meta-analysis, children without serious illnesses can be retained from these toxic drugs [128].

In a meta-analysis of eight studies investigating the effect of HIV coinfection on HL in treating MDR-TB, one of which included pediatric patients [131], an evaluation was made with pure tone audiometry and OAE testing [141]. Human immunodeficiency virus-infected individuals had a 22% higher risk of developing aminoglycoside-related HL in MDR-TB treatment than non-HIV-infected individuals.

In a systematic review of 22 studies in treating DR-TB from India, the development of ototoxicity with injectable drugs was found to be 10%. Ranking from most ototoxic to least was capreomycin 25.0% (maximum) > amikacin > kanamycin > streptomycin 11.8% (minimum). When toxicity developed, the drug was discontinued or changed to another drug [194].

In a meta-analysis involving 53 centers from 30 countries, the order of side effects of injectable second-line drugs in more than 13,000 MDR-TB patients was amikacin > kanamycin > capreomycin > streptomycin [195]. Considering higher treatment success and less mortality, the ranking changed as amikacin > streptomycin > kanamycin and capreomycin [146].

In 131 studies with 217,475 patients from 49 countries, according to the results of the tuberculosis-related disability meta-analysis, hearing impairment/loss occurred with a frequency of 14.5%. Hearing impairment in DR-TB was seven times higher than in drug-susceptible tuberculosis (15% vs. 2.3%) [124].

The aminoglycoside-related HL in 12,793 patients with MDR-TB enrolled in 64 studies from 25 countries was 28.3% in a systematic review and meta-analysis and was the highest among patients treated with amikacin [196].

In a systematic review of 18 studies from 10 countries, the frequency of aminoglycoside-induced HL in DR-TB patients was 41% [197]. The prevalence of HL was highest in adults (44%) and lowest in children (24.5%). The authors concluded that approximately 50,000 HL per year could be prevented by avoiding aminoglycosides. The order of HL from most to least was kanamycin > amikacin > capreomycin [197].

Hearing loss causes economic difficulties and health problems, reducing individuals' quality of life. Hearing loss in children negatively affects language development and hinders literacy and educational activities [197].

In a systematic review of seven prospective studies published between 2010 and 2019, ototoxicity was reported between 1.4 and 44.3% when kanamycin was used in adults receiving short-term (6–12 months) MDR-TB therapy [198].

According to a systematic review of 29 studies examining the development of ototoxicity related to the use of aminoglycosides for various indications in children, the frequency of HL is seen between 0 and 57% [199]. In children, the severity of ototoxicity varies according to the type of aminoglycoside, duration of use, and the cause of the disease [200]. Concomitant use of potentially ototoxic drugs also increases the toxic effect on the ear. Children receiving aminoglycoside therapy

should undergo an age-matched audiological examination to detect the development of HL early.

70.5 Evaluation Before and During Ototoxic Antituberculous Treatment

Hearing loss may develop in tuberculosis patients predominantly using aminoglycosides, without being symptomatic, and can only be detected by audiological assessment [136]. Compared to the diagnosis of HL based on clinical findings alone, HL is detected in more patients by performing an audiometer [122]. Therefore, an audiometric examination is recommended for all patients using aminoglycosides [33, 126, 201]. With the initial identification of ototoxicity, the recommendation to monitor hearing was voiced [18].

Even the audiometric evaluation performed within 2 weeks of the start of antituberculous therapy may differ from the measurement at the beginning of the treatment. In other words, ototoxicity can develop as early as 2 weeks, and this change can be detected clearly by the audiometer [117]. Unfortunately, over the years, research has shown that ototoxicity monitoring is not noticeably understood by patients or professionals and is still an area that requires further development and training [202].

The tests used in the hearing evaluation should be accessible in patient monitoring centers. When testing fails and the patients report complaints, the physician prefers to discontinue aminoglycoside therapy, even if there is no laboratory evidence of HL [203].

If aminoglycosides are used in children, the hearing level should be checked before and during MDR-TB treatment and monitored with appropriate tools and equipment [130].

The external ear canal should be examined with an otoscope; infection, wax, foreign bodies, or other obstruction should be sought, middle ear function should be evaluated with tympanometry, and tympanic membrane compliance should be checked. An audiometer should be preferred for cooperative children and performed as much as possible in children aged >5 years. Otoacoustic emission testing can be performed in uncooperative children, which measures the patency of the neuronal auditory circuit [145]. However, OAE testing does not measure what the patient is hearing; it is just a screening test. The use of OAE testing is beneficial as antituberculous drugs affect the cochlea; the test is rapid and can be performed at the bedside. Brainstem auditory-evoked response testing measures the entire length of the sensorineural pathway, but sedation is required in young children [130]. A hearing monitoring program should be offered to all children using ototoxic drugs for tuberculosis [133].

Tele-audiology and smartphone technology are being developed in cochlear toxicity research. Extended high-frequency (EHF) audiometry testing using a smartphone application and specially calibrated headphones can provide cost-effective, accurate, and reliable monitoring [204].

The use of antioxidant drugs may be protective against the toxic effect of ROS [102]. Animal studies in which antidote or preventive treatments were applied to avoid ROS and free radicals exist [100]. Deferoxamine, acetylsalicylate, D-methionine, glutathione, and N-acetylcysteine (NAC) have been potentially helpful in animal models [100]. N-acetylcysteine, as an antioxidant, scavenges free oxygen radicals, has a protective effect, and is beneficial for aminoglycoside-related ototoxicity for several reasons [205]. Because of the long half-life and accumulation of aminoglycosides in the hair cell, NAC should be given for a while after stopping the drug. N-acetylcysteine has also been reported to be synergistic with first-line and some second-line antituberculous drugs, thus showing antimycobacterial effects [205]. To reduce the risk of ototoxicity, NAC administration is recommended by some authors as a rescue treatment for children with MDR-TB for whom amikacin should be used [145].

70.6 Conclusion

The disease burden of tuberculosis has decreased in the last three decades, and effective therapy regimens certainly contribute to this [206]. On the other hand, adverse drug effects pose a challenge for patients and physicians. As MDR-TB cases increase, combination treatments, including drugs with noticeable side effects on hearing, primarily aminoglycosides, have been given widely. Aminoglycoside-induced ototoxicity can cause severe HL. Hearing impairment for children will lead to a handicap not only in terms of deafness but also gives harm to their capacity for learning, literacy, and social integration. Ototoxic drugs should be avoided as much as possible in treating pediatric tuberculosis, and hearing monitoring should be indispensable in all cases where they are prescribed.

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Antiviral Agents for Pediatric Infections, and Hearing Loss

71

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71.1 Introduction

Viruses are the most minute infectious agents that can cause disease in the human body. They do not have a complete, complex cell structure like bacteria and fungi. They live as obligate intracellular parasites since they cannot produce energy or synthesize macromolecules (proteins) necessary for living independently from the host cell.

There are six common steps of viral infection: attachment and penetration, virus uncoating, replication and transcription of the viral genome, protein synthesis, assembly, and release [1]. The virus binds to the host surface molecules early in the viral life cycle. After binding, the virus fuses with the host cell membrane. When the virus reaches the cytoplasm, it sheds its capsid. After the uncoating, the viral genome is used for gene expression and replication. In the last stage, when the viral proteins and genomes are accumulated, they are assembled to form a progeny virion particle and then released extracellularly. Naked viruses exit cells via cell lysis, while enveloped viruses exit cells via budding through cellular membranes [2].

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Antiviral drugs act on the different stages of the viral life cycle to be effective. They can kill or inactivate viruses by several mechanisms. Antiviral drugs act by directly targeting viruses or host cell factors that viruses need. According to target action on viruses, antiviral agents are classified as inhibitors of attachment and entry, virus uncoating inhibitors, viral polymerase inhibitors, viral protein synthesis inhibitors, viral genome assembly inhibitors, and viral release inhibitors. Host cellular cytokine interferon, produced in response to viral infection, is used in some viral infections such as hepatitis B and C and has antiviral immunomodulating and antiproliferative effects. Due to the growing number of emerging viruses in recent years, the development of antiviral agents is on the rise.

Antiviral agents can be used primarily for prophylaxis and treatment. Viral infections, such as herpes simplex virus (HSV), cytomegalovirus (CMV), influenza A and B viruses, hepatitis B and C viruses, and human immunodeficiency virus (HIV) infections, may benefit from antiviral therapy in pediatric patients. This chapter will discuss the antiviral agents used in the most common viral infections, including their mechanism of action, pharmacokinetics, toxicity, and their impact on hearing loss (HL), if any.

71.2 Antiviral Agents for Herpesviruses

71.2.1 Ganciclovir and Valganciclovir

71.2.1.1 Pharmacology and Pharmacokinetics

Ganciclovir and its prodrug valganciclovir are nucleoside analogs that inhibit the incorporation of deoxyguanosine triphosphate into elongating deoxyribonucleic acid (DNA) [2]. Ganciclovir can inhibit all herpesviruses, primarily CMV [3]. It must be phosphorylated by viral and cellular kinases and converted to ganciclovir triphosphate, an active antiviral compound. This viral kinase is encoded in the UL97 gene of CMV ten times more potently in CMV-infected cells than uninfected cells [3, 4]. Ganciclovir monophosphate is added to the end of the growing DNA chain, slowing replication. Additionally, it serves as a poor substrate for chain elongation [3]. When given intravenously, the ganciclovir concentration rises quickly above the level that inhibits CMV replication (0.1–3.48 mg/mL) [2, 3]. Oral absorption of ganciclovir is poor (<10% oral bioavailability). With intravenous administration, the desired ganciclovir concentration inhibits CMV in many tissues, including the brain and aqueous humor. The elimination half-life is 2–3 h, and the majority of ganciclovir is eliminated unchanged by the renal route [1].

Valganciclovir is another drug effective against CMV. It is a ganciclovir prodrug with a similar activity spectrum [5]. Valganciclovir is cleaved by hepatic and gut esterases to produce ganciclovir. Valganciclovir has a high oral bioavailability (41–60%) [1, 5, 6]. A dose of 16 mg/kg twice daily of valganciclovir is equivalent to a 6 mg/kg daily intravenous ganciclovir dose when used in symptomatic congenital CMV infection (cCMVI) [5].

Ganciclovir doses should be adjusted according to body surface area and creatinine clearance, and it should be given at a 50% dose in mild renal dysfunction [3].

71.2.1.2 Indications

The indication of ganciclovir and valganciclovir is the treatment of symptomatic cCMVI, systemic and ocular CMV infections in immunocompromised patients, and prevention of CMV infection in transplant patients (Table 71.1).

In moderate to severely symptomatic infants with cCMV at birth, early therapy with ganciclovir or valganciclovir can prevent HL and other developmental sequelae [7, 9, 10]. In the absence of data showing the efficacy of antiviral treatments in mild symptomatic congenital CMV disease and isolated HL, routine antiviral therapy is not recommended [7, 9].

The doses of ganciclovir and valganciclovir and the treatment duration vary depending on whether they are given for prophylaxis or treatment and the type of disease caused by CMV (Table 71.2).

71.2.1.3 Toxicity

The most common side effect of ganciclovir is myelosuppression [3, 7, 8]. The risk of myelosuppression increases with the concomitant use of other myelosuppressive agents. Infants receiving ganciclovir are more likely to have myelosuppression than infants receiving valganciclovir [7]. Therefore, weekly complete blood count (CBC) checks during the initial period of ganciclovir therapy should be continued monthly [1, 8]. This reversible adverse effect resolves after the first week of discontinuing

Table 71.1 Antiviral treatment indications in cytomegalovirus (CMV) infections[a]

1. Treatment of CMV disease in the immunocompromised host
   - Acquired CMV retinitis
   - Disseminated CMV and retinitis
2. Prevention of CMV disease in the immunocompromised host (AIDS, transplant patients)
   - Prophylaxis of CMV in high-risk host
3. Symptomatic congenital CMV disease
   - CNS disease: Microcephaly, CNS calcification, chorioretinitis, white matter changes (or other abnormalities on MRI consistent with CMV disease)
   - Severe disease (includes life-threatening or severe single-organ or multi-organ non-CNS disease
   - Moderate disease (e.g., multiple XXX minor findings consistent with CMV disease)[b]
4. Treatment of active CMV disease in other immunocompromised hosts
   - Pneumonitis in premature infants
   - CMV colitis in those with inflammatory bowel disease

AIDS acquired immunodeficiency syndrome, *CNS* central nervous system, *MRI* magnetic resonance imaging

[a]Adopted and modified from Ref. [7–9]

[b] Persistent (e.g., more than 2 weeks duration) abnormalities of hematologic or biochemical indices or more than 2 "mild" disease manifestations (petechiae, mild hepatomegaly or splenomegaly) or biochemical or hematologic abnormalities (such as thrombocytopenia, anemia, leukopenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinemia) or small for gestational age (SGA) defined as weight for gestational age < −2 standard deviations without microcephaly

Table 71.2 Valganciclovir and ganciclovir indications and doses in cytomegalovirus (CMV) infection[a]

Drug	Indications	Route	Recommended dosage	Adverse effects
Valganciclovir	Congenital infection in newborn	Oral	32 mg/kg/day, in 2 divided doses, 6 months	Myelosuppression: Neutropenia Anemia, Thrombocytopenia Hepatotoxicity
	CMV retinitis in the immunocompromised patient (adolescent)	Oral	Treatment: 2 × 900 mg, for 2–3 weeks Suppression: 1 900 mg, 3–6 months	
	Prevention of CMV disease in a high-risk patient (transplant)	Oral	7× body surface area x creatinine clearance (maximum 900 mg/day)[b]	
	Prevention of CMV disease in HIV infection	Oral	7× body surface area × creatinine clearance (maximum 900 mg/day)[a]	
Ganciclovir	Congenital infection in newborn	Intravenous	12 mg/kg/day, in 2 divided doses, 6 weeks	
	CMV retinitis in the immunocompromised patient	Intravenous	10 mg/kg per day, in 2 divided doses, for 14–21 days (treatment)	
	Prophylaxis of CMV in the high-risk patient (transplant)	Intravenous	10 mg/kg per day, in 2 divided doses, for 5–7 days, then 5 mg/kg per day, in 1 dose for 100 days	
	Preemptive therapy of CMV in the high-risk patient (transplant)	Intravenous	10 mg/kg per day, in 2 divided doses, for 14–21 days, then 5 mg/kg per day if CMV viremia continues	

HIV, human immunodeficiency virus

[a] Adopted and modified from Ref. [7–10]

[b] The Schwartz equation calculates the dose (mg) of valganciclovir by this formula; 7 × body surface area x creatinine clearance (CrCl) in the post-transplant period. Usually, the maximum recommended daily dose of valganciclovir is 900 mg for post-transplant patients (≥17 years)

ganciclovir. In treating cCMVI, antiviral agents' safety and long-term side effects are not known precisely. Gonadal toxicity and carcinogenicity have been detected in animal experiments [3].

71.2.1.4 Resistance

Ganciclovir and valganciclovir resistance among CMV strains occurs due to mutations in either UL97 or the UL 54 genes [1, 4, 11]. Some factors, such as exposure to low levels of ganciclovir in the plasma, high viral load, and long-term therapy, may cause the development of resistance [1, 11].

71.2.2 Cidofovir

71.2.2.1 Pharmacology and Pharmacokinetics

Cidofovir is a nucleotide analog that requires host kinase to convert to the active diphosphoryl form and cidofovir diphosphate [8, 12]. The active form of cidofovir has a greater affinity to viral DNA polymerase, causing inhibition of viral DNA synthesis. The half-life of cidofovir is approximately 24 h. Cidofovir diphosphate remains in the cell for a long time. The nephrotoxicity associated with cidofovir limits its use [13].

71.2.2.2 Indications

Cidofovir has a broad antiviral activity for herpes viruses and other DNA viruses such as adenovirus, human papillomavirus (HPV), and polyomaviruses [1, 8, 14, 15]. Cidofovir is used in ganciclovir-resistant CMV infections, BK virus infections in renal transplant recipients, adenovirus infections in the immunocompromised host, and patients with laryngeal papillomatosis. It also effectively treats acyclovir-resistant VZV and HSV, ganciclovir-resistant CMV, HHV-6 infections in immunocompromised hosts, and CMV retinitis in patients with HIV infection (Table 71.3) [16].

71.2.2.3 Toxicity

Cidofovir may cause acute tubular necrosis [1]. Cidofovir nephrotoxicity can be reduced by maintaining hydration and administering probenecid [15]. Other reported adverse effects are metabolic acidosis, neutropenia, loss of visual acuity, iritis, and intraocular pressure changes [16].

71.2.2.4 Resistance

Drug resistance can develop while on treatment. The development of resistance is associated

with viral DNA polymerase gene mutations [17].

Table 71.3 Indications, doses, and adverse effects of cidofovir and foscarnet[a]

Drug	Indications	Route	Recommended dosage	Adverse effects
Cidofovir	CMV retinitis in the immunocompromised patient (adolescent)	IV	Induction: 5 mg/kg, once weekly with probenecid and hydration Maintenance: 5 mg/kg, once every 2 weeks with probenecid and hydration	Nephrotoxicity Neutropenia metabolic acidosis ocular hypotonia
Foscarnet	CMV retinitis in the immunocompromised patient (adolescent)	IV	180 mg/kg per day, in 2–3 divided doses for 14–21 days, then 90–120 mg/kg once a day for maintenance therapy and secondary prophylaxis	Nephrotoxicity Seizure
	HSV infection resistant to acyclovir in the immunocompromised host	IV	90–120 mg/kg per day, in 2–3 divided doses for 3 week. or until the infection resolves	
	VZV infection resistant to acyclovir	IV	40–60 mg/kg per dose, every 8 h for 7–10 days	

CMV cytomegalovirus, *h* hour *HSV* herpes simplex virus, *IV* intravenous, *VZV* varicella-zoster virus
[a]Adopted and modified from Ref. [1, 16]

71.2.3 Foscarnet

71.2.3.1 Pharmacology and Pharmacokinetics

Foscarnet is a pyrophosphate analog that directly inhibits viral DNA polymerase by binding to the pyrophosphate binding site and preventing cleavage of pyrophosphate from the deoxynucleotide triphosphate [1, 17]. It is available only as an intravenous medicine. The serum half-life of foscarnet is 48 h, and most of the doses are eliminated by the kidneys.

71.2.3.2 Indications

Foscarnet is an active agent of all herpes viruses and is approved for treating CMV retinitis in patients with HIV infection (Table 71.3). It is also the preferred medicine for acyclovir-resistant HSV, VZV, and ganciclovir-resistant CMV infections.

71.2.3.3 Toxicity

Nephrotoxicity is the most frequent side effect, and foscarnet therapy can cause acute tubular necrosis and interstitial nephritis. Dose adjustment for foscarnet is necessary for patients with renal impairment. Foscarnet can cause granulocytopenia, seizures, and electrolyte disturbances such as hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, and prolonged QT interval [16].

71.2.3.4 Resistance

During treatment with foscarnet, drug resistance can be seen through mutations of the viral DNA polymerase gene.

71.2.4 Letermovir

Letermovir is a newer drug in both oral and intravenous formulations, which has been licensed for the prophylaxis of adult cytomegalovirus seropositive recipients of allogeneic hematopoietic cell transplants. Letermovir inhibits CMV replication by targeting subunits of the viral terminase enzyme complex (pUL56, pUL51), necessary for CMV DNA processing [18]. However, studies indicated letermovir could also be used safely in children [19, 20]. But the experience in pediatric use of letermovir is limited.

Myelotoxic and nephrotoxic side effects due to letermovir and significant interaction with mycophenolate or posaconazole have not been reported.

71.2.5 Acyclovir and Valacyclovir

71.2.5.1 Pharmacology and Pharmacokinetics

Acyclovir and its prodrug valacyclovir, nucleoside analogs, are polymerase inhibitors used to treat HSV and VZV infections [21]. The viral enzyme thymidine kinase first phosphorylates acyclovir to convert to monophosphate, followed by a change to the active form of acyclovir-triphosphate. Acyclovir-triphosphate inhibits viral DNA polymerase to terminate viral replication. Acyclovir is relatively specific for HSV and VZV. The bioavailability of acyclovir is low when taken orally [21, 22].

After intravenous administration, acyclovir is widely distributed in the body and shows high concentrations in the skin vesicles, kidney, heart, lung, and liver tissues [1]. The half-life of acyclovir is about 5 h in neonatal patients and 2–3 h in older children. Almost all of the dose of acyclovir is excreted unchanged by the urine, primarily via glomerular filtration and tubular secretion [22]. In contrast to acyclovir, valacyclovir has higher bioavailability (15–20% versus 50–64%) [22]. Acyclovir and valacyclovir have similar pharmacokinetic features [1].

71.2.5.2 Indications

Intravenous acyclovir is preferred for severe life-threatening infections, such as herpes simplex virus encephalitis, any form of neonatal HSV disease, and severe HSV and VZV infection in immunocompromised patients [1, 8]. Herpes simplex virus can cause disseminated infections (25%) with multi-organ involvement or localized infections with skin–eye–mouth (SEM; 45%) or central nervous system (CNS; 30%) involvement in newborns [23, 24]. The recommended dose of acyclovir for neonatal HSV infection is parenterally 60 mg/kg daily in 3 divided doses (Table 71.4).

Table 71.4 Dosage and indications of acyclovir, valacyclovir, and famciclovir in herpes simplex virus (HSV) infections[a]

Drug	Indications	Route	Recommended dosage
Acyclovir	Neonatal SEM disease Neonatal Disseminated CNS disease HSV encephalitis	IV IV IV	20 mg/kg, tid, 14 days 20 mg/kg, tid, ≥21 days 30–45 mg/kg per day, in 3 divided doses
	HSV infection in an immunocompromised patient	IV	30 mg/kg per day, in 3 divided doses
	Chickenpox in an immunocompromised patient	IV	30 mg/kg per day, in 3 divided doses
	Chickenpox in an immunocompetent patient	Oral	80 mg/kg per day, in 4 divided doses (maximum 3200 mg/day)
Valacyclovir	Varicella (2–18 years)	Oral	60 mg/kg per day, in 3 divided doses (not to exceed 1 g per dose)
	Genital HSV infection in adolescent	Oral	2 × 1 g (first episode) 1 × 1 g (episodic, recurrent)
	Herpes zoster in adolescent	Oral	3 × 1 g
Famciclovir	Herpes zoster in adolescents	Oral	1500 mg/day, in 3 divided doses
	Genital HSV infection in adolescent	Oral	2 × 1 g

CNS central nervous system, *IV* intravenous, *SEM* skin, eyes, and mouth, *g* gram
[a] Adopted and modified from Ref. [1, 8, 21, 23, 24]

Suppressive therapy with oral acyclovir (3 × 300 mg/m^2) for 6 months after primary intravenous treatment improves neurodevelopmental outcomes in infants with CNS disease [23].

Acyclovir or valacyclovir is usually recommended for transplant and oncology patients with an increased risk for severe HSV disease [1, 8, 18]. Oral therapy with acyclovir or valacyclovir is effective for non-severe VZvV and HSV infections (Table 71.4).

Valacyclovir is licensed to treat recurrent orolabial HSV infections ≥12 years of age and varicella (2–17 years of age). The recommended dose of valacyclovir is 20 mg/kg per dose (maximum 1 g/dose), administered twice a day for HSV and three times a day for VZV infections [1].

71.2.5.3 Toxicity

The most common side effects of acyclovir are acute renal injury associated with crystal deposition in the renal tubule and neurotoxicity [25]. A decreased kidney function and rapid increase in serum creatinine indicate acute renal injury due to acyclovir. This adverse effect is usually seen within 24–48 h after treatment. The cause of nephrotoxicity is not clear. To decrease nephrotoxicity, slow infusion rate and additional hydration of patients are important.

Another nephrotoxic drug used with acyclovir is a risk factor for the development of acute kidney injury [25, 26]. Other adverse neurologic effects include tremors, seizures, hallucinations, altered consciousness, and extrapyramidal signs, which can be seen with high serum acyclovir levels [25].

Valacyclovir has fewer side effects than acyclovir but can cause headaches and vomiting.

71.2.5.4 Resistance

Herpes simplex virus 1 strains resistant to acyclovir have developed mainly in immunocompromised patients [1–3]. Most resistant HSV-1 isolates have mutations in the thymidine kinase genes and less frequently have mutations in the viral DNA polymerase genes [23].

Acyclovir resistance in VZV has been reported mostly in children with HIV infection who have CD4+ cells $\leq 100/mm^3$ with prolonged use of acyclovir [1]. Acyclovir-resistant HSV strains are rarely seen in newborns, bone marrow and solid organ transplant recipients, and patients with cancer.

71.3 Antiviral Agents for Influenza

Four classes of antiviral therapies have been approved for the treatment and prophylaxis of influenza infections:

1. Neuraminidase inhibitors (zanamivir, oseltamivir, peramivir, laninamivir),
2. Endonuclease inhibitors (baloxavir marboxil),
3. Ribonucleic acid (RNA) polymerase inhibitors (favipiravir), and
4. Adamantanes (amantadine).

Among these, zanamivir, oseltamivir, peramivir, and baloxavir are approved to treat influenza virus infections in the pediatric population [27–30]. The target side for adamantanes is the M2 ion channel protein of influenza A viruses but not influenza B viruses. Circulating influenza A viruses have high levels of resistance to adamantanes. For this reason, adamantanes are not recommended for the treatment and prophylaxis of influenza A and B infections.

Neuraminidase is a sialidase releasing progeny virions from the cell surface. The neuraminidase interferes with the neuraminidase of influenza [29, 30]. Baloxavir marboxil reduces viral proliferation by inhibiting cap-dependent endonuclease and mRNA synthesis [31].

Antiviral treatment is recommended for patients with suspected or confirmed influenza infection, hospitalized, has a progressive, severe, or complicated illness, or is at higher risk for complications. Antiviral agents should begin within the first 48 h of illness onset. Oseltamivir is recommended first-line treatment for both non-hospitalized and hospitalized patients. The age-dependent use of oseltamivir, zanamivir, peramivir, or baloxavir is listed (Table 71.5) [27, 28, 32].

Favipiravir, a selective viral RNA polymerase inhibitor, inhibits viral RNA synthesis [33]. But it is not approved by FDA. Due to the high resistance to adamantanes, their use is not recommended unless the resistance status changes.

Table 71.5 Doses, indications, and adverse effects of antiviral agents against influenza[a]

Drug	Activity against	Recommended age	Route	Dose	Adverse effects
Oseltamivir	Influenza A and B	≥2 weeks	PO	*Treatment*[b] *Children younger than 1 year old:* 3 mg/kg/dose twice daily for 5 days *≥1 year old:* ≤15 kg; 30 mg twice daily 16–23 kg; 45 mg twice daily 24–40 kg; 60 mg twice daily >40 kg; 75 mg twice daily For 5 days *Prophylaxis* [c] Children younger than 1 year old: 3 mg/kg/dose once daily for 7 days *≥1 year old:* ≤15 kg; 30 mg once daily 16–23 kg; 45 mg once daily 24–40 kg; 60 mg once daily >40 kg; 75 mg t once daily For 7 days	Nausea, vomiting, transient neuropsychiatric events
Zanamivir	Influenza A and B	≥7 years	Inhalation	*Treatment:* 10 mg twice daily for 5 days *Prophylaxis* [d] 10 mg once daily for 7 days	Bronchospasm, sinusitis, dizziness, skin reaction, transient neuropsychiatric events

Table 71.5 (continued)

Drug	Activity against	Recommended age	Route	Dose	Adverse effects
Peramivir	Influenza A and B	≥6 months	IV	*Treatment:* *6 months to 12 years old:* 12 mg/kg/dose (maximum 600 mg), single dose >13 years: One 600 mg, single dose *Prophylaxis:* Not recommended	Diarrhea, skin reactions, transient neuropsychiatric events
Baloxavir	Influenza A and B	≥5 years	PO	*Treatment:* <20 kg; 2 mg/kg single dose 20–79 kg; 40 mg single dose >80 kg; 80 mg single dose *Prophylaxis:* The dosage is the same as for the treatment	

PO peroral, *IV* intravenous

[a] Adopted and modified from Ref. [27, 28]

[b] The use of oseltamivir for treatment in children less than 14 days old is not approved by the United States of America (USA) Federal Drug Administration (FDA) but is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP)

[c] Use of oseltamivir for prophylaxis in children less than 3 months old is not recommended unless the situation is not judged critical

[d] Zanamivir is not recommended for prophylaxis in children under 5 years old

71.4 Antiviral Agents for Chronic Hepatitis B Infection

Hepatitis B virus is a significant cause of acute and chronic hepatitis in children. The acute or chronic clinical course of infection due to HBV depends on the underlying disease and the age of the patients. One-fourth of infants and children who do not receive hepatitis B treatment die from cirrhosis or hepatocellular carcinoma. Early cirrhosis and hepatocellular cancer have been reported in pediatric patients who did not receive appropriate treatment [34].

Table 71.6 Antiviral agents in chronic hepatitis B virus infection treatment[a]

Drug	Age	Route	Dose	Adverse effects
Interferon-alpha 2b	≥1 year	Subcutaneous	6 million IU/m^2 3 times a week	Flu-like symptoms Transient neutropenia Autoimmune disease
Lamivudine	≥2 years	Oral	3 mg/kg once daily (max. 100 mg)	Pancreatitis, paresthesia Peripheral neuropathy neutropenia, anemia, rash
Adefovir	≥12 years	Oral	10 mg once daily	Acute renal failure Fanconi syndrome Lactic acidosis
Entecavir	≥2 years	Oral	0.015 mg/kg once daily (max. 0.5 mg)	Lactic acidosis (decompensated cirrhosis only)

[a]Adopted and modified from Ref. [35, 36]

Viral genotypes are important in determining the response and outcome of treatment in HBV infection [35]. Two classes of drugs, immune modulators (interferons) and nucleoside/nucleotide analogs, have been approved for children with chronic HBV infection (Table 71.6).

Antiviral treatment is not recommended for uncomplicated acute HBV infection unless it progresses to acute liver failure [34, 35]. In chronic HBV infection, the treatment is determined according to the phase of the disease [35, 37]. In general, treatment can be started in the immune-active and immune-escape phases. Table 71.6 summarizes the current approaches for treating chronic HBV infection [34, 35, 37].

The American Association for the Study of Liver Diseases (AASLD) recommends treating children with detectable HBV DNA in serum, positive hepatitis B e antigen (HBeAg) with elevated alanine aminotransferase (ALT)-positive children [36]. Treatment of cirrhosis or active hepatitis in all age groups is recommended [35–37].

71.4.1 Interferon-Alpha and Polyethylene Glycol Interferon-Alpha

Interferon-alpha (IFN-α) and pegylated (polyethylene glycol) interferon-alpha (Peg-IFN-α) are immunomodulatory agents used to suppress long-term viral replication by activating the host's immune system [37]. Interferon-alpha and Peg-IFN-α are used in children in the presence of the same indications as other drugs (Table 71.7) [37, 38]. The main advantages of IFN-α and Peg-IFN-α treatment are not associated with viral resistance [35].

Flu-like symptoms with mild fever, malaise, and transient neutropenia may be seen in the early period of interferon treatment. Complete blood count (CBC) and thyroid function should be checked every 3 months during the treatment for transient neutropenia and thyroiditis [37]. In addition, clinical follow-up is

Table 71.7 Current approaches for treating chronic hepatitis B virus infection

• HBeAg negative	• HBV DNA >20,000 IU/mL	Longer than 6 months
• HBeAg positive	• HBV DNA >2000 IU/mL • Elevated ALT concentration • Evidence of chronic hepatitis on liver biopsy	Longer than 6 months

ALT alanine aminotransferase, *DNA* deoxyribonucleic acid, *HBeAg* hepatitis B e antigen, *HBV* hepatitis B virus

recommended for neuropsychiatric, ischemic, and infectious complications of interferon.

Interferon therapy is not recommended for infants due to its toxicity. It is also contraindicated in patients with decompensated cirrhosis, autoimmune disease, uncontrolled seizures, severe cardiac disease, and cytopenia [35].

71.4.2 Lamivudine

Lamivudine, a dideoxynucleoside cytosine analog, is a reverse transcriptase inhibitor used to treat HBV and HIV-1 infections [1]. The bioavailability of lamivudine is very high and reaches maximum serum levels quickly after oral administration. But lamivudine resistance during treatment is the main disadvantage [39].

Lamivudine is the first antiviral drug approved for chronic HBV infection in children. The current studies demonstrate that lamivudine effectively decreases HBV DNA levels by 3–4 log copies/mL. After lamivudine treatment, relapse can be seen because nucleoside analogs cannot eliminate the covalently closed circular DNA in the liver [1, 39]. Therefore, lamivudine must be used carefully to treat chronic HBV infection in children [37, 40]. Lamivudine can cause side effects such as peripheral neuropathy, hair loss, pancreatitis, paresthesia, anemia, neutropenia, and rashes [1, 39].

71.4.3 Adefovir Dipivoxil

Adefovir dipivoxil is a prodrug and nucleotide analog of adefovir monophosphate. In the body, adefovir is converted to diphosphate form by intracellular enzymes. It is a competitive inhibitor of viral DNA polymerase. When combined with lamivudine, telbivudine, or entecavir, adefovir shows enhanced activity in treating chronic HBV infection [1]. The most important problem experienced in adefovir dipivoxil treatment is the increasing resistance over time [1, 35].

The bioavailability of adefovir dipivoxil is about 59%. Adefovir is excreted from the kidneys as an unchanged drug by tubular secretion and glomerular filtration. The dose adjustment is necessary for patients with CrCl <50 mL/min [1].

Adefovir treatment is generally well-tolerated; some patients suffer from mild side effects such as headache, diarrhea, abdominal discomfort, and diarrhea [1].

71.4.4 Entecavir and Tenofovir

Entecavir, a first-line drug, and guanosine nucleoside analog inhibit HBV replication by inhibiting viral DNA polymerase. Inhibition of HBV is 20–30 fold higher than lamivudine. Entecavir is superior to adefovir dipivoxil and lamivudine [1].

Entecavir and tenofovir also inhibit hepatitis B virus DNA polymerase and HIV-1 reverse transcriptase enzymes after conversion to tenofovir diphosphonate.

In naive patients, entecavir monotherapy induces a low rate of drug resistance (1%); the resistance rate is high (50%) in lamivudine-refractory patients. Because of the high risk of resistance development, entecavir should not use in patients with telbivudine and lamivudine-resistant infections [36].

The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), AASLD, and The Asian Pacific Association for the Study of the Liver (APASL) recommend the use of entecavir and tenofovir for HBV infection in children.

Entecavir and tenofovir disoproxil fumarate are recommended to treat chronic HBV infection in children [35–37].

Entecavir and tenofovir inhibit the synthesis of mitochondrial (mt)-DNA, leading to the depletion of mtDNA and impaired mitochondrial function. Therefore, follow-up for lactic acidosis is recommended [36].

71.5 Antiviral Agents for Chronic Hepatitis C Virus Infection

Hepatitis C virus (HCV) infection is usually asymptomatic during childhood, but it may progress to cirrhosis and primary hepatocellular carcinoma within time. The vertical transmission of HCV is rare, and in the first 4 years of life, 25–40% of infected children spontaneously clear the infection [41]. Two pediatric studies with long-term follow-up have shown that 80% of the patients had normal liver biopsies in the second and third decades of life [41].

The recommended treatment of HCV infections in children younger than 12 years is twice-daily ribavirin and weekly injections of Peg-IFN-α-2a or Peg-IFN-α-2b. The duration of therapy depends on the HCV genotype. The treatment duration for genotypes 2 and 3 is 24 weeks and for genotypes 1 and 4 is 48 weeks (Table.71.8).

Due to the toxic effects, such as type 1 diabetes, growth impairment, thyroid disease, and ophthalmological complications, and low sustained virologic response seen in the combined use of ribavirin and interferons, direct-acting antivirals (DAAVs) used in adults have become important treatment alternative for children. With DAAV drugs, the cure rate for chronic HCV has exceeded 90% [41].

European Medicine Agency (EMA) and FDA approved the use of sofosbuvir-ribavirin for HCV genotype 2 or 3 infections among 12–17 years old and body weight $\geq$ 35 kg and sofosbuvir-ledipasvir combination for patients infected with genotype 1, 4, 5, and 6 (Table.71.8).

Table. 71.8 Antiviral agents in chronic hepatitis C virus infection[a]

Drug	Age	Route	Dose	Adverse effects
Interferon-alpha 2b Peginterferon-alpha 2a	≥1 year ≥3 years	Subcutaneous	6 million IU/m^2 3 times a week 180 mg/1.73 m^2 once a week	Thyroid disease Type 1 diabetes Ophthalmological complications Growth impairment
Ribavirin		Oral	Weight-based dosing	Anemia Extravascular hemolysis (low doses) Marrow suppression (high doses)

Direct-acting antiviral agents in chronic HCV				
Drug	Age (year)	Genotype	Duration (weeks)	
Sofosbuvir (400 mg) + Ledipasvir (90 mg) Sofosbuvir (400 mg) + ribavirin (15 mg/kg) Glecaprevir (300 mg) + Pibrentasvir (120 mg)	≥12 12–17 ≥12	Genotype 1,4,6 Genotype 2,3 Any genotype	12–24 24 8	Ototoxic Ototoxic

[a] Adopted from Ref. [42]

The European Association for the Study of the Liver (EASL), ESPGHAN, and World Health Organization (WHO) recommend DAAV regimens (sofosbuvir with ledipasvir and sofosbuvir with ribavirin) in adolescents aged 12 years and older with HCV infection [42]. On the other hand, the AASLD recommends antiviral agents for all children over the age of 3, regardless of the severity of the disease [41].

When interferon-free DAAV regimens are approved in children aged 3–11 years, interferon-free DAAV regimens can be considered for all children to eradicate the HCV infection as early as possible, irrespective of liver disease stage and rate of disease progression.

71.6 Antiretroviral Agents for Pediatric HIV Infection

The immediate initiation of antiretroviral (ARV) therapy reduces mortality by 75% [42]. ARV therapy should begin as soon as possible in all pediatric patients with HIV infection [43]. Treatment aims to suppress the virus at undetectable levels [42]. When choosing antiviral therapy, the patient's age, drug susceptibility test results, dose frequency, and size of medicine should be considered.

An ARV therapy for children should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) class (Tables 71.9, 71.10, and 71.11) [42].

Table 71.9 Antiretroviral agents[a]

NRTI	NNRTI	INSTI	PI
Abacavir (ABC)	Doravirine	Bictegravir	Atazanavir
Emtricitabine (FTC)	Efavirenz	Cabotegravir	Darunavir
Lamivudine (3TC)	Etravirine	Dolutegravir (DTG)	Lopinavir/ritonavir (LPV/r)
Tenofovir	Nevirapine	Elvitegravir	
Zidovudine (ZDV)	Rilpivirine	Raltegravir (RAL)	

INSTI integrase strand transfer inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor
[a]Adopted from Ref. [42]

Table 71.10 Drugs preferred to be combined with nucleoside reverse transcriptase inhibitors (NRTIs) for human immunodeficiency virus (HIV) infection in children

- newborns aged <14 days: Nevirapine (NVP)
- Newborns aged <4 weeks and weighing ≥2 kg: Raltegravir
- Neonates aged ≥14 days to <4 weeks: Lopinavir/ritonavir
- Infants and children aged ≥4 weeks and weighing ≥3 kg: Dolutegravir
- Children aged ≥6 years and weighing ≥25 kg: Dolutegravir or Bictegravir (BIC)
  - Bictegravir (BIC) is available only as a component of the fixed-dose combinations (FDC) tablet; bictegravir (BIC)/emtricitabine(FTC)/tenofovir alafenamide (TAF): (BIC/FTC/TAF)

Dolutegravir (DTG) plus two-NRTIs is recommended by the Office of AIDS Research Advisory Council (OARAC) as an INSTI-based regimen for children and adolescents aged ≥4 weeks and weight ≥ 3 kg

Table 71.11 Preferred initial antiretroviral treatment regimens[a]

Age	Regimen	Side effects
Newborns aged <14 days	2 NRTI: (ZDV plus 3TC or FTC) + NVP	Skin rash, including SJS and hepatic toxicity Lactic acidosis Bone marrow suppression
• Neonates aged ≥14 days to <4 weeks	: 2 NRTI: (ZDV plus 3TC or FTC) + LPV/r	Skin rash Bone marrow suppression CNS depression Hyperlipidemia, especially hypertriglyceridemia QT interval prolongation and Torsades de Pointes
Infants and children aged ≥4 weeks and weighing ≥3 kg	2 NRTI: (ABC plus (3TC or FTC) + DTG	Skin rash Neuropsychiatric symptoms Insomnia, headache Elevation in serum creatinine

ABC indicates abacavir, *CNS* central nervous system, *DTG* dolutegravir, *FTC* emtricitabine, *INSTI* integrase strand transfer inhibitor, *LVP/r* lopinavir/ritonavir, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *NVP* nevirapine, *PI* protease inhibitor, *SJS* Stevens–Johnson syndrome, *ZDV* zidovudine, *3TC* lamivudine
[a]Adopted from Ref. [42]

Dolutegravir (DTG) plus two-NRTIs is recommended by the Office of AIDS Research Advisory Council (OARAC) as an INSTI-based regimen for children and adolescents aged ≥4 weeks and weight ≥ 3 kg.

Antiretroviral prophylaxis should be given to all infants according to the presence of risk factors for perinatal HIV exposure. In newborns, prophylaxis with zidovudine is recommended for low-risk perinatal HIV exposure. Zidovudine plus lamivudine plus nevirapine or raltegravir are recommended for high-risk perinatal HIV exposure [43].

71.6.1 Toxicity

Antiretroviral treatment may cause a wide range of toxicity in pediatric and adult patients. These are CNS toxicity (psychosis, dizziness, impaired concentration, seizure, cerebellar dysfunction, altered state of consciousness, abnormal electroencephalogram [EEG], headache, suicidal ideation), lactic acidosis, hematologic (anemia, neutropenia, macrocytosis), nephrotoxicity (elevation in serum creatinine, renal dysfunction, nephrolithiasis), hepatic toxicity (hepatitis, indirect hyperbilirubinemia), lipodystrophy, weight gain, dyslipidemia, osteoporosis and osteopenia, insulin resistance, asymptomatic hyperglycemia, diabetes mellitus, gastrointestinal side effects (vomiting, diarrhea, pancreatitis), rash, Stevens–Johnson syndrome, erythema multiforme, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and toxic epidermal necrolysis.

71.7 Antiviral Agents and Hearing Loss

Antiviral drugs generally appear safe for the auditory system, but a few are reported to have ototoxic effects (Table 71.12) [44–46].

As a general mechanism, hydrophilic ototoxic drugs pass the blood–labyrinth barrier and reach hair cells before inducing ototoxicity [47]. Damage in the cochlear sensory hair cells and neurons causes cochleotoxicity; on the other hand, damage in the peripheral vestibular sensory cells provokes vestibulotoxicity [47].

Table 71.12 Ototoxic antiviral drugs[a]

	Cochleotoxicity Hearing loss and tinnitus		Vestibulotoxicity Dizziness, ataxia	Virus
Hydroxychloroquine	+		+	SARS-CoV-2
Efavirenz	+			HIV
Sofosbuvir/ledipasvir	+			HCV
Favipiravir, remdesivir	+			SARS-CoV-2
Ribavirin+interferons	+			HCV

HCV hepatitis C virus, *HIV* human immunodeficiency virus, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2

[a]Adopted from Ref. [44, 45]

The first signs of ototoxicity are high-pitched tinnitus, HL, and vertigo. While tinnitus and sensorineural HL (SNHL) are signs of cochlear toxicity, vestibular toxicity is presented with dizziness and balance problems [48]. Hearing loss may occur within 3–4 days, weeks, or months after treatment is completed and may be temporary or permanent [48].

Antiviral agents like ganciclovir/valganciclovir and acyclovir have been shown to reduce HL in congenital CMV and neonatal HSV infections, respectively.

Antiviral agents such as IFN-α, pegylated interferons, ribavirin, sofosbuvir/ledipasvir, efavirenz, and telaprevir are associated with ototoxicity [44, 45, 49–51]. Interferon-related ototoxicity may be related to the disruption of cochlear metabolic homeostasis.

Controversial results are present regarding the ototoxicity of antiretroviral drugs in the literature. It has been reported that antiretroviral drugs have a toxic effect on the House Ear Institute-Organ of Corti 1 (HEI-OC1) cells by impairing cell proliferation or inducing cell death [52]. Some antiretroviral such as ritonavir, nelfinavir, efavirenz, and delavirdine reduce the auditory cell viability [47, 52]. A combination of antiretroviral drugs is also more ototoxic than individual ones due to the synergistic effect. Long-term antiretroviral therapy may be responsible for HL [47]. Ototoxicity effects due to medicines are heightened in the presence of confounders such as ear infections and tuberculosis treatment [53].

71.8 Conclusion

Antiviral therapy for viral infections is essential to prevent mortality and morbidity. But increased use of antiviral agents may increase known and unknown side effects. Studies specifically report the ototoxicity of antiviral drugs used to treat HBV, HCV, and HIV infections. It should be known that antiviral drugs such as IFN-α, pegylated interferons, ribavirin, telaprevir, and sofosbuvir/ledipasvir are recommended for the treatment of HBV and HCV infections, and combinations used in the treatment of HIV and antiretroviral drugs such as efavirenz have ototoxic effects. Hearing screening should be performed during the treatment of patients using these drugs.

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Antifungal Agents for Pediatric Infections, and Hearing Loss

72

Sefika Elmas Bozdemir, Solmaz Çelebi, and Ryan Henry Rochat

72.1 Introduction

Diagnosing and managing an adverse drug reaction on time with the least possible sequela is important. As an adverse drug reaction, ototoxicity is more common than doctors and patients realize. Ototoxicity is reversible or irreversible hearing impairment ranging from mild hearing loss (HL) to complete deafness due to damage to the inner ear and auditory nerve cells by some therapeutic agents and chemicals. Ototoxicity can develop as a direct toxic effect of the drug when the drug accumulates and damages the cells in the inner ear or as a result of both of these processes [1]. In general, drug-induced HL typically manifests as sensorineural HL (SNHL) and is reported within manufacturer labeling as either on-study or post-market analysis. Some of the most well-known ototoxic agents include aminoglycosides, macrolides, antimalarials, loop diuretics, antineoplastics, and chelating agents [2]. While many of these ototoxic drugs are well known by most pediatricians, other agents or substances may not have been reported yet.

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This chapter aims to review the available literature on antifungal agents commonly used in pediatric practice and whether there is any risk of ototoxicity due to their use. Surprisingly, there is little data about the ototoxicity of antifungal agents in the medical literature. Most evidence for the ototoxic effect of these medications is derived from case reports and/or experimental studies on animals. A recursive search of the United States of America (USA) Food and Drug Administration (FDA) drug library identifies only four antifungals as having associated ototoxic effects. As such, the ototoxicity of these agents in humans is primarily derived from nonhuman studies.

72.2 Polyene Antifungals and Hearing Loss

Polyene antifungals are macrolide antibiotics produced from some *Streptomyces* species [3]. Polyenes bind to ergosterol of the fungal cell membrane, thus weakening it, causing potassium and sodium ions to leak, resulting in membrane potential loss and fungal cell death [4]. Amphotericin B (AmB) and nystatin are two of the most commonly used polyene antifungals.

72.2.1 Amphotericin B and Hearing Loss

Amphotericin B is a polyene antifungal drug used intravenously for systemic infections of yeasts, molds, and the protozoan parasite *Leishmania* spp. Amphotericin B binds with ergosterol in the fungal cell membrane, forming a transmembrane channel leading to potassium and sodium ions leakage, causing the death of fungal cells [5].

The recommended daily dose of AmB deoxycholate is 1–1.5 mg/kg/day in neonates and 0.25–0.5 mg/kg/day in infants, children, and adolescents; however, the dose may be increased to 1.5 mg/kg/day in severe infections. Recommended doses for liposomal amphotericin B (L-AmB) and amphotericin B lipid complex are 3–5 mg/kg/day in newborns and > 1 month-old children and up to 7 mg/kg/day in severe cases [6, 7].

Intravenously administered AmB in therapeutic doses may cause multiple organ damage. Nephrotoxicity is a common side effect of AmB and can sometimes be severe and irreversible [8]. While infusion toxicity may be seen in about 20–90% of the cases, the probability of developing renal failure is 80% in treatments longer than 2 weeks [8]. Electrolyte imbalances, such as hypokalemia, hypomagnesemia, and hepatotoxicity, rarely fulminant liver failure, have also been reported frequently [8]. Other less common adverse effects of AmB include anemia, thrombocytopenia, leukopenia, serious arrhythmias, hypertension, and cardiac failure [9].

Though tinnitus is a known chronic adverse effect of AmB, ototoxicity has rarely been reported [10]. In the study of Sundar et al. [11], visceral leishmaniasis patients treated with AmB or paromomycin were evaluated with audiometry; none in the AmB group developed threshold shifts for ototoxicity. However, in one of the case

reports of AmB ototoxicity revealed by a literature search on databases, a 65-year-old man treated with L-AmB for visceral leishmaniasis complained of HL in both ears on the fifth day of treatment [12]. The bilateral SNHL detected on pure tone audiometry (PTA) was attributed to L-AmB, the only medication he had received. The treatment with L-AmB was stopped, and he was treated with a 30 mg/day prednisone for 4 weeks, and SNHL recovered fully.

In the other case report of HL due to AmB, a 40-year-old man diagnosed with visceral leishmaniasis developed bilateral mixed HL after receiving a 450 mg cumulative dose of AmB. No medication or disease could be attributed to an etiology other than AmB, so it was stopped after 500 mg of cumulative dose. The HL improved after the cessation of the drug, confirmed by audiometry [13].

In a study by Mohindra et al. [8], 24 immunocompetent patients of invasive rhinoorbitocerebral fungal sinusitis treated with AmB were evaluated for HL in dosages of 500, 1000, and 2000 mg. A high-frequency PTA and cold caloric test (CCT) were applied to all patients before starting treatment with AmB. Tests were repeated after the doses of AmB administration and at 3 and 6 months after cessation of therapy. While all patients complained of subjective HL during treatment, some showed paradoxical improvement in the audiograms. The authors concluded that AmB causes some change in the hearing pattern during the treatment; however, the results were not statistically significant for reporting ototoxicity.

With so few case reports, the mechanism of ototoxicity related to AmB is challenging to explain. Some experimental and hypothetical explanations of reversible ototoxicity induced by loop diuretics, aminoglycosides, and salicylates have been attributed to the involvement of stria vascularis of the inner ear, which becomes edematous and changes in the ionic gradients between the perilymph and endolymph occur by inhibiting adenylate cyclase and G-proteins. It has been hypothesized that the immunological and biochemical similarities between the inner ear and kidney tissues might explain the deposition and damage of AmB on ionic homeostasis leading to a functional ototoxic effect [8, 12]. Cumulative dose-related effects of AmB can cause mild HL and progress to severe HL in the presence of renal insufficiency [8, 13].

72.2.2 Nystatin and Hearing Loss

Nystatin is a polyene antifungal agent with a broad spectrum of antifungal activity against *Candida* spp., *Aspergillus, Epidermophyton, Trichophyton, Cryptococcus neoformans, Microsporum* spp., and dimorphic fungi; such as *Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Rhodotorula* spp., *Trichosporon, and Blastoschizomyces capitatus* [14]. Nystatin binds to ergosterol in the fungal cell membrane and increases the permeability, causing leakage of potassium and sodium ions, which leads to fungal cell death [14]. Nystatin is used to treat superficial Candida infections and otomycosis in topical and oral forms.

In the animal study by Daniel et al. [15], topical application of 1.2 mL of nystatin suspension twice daily for 7 days to the ears of the chinchillas did not

cause any long-term ototoxic effects detectable by distortion product otoacoustic emissions [DPOAE] or scanning electron microscopy. The authors concluded long-term functional hearing tests and histology showed nystatin as a safe topical antifungal drug in the animal model, even in the presence of a non-intact tympanic membrane.

In the animal study by Perez et al. [16], vestibular evoked potentials (VEPs) and brainstem auditory evoked responses [BAERs] were measured before and after the application of nystatin 3% to sand rats. Though it had no toxic effect on vestibular function, an apparent toxic effect on the cochlear function was observed. Authors reported that although this was an animal study, these preparations should be used cautiously in infected ears of humans having perforated tympanic membranes.

While reports of a nystatin-containing topical ointment (nystatin-neomycin (Animax®)) has been associated with ototoxicity, it is unclear if this effect is due to aminoglycoside use or nystatin alone. Nevertheless, this combination has not been approved for use in humans.

72.3 Azole Antifungals and Hearing Loss

All members of the azole antifungals have a 5-membered azole ring [17]. The imidazoles contain two nitrogen atoms, while the triazoles have the third one. The imidazoles, including butoconazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sulconazole, terconazole, and tioconazole, are limited to largely topical use because of their pharmacokinetic properties and indefinite safety profiles. Triazoles, including fluconazole, itraconazole, isavuconazole, voriconazole, and posaconazole, have a broader spectrum of activity that makes them first-line drugs to treat serious systemic fungal infections [17]. Azole antifungals inhibit the cytochrome p450-dependent enzyme lanosterol 14-alpha-demethylase, which converts lanosterol to ergosterol, leading to fungal cell destruction and death [18].

72.3.1 Topical Azoles

Some topical azoles, including bifonazole, clotrimazole, econazole, fluconazole, and ketoconazole, used to treat otomycosis, were evaluated for HL side effects [1]. In an animal study, Marsh and Tom [19] found that clotrimazole and tolnaftate had no ototoxic effect. Bassiouny et al. [20] reported that using econazole solution was safe even in an ear with a perforated tympanic membrane. On the other hand, Paulose et al. [21] did not find any ototoxic reactions due to instilled clotrimazole and econazole into patients' ears with tympanic membrane perforations and open mastoid cavities.

In the study by Perez et al. [16], two common topical antimycotic agents, clotrimazole (1% solution) and bifonazole (1% solution), used in otomycosis

treatment, did not affect the vestibular function of the sand rats, as revealed by recording VEPs before and after drug application. In contrast, this treatment had an apparent toxic effect on the cochlear function, as demonstrated by the BAER test. However, their solvents appeared to be responsible for the significant ototoxic component. The authors concluded that these preparations should be used cautiously in ears with perforated tympanic membranes.

72.3.2 Systemic Azoles

Fluconazole, the first member of triazole antifungals, exhibits activity against *Candida, Cryptococcus*, and some dimorphic and dermatophyte fungi. It has an excellent effect on most *Candida* species; however, it has a poor effect on *Candida glabrata* and no effect on *Candida krusei*. Fluconazole activity for other yeasts, including *Trichosporon* and *Saccharomyces* spp., was lower than that observed for candida isolates. A single daily dose of 6–12 mg/kg/day (maximum 600 mg/day) is recommended in children. The treatment duration and drug dosage depend on the type of fungus, infection site localization, and disease severity [6]. Fluconazole is the recommended therapy of choice in immunocompetent individuals who are clinically stable and either felt to have a low likelihood of a resistant species or culture susceptibility [22].

Itraconazole has a broader spectrum of activity than fluconazole on some mold pathogens, such as *Aspergillus* species and dimorphic fungi. Parenteral itraconazole is not available, but absorption of oral solution is relatively high. A dosage of 2.5–5 mg/kg twice daily is recommended for the treatment and once daily for relapse prevention [18].

Voriconazole has fungicidal activity against *Candida* spp. and *Aspergillus* spp. It is the most commonly used antifungal agent for invasive aspergillosis. Voriconazole also has activity against common dermatophytes and pathogens causing endemic mycoses. In children ≥2–12 years old, the recommended parenteral dosage is 9 mg/kg/dose on day 1, 8 mg/kg/dose on the following days, twice daily, and 9 mg/kg/dose orally every 12 h with suspension form. The dosage for children >12 years old varies according to the patient's weight [18].

Posaconazole produced by hydroxylation of itraconazole has a broader spectrum than voriconazole; thus, it is also effective against Zygomycetes [3]. The Federal Drug Administration approved oral suspension and delayed-release tablet forms in children ≥13 years old and intravenous injection formulation of posaconazole in patients aged ≥18 years. The preferred daily oral dosage is 200 mg, three times for prophylaxis, and 800 mg/day, two to four times for treatment [18].

Some adverse effects, such as gastrointestinal disturbances, skin reactions, abnormal hepatic function tests, and hepatitis, can be seen with fluconazole use. Voriconazole treatment's most common side effects are reversible visual impairments such as brightness and blurred vision, elevated liver enzymes, and skin

reactions (photosensitization). Hypokalemia, arrhythmia, QT prolongation, hepatotoxicity, vomiting, nausea, diarrhea, fever, headache, thrombocytopenia, rash, and abdominal pain can be listed as the side effects of posaconazole use [3, 18, 23].

While HL due to systemic preparations of azole antifungals is noted in the drug labels accompanying only two of these agents, itraconazole and voriconazole, there are no case reports associating these antifungals with ototoxicity. Furthermore, true ascertainment of the ototoxic effect of these antifungals is likely convoluted by the concomitant use of multiple medications in the treatment of invasive fungal disease.

72.4 Echinocandins and Hearing Loss

Echinocandin antifungals are a group of large, semisynthetic, cyclic lipopeptides having a large molecular weight, which causes them to have poor absorption through the digestive tract and are being used only intravenously. Echinocandins block fungal cell wall synthesis by inhibiting 1-3 beta-D-glucan synthase. Caspofungin, micafungin, and anidulafungin are currently available echinocandins in clinical usage, with fungicidal effects against *Candida* spp. and fungistatic effects against *Aspergillus* spp. [3]. Echinocandins are becoming increasingly utilized in the first-line treatment of invasive candidiasis as recommended by the Infectious Diseases Society of America (IDSA) guidelines on the management of invasive candidiasis [22].

Caspofungin and micafungin have FDA approval for use in children. Dosing instructions for caspofungin are based on body surface area for children ≥3 months. The preferred daily dosage is 70 mg/m^2 loading on day 1, followed by 50 mg/m^2/day on subsequent days (maximum 70 mg/day) [16]. According to body weight and approved indications, micafungin is used in children ≥4 months in appropriate doses. A dose of 2–3 mg/kg daily is recommended for the treatment [18].

All three echinocandins are well tolerated and have similar adverse effects. Nausea, vomiting, diarrhea, abdominal pain, hepatotoxicity, infusion and hypersensitivity reactions, and injection site pain are common side effects of echinocandins. Anemia, leukopenia, neutropenia, thrombocytopenia, and cardiac events may rarely be seen as side effects [18]. Hearing loss due to echinocandins has not been reported in the literature.

72.5 Pyrimidine Analogs and Hearing Loss

The pyrimidine analogs are hydrophilic molecules requiring specialized membrane transporters to enter cells. Intracellular enzymes convert these drugs to active metabolites. Afterward, they interfere with the nucleic acid synthesis, causing an antiproliferative effect resulting in the inhibition of deoxyribonucleic acid (DNA) synthesis. In this class, 5-flucytosine has an antifungal effect on *Candida* spp. and *Cryptococcus* spp.

72.5.1 Flucytosine and Hearing Loss

Flucytosine is generally active against *Candida* spp. and *Cryptococcus neoformans*. However, *C. krusei* and *C. neoformans* have higher minimal inhibitory concentrations (MICs) for flucytosine than other *Candida* species [17]. Flucytosine penetrates the fungal cell wall with the help of cytosine permease and is deaminated to 5-fluorouracil (5-FU), incorporated into fungal ribonucleic acid (RNA) to interrupt protein synthesis. The 5-fluorouracil is then converted to 5-fluoro-deoxy uridylic acid monophosphate, a noncompetitive inhibitor of thymidylate synthetase, which interferes with DNA synthesis. The resulting antifungal activity may be fungistatic or fungicidal, depending on conditions and organisms' susceptibility. The most common side effects of flucytosine are abdominal pain, leukopenia, and myelosuppression. Because of these side effects, flucytosine use today is mainly limited to treating cryptococcal meningitis and candida meningitis, combined with AmB, given concerns for the development of resistance [19, 20, 24]. Flucytosine is available only as an oral formulation, and the recommended dose depends upon the patient age and weight. 150 mg/kg/day, divided into 4 doses [18].

The efficacy and safety of flucytosine have not yet been systematically studied in pediatric patients; however, dosing in neonates and ototoxicity due to the systemic use of flucytosine with Amp B or alone have not been reported in the literature. However, the manufacturer of flucytosine's most well-known formulation, Ancobon®, declared in the prospectus that in a small number of neonates treated for systemic candidiasis with 25–200 mg/kg/day of flucytosine, with and without the addition of amphotericin B, HL could occur as an adverse neurological effect [25].

In the only study in the literature, the 5-fluorocytosine topical ointment was evaluated as an antimycotic agent for otomycosis treatment by Schönebeck and Zakrisson [26], and no difference was found in pretreatment and posttreatment audiograms of the study population. The authors concluded that 5-fluorocytosine has no ototoxic adverse effect in humans.

72.6 Allylamines and Benzylamine Derivatives

72.6.1 Terbinafine and Hearing Loss

Terbinafine is an allylamine antifungal developed by the chemical modification of naftifine. Terbinafine inhibits the enzyme squalene epoxidase, which depletes ergosterol in the fungal cell wall. It has both fungicidal and fungistatic activity. It exhibits good activity against almost all dermatophytes; however, it has poor activity against most *Candida* and *Aspergillus* species. Terbinafine is used in oral and topical formulations to treat fungal infections of the nails, skin, and hair [27].

Terbinafine is generally well tolerated, but some adverse events may occur. In an uncontrolled surveillance study of 25,884 patients, adverse reactions due to terbinafine were reported in 10.4% of patients [28]. The adverse reactions were mainly

associated with the gastrointestinal system and skin, including eczema, urticaria, pruritus, and rash. Hearing loss was not reported in this study.

In the study of Scholl and van Puijenbroek [29], 6 of 849 patients treated with terbinafine had hypoacusis, which was found to be statistically significant with oral terbinafine. Three hypotheses on the mechanism of hearing impairment due to terbinafine were discussed. Firstly, in human cells, squalene epoxidase converts squalene into lanosterol together with squalene cyclase. Inhibition of squalene epoxidase by terbinafine might decrease cholesterol levels in also human cells. This hypothesis is supported by an in vivo study showing that terbinafine inhibited squalene epoxidase in *Candida albicans* and rat liver cells [29].

However, subsequent studies showed that oral terbinafine does not affect cholesterol levels or biosynthesis in animals or patients treated with terbinafine. Mammalian epoxidase is much less sensitive than the fungal enzyme to inhibition by terbinafine at the enzymatic level [30]. The second hypothesis suggests that lateral wall membranes of cochlear outer hair cells contain less cholesterol than the apical and basal membranes [29]. Animal experiments showed that changes in cholesterol levels in the cochlea influence outer hair cell membrane capacitance and otoacoustic emissions (OAEs) [29]. This data might show that reducing cholesterol levels can cause cochlear dysfunction leading to HL. The third hypothesis suggests that a large distribution volume of terbinafine within the cochlea could harm hearing [30]. According to Scholl and van Puijenbroek [29], there might have been a relationship between hearing impairment and the use of oral terbinafine, especially in higher doses and for long periods.

72.7 Conclusion

Polyenes, azoles, and echinocandins are the most frequently used antifungal agents to treat children's superficial and invasive fungal infections. Hearing loss due to amphotericin B has rarely been reported. Terbinafine can cause cochlear dysfunction leading to HL. Any data for HL due to antifungal agents, including flucytosine, azoles, and echinocandins, has not been reported in the literature.

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Antiparasitic Agents for Pediatric Infections, and Hearing Loss

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73.1 Introduction

Parasitic diseases are responsible for significant morbidity, mortality, disability, and healthcare costs worldwide [1]. Most parasitic diseases affect tropical and subtropical low- and middle-income countries and impoverished people. Parasites live on or inside the host and obtain their nutrients from the host. These organisms can be classified as protozoa, helminths, and ectoparasites [2]. Most parasitic organisms are responsible for the neglected diseases categorized, and more research is needed for their treatment and eradication. Most currently used antiparasitic drugs were developed decades ago, and pharmaceutical companies have not shown much interest in developing new drugs. Many organizations have started to make great efforts to recover patients with these diseases and develop new drugs in recent years.

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Antiparasitic drugs are classified according to the parasite group they affect. Treatment options vary according to the specific organism [3]. Considering the incidence of parasitic diseases in the pediatric age group, effective and safe antiparasitic drugs for children are of great importance [4]. Antiparasitic drugs have many side effects and are relatively toxic [5]. One of the important side effects of antiparasitic agents is on the audio-vestibular system.

73.2 Ototoxicity

As polypharmacy has increased, drug side effects such as ototoxicity have become an increasingly important public health problem [6]. Although few drugs are strongly associated with ototoxicity, most healthcare professionals do not know the relationship between these drugs and ototoxicity. Evidence-based ototoxicity was primarily recognized after aminoglycosides, and their ototoxic side effects were discovered in the 1940s.

Ototoxicity is an adverse pharmacological reaction that affects the inner ear or auditory nerve, characterized by vestibular and/or cochlear dysfunction [7]. Drugs used to treat serious infections risk significant side effects such as ototoxicity. These drugs are necessary to save lives, but their negative impact on survivors' quality of life is becoming more of a concern for families and healthcare professionals. Ototoxicity, a significant cause of acquired hearing loss (HL) in children, is one of the considerable side effects of drugs.

More than 600 drugs are known to be associated with ototoxicity, drug-induced damage to the auditory balance system, dizziness, imbalance, tinnitus, a feeling of fullness in the ear, hyperacusis, and HL [7, 8]. High-dose loop diuretics, antibiotics, especially aminoglycosides and macrolides, antimalarial agents, and chemotherapeutics such as cisplatin are the most-known ototoxic drugs [9]. In addition, any medication can have the potential for a toxic reaction to inner ear structures, including the cochlea, vestibulum, semicircular canals, and otoliths.

The panorama of drug-induced HL has become widespread in the last few decades through the advancement of scientific knowledge and the increased awareness of pharmaceutical companies and institutions that control drug production. The incidence of ototoxic HL is dose-dependent and cumulative in fashion. It may be affected by other factors such as gender, age, route of administration, duration of treatment, bioavailability, pre-existing HL, dehydration, congestive heart failure, decreased drug elimination due to kidney failure, hypertension, genetic predisposition, and geographical effects [7, 9]. Drug ototoxicity mainly depends on dose and exposure period. If treatment is continued, HL may worsen, sometimes even after the drug is discontinued [10].

It is essential to determine the anatomical location of the problem and the degree of lost function in defining HL. Symptoms can develop rapidly or gradually, improve with drug discontinuation, or become irreversible. Although drug-induced HL is not a life-threatening condition, it can harm the quality of life, education, social communication, and occupation [11]. Due to the nature of oral or intravenous systemic administration of drugs, HL is almost always symmetrical, bilateral, and sensorineural. With the increasing dose and duration of the treatment, HL is affected in both high and low frequencies [12–15].

Antiparasitic drugs that cause ototoxicity and HL are limited. Clinicians need to recognize the effects of these drugs and perform tests to evaluate the hearing function of patients using them. Even mild HL can interfere with speech, language, cognitive and social development, specifically in children. Hearing loss may cause poor academic performance and inadequate psychosocial functioning. Therefore, early diagnosis of HL is the key to children's communication success. Management of ototoxicity aims to minimize or prevent communication disruption and plan appropriate rehabilitation [9].

73.3 Mechanism of Ototoxicity

Ototoxic drugs can damage the inner ear in different ways. Most ototoxic drugs first affect the outer hair cells in the cochlea. Platinum-based chemotherapies and aminoglycosides act on the outer hair cells in the basal turn of the cochlea before affecting the inner hair cells and apical cells. These two drug classes impair mitochondrial functions by entering the marginal and hair cells of the stria vascularis [6, 16]. Another mechanism is the change in blood flow in the inner ear. Decreased cochlear blood flow can lead to an ischemic process that alters hair-cell metabolism and causes neuronal damage, loss of supporting hair cells, and stria vascularis atrophy. Like salicylates and quinines, loop diuretics also reduce blood flow to the inner ear through changes in circulating blood volume [17, 18]. The mechanism by which quinine causes ototoxicity is known as vasoconstriction, but other ototoxic drugs' action mechanism is not well understood [17].

Pharmacogenetic factors play a significant role in determining the susceptibility of patients to the undesirable effects of ototoxic drugs. The most common drug group causing ototoxicity is antimicrobial drugs [6]. Antiparasitic agents should also be kept in mind for these side effects. Antiparasitic agents with ototoxic effects are listed in Table 73.1.

Table 73.1 Ototoxic antiparasitic agents and hearing loss

Ototoxic 5.antiparasitic drugs	Hearing loss
Antiprotozoal drugs	
Antimalarial drugs	
Artemether-lumefantrine	Y
Artemisinin-naptoquine	Y
Artesunate-mefloquine	Y
Atovaquone-proguanil	Y
Chloroquine/hydroxychloroquine	Y
Doxycycline	N
Mefloquine	Y
Pyronaridine-artesunate	Y
Quinine	Y
Other drugs with antiprotozoal activity	
Amphotericin B	Y
Clindamycin	NK
Macrolide	Y
Meglumine antimoniate	Y
Metronidazole	Y
Niclosamide	N
Paromomycin	Y
Pentamidine	N
Spiramycin	Y
Sulfadiazine	N
Tinidazole	N
Trimethoprim-sulfamethoxazole	N
Anthelmintic drugs	
Albendazole	N
İvermectin	N
Praziquantel	NK

Y yes, *N* no, *NK* not known

73.4 Antiparasitic Drugs and Hearing Loss

Antiparasitic drugs act to destroy parasites or inhibit their growth. They usually affect a particular class or a limited number of parasites. Antiparasitic drugs are classified according to the parasites they act on. Antiparasitic drugs are divided into five categories: anthelmintics, antimalarials, antibacterial agents with antiprotozoal activity, agents against luminal protozoans, and kinetoplast protozoans [19].

73.4.1 Anthelmintic Drugs and Hearing Loss

Helminths, multicellular worms, are classified as roundworms (nematodes), tapeworms (cestodes), and leaf-shaped flatworms (trematodes [flukes]). The action mechanisms of many anthelmintic agents are not fully understood. Ivermectin,

benzimidazoles (albendazole, mebendazole, triclabendazole), praziquantel, diethylcarbamazine, pyrantel, and nitazoxanide are anthelminthic drugs [20]. Most helminth infections are treated with albendazole, ivermectin, or praziquantel. Albendazole has a broad spectrum of activity against helminthic infections, including neurocysticercosis, echinococcosis, ascariasis, hookworm infections, and trichuriasis.

Albendazole-induced HL has not been reported, but other ototoxic side effects, such as dizziness, have been recognized [21]. Ivermectin, developed for veterinary use in the 1970s, has broad activity against roundworm larvae and several arthropods. It is also a drug with broad spectrum recommended therapeutically in coronavirus disease 2019 (COVID-19), as it has been shown to inhibit the in vitro replication of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [22]. Dizziness has been reported after anthelminthic therapy and COVID-19 treatment, but HL has not been recorded [23, 24]. Dizziness has been reported as a common, mild, and transient side effect with praziquantel use [19]. Information on the ototoxic side effects of pyrantel, nitazoxanide, and diethylcarbamazine is limited.

73.4.2 Antiprotozoal Drugs and Hearing Loss

73.4.2.1 Antimalarial Drugs and Hearing Loss

Malaria is an infectious disease caused by a unicellular and intracellular parasite called *Plasmodium* with five different types: *Plasmodium vivax, Plasmodium malaria, Plasmodium ovale, Plasmodium falciparum*, and *Plasmodium knowlesi* [25]. Antimalarial drugs are used for the prophylaxis and treatment of malaria. Appropriate drug selection is determined by the infecting species, drug resistance, and host condition. Drugs in this group are quinoline derivatives (chloroquine, amodiaquine, quinine, quinidine, mefloquine, primaquine, lumefantrine, and halofantrine), antifolates (sulfonamides, pyrimethamine, proguanil, and dapsone), antimicrobials (tetracycline, doxycycline, and clindamycin), artemisinin derivatives, and artemisinin-based combination therapies [26].

Chloroquine was the first drug produced for the prophylaxis and treatment of malaria. It is preferred to treat uncomplicated malaria caused by all *Plasmodium* species except *P. falciparum* due to its resistance problem. Chloroquine has also been used to treat autoimmune and connective tissue diseases [19]. Quinine is a drug widely used to treat malaria in endemic areas. Due to the narrow therapeutic range of quinine and quinidine, an overdose can lead to arrhythmia, blindness, and HL [26]. Antimalarial drugs can affect the central and peripheral vestibular systems, but these effects have rarely been reported [27]. The most known in this group are chloroquine and quinine.

Audio-vestibular toxicity of antimalarial drugs, including chloroquine and hydroxychloroquine, is not a common side effect. Audio-vestibular complications were reported in only 61 (2.6%) of 2339 patients who used antimalarial drugs between 1986 and 2010 in the database of the French pharmacovigilance network [27]. This study reported that symptoms appeared within 24 h of starting the drug in

4 patients, after 1 month in 53%, and after a dose increase in 2 patients. Significant and irreversible side effects (HL and vertigo) were observed in 2 patients. It has been reported that 16.4% of patients used it concomitantly with another drug that may cause ototoxicity [27].

The mechanisms underlying the ototoxicity of antimalarial drugs are not fully understood. There are few reports about other antimalarial drugs related to ototoxicity, which cause vasoconstriction in the cochlea and a decrease in cochlear blood flow. Various hypotheses have also proposed quinine-related changes in the cochlea, such as disruption of outer hair cells by quinine, decreased blood flow and quinine-induced thrombocytopenia, and microangiopathy due to diffuse intravascular coagulation [28, 29].

Mefloquine is a 4-quinolinemethanol analog of quinine [19]. It has been added to the side-effects list of mefloquine that, in some cases, vertigo and loss of balance may be permanent [29]. While it was formerly used in the prophylaxis and treatment of malaria, its use has been blacklisted due to its association with neuropsychiatric, vestibular, and sleep disturbances [19]. It is contraindicated in patients with neurological and psychiatric disorders. In a study reviewing auditory symptoms, tinnitus and HL were reported to be the most common. Vertigo/dizziness and imbalanced vestibular changes also have been common [30]. Furthermore, HL has been reported using mefloquine (alone or in combination with artesunate, artemether, or sulfadoxine-pyrimethamine) to treat uncomplicated malaria [31].

The artemisinins are produced from the leaves of the Chinese sweet wormwood plant called *Artemisia annua* [26]. The World Health Organization (WHO) recommends artemisinin-based therapy as the first agent for treating chloroquine-resistant *P. falciparum* [19]. However, it is not recommended for malaria prophylaxis. Artemisinins have a fast clearance time against all malaria strains. Initially, monotherapy was recommended, but artemisinin-based combination therapies were created later, combined with another antimalarial drug to prevent drug resistance. While artemisinin derivatives contain artesunate, arteether, artemether, and dihydroartemisinin, the combinations consist of artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, artesunate-sulfadoxine-pyrimethamine, dihydroartemisinin-piperdineaquine, and artesunate-pyronaridine [19, 26]. They are generally well tolerated. There are a few reports on the ototoxic effects of artemisinin derivatives. It has been reported that their adverse effects on hearing and balance may cause brain stem necrosis in animals [32, 33]. When used to treat uncomplicated malaria, artemether-lumefantrine has been reported to cause HL [34]. Age-related HL may occur in people using the artesunate-mefloquine combination [35].

An article compiled of 22 studies reporting ototoxicity after antimalarial therapy between 2005 and 2018 reported quinine, chloroquine, atovaquone-proguanil, pyronaridine-artesunate, artemether-lumefantrine, artesunate-mefloquine, and artemisinin-naptohquine could cause HL [36]. It has been reported that atovaquone-proguanil causes dizziness [37], and doxycycline causes tinnitus [8].

Hearing loss with antimalarial drugs is typically bilateral, mild to moderate sensorineural, and primarily reversible [38]. In a study, chloroquine was used at an

appropriate dose in treating uncomplicated malaria; ototoxicity was rare and reversible [39]. Irreversible HL has been reported in different studies [36, 40]. In many endemic countries, rare cases of irreversible ototoxicity with artemether-lumefantrine as artemisinin-based combination therapy in falciparum malaria have been reported [34, 41].

Hydroxychloroquine is a better-tolerated form in children. At the beginning of the SARS-CoV-2 pandemic, many centers tried chloroquine and hydroxychloroquine in the treatment [42]. However, the mortality and morbidity of SARS-CoV-2 were not prevented; it was removed from use with this indication. A study showed sensorineural HL (SNHL) developed in 6 patients using these drugs to treat COVID-19. Although the drug was discontinued, 5 patients had irreversible HL [43].

73.4.2.2 Other Drugs with Antiprotozoal Activity and Hearing Loss

Protozoa are single-celled organisms divided into four groups: amoebae, flagellates, ciliates, and sporozoa. Metronidazole, paromomycin, albendazole, atovaquone, benznidazole, nitazoxanide, trimethoprim-sulfamethoxazole, tinidazole, tetracycline, suramin, sodium stibogluconate, spiramycin, quinacrine, pentamidine, and nifurtimox are antiprotozoal drugs [44].

Metronidazole and tinidazole are derivatives of 5-nitroimidazole [3]. Metronidazole is the essential drug used in the treatment of anaerobic infections and has also been approved for use in the treatment of protozoal diseases. Metronidazole is used to treat giardiasis, intestinal and extraintestinal amebiasis, and trichomoniasis. Metronidazole has a well-tolerated and relatively safe drug profile. Few reports show that very high doses and long-term use of metronidazole can cause serious side effects; however, the exact mechanism is unknown [45]. It has been reported to cause vertigo and dizziness [46, 47]. Sudden SNHL has been reported because of metronidazole [45, 48]. Metronidazole use can increase gentamicin-induced ototoxicity [49].

Aminoglycosides are important drugs used to treat aerobic gram-negative bacilli infections. In this group, gentamicin, tobramycin, amikacin, plazomicin, streptomycin, neomycin, and paromomycin were approved for clinical use. Aminoglycosides are the most known ototoxic drugs among antimicrobial drugs. Paromomycin is mainly used to treat leishmaniasis and cryptosporidiosis and has an anti-amoebic effect. A case of HL has been reported while using paromomycin [50].

Sulfadiazine causes tinnitus and dizziness; tinidazole, used to treat giardiasis, trichomoniasis, and amebiasis, causes dizziness; and trimethoprim-sulfamethoxazole causes tinnitus and dizziness [8].

In addition to their antibacterial effects, tetracyclines are effective agents for *infections of Balantidium coli and Dientamoeba fragili*s. Drugs commonly used in this group are doxycycline, minocycline, tetracycline, and tigecycline. Minocycline causes vertigo and mild dizziness as common side effects [51]. Limited information exists in the literature on the ototoxic effects of tetracyclines [6, 46].

Sodium stibogluconate and meglumine antimoniate, pentavalent antimony compounds, are two parenteral agents. There is limited information on cochlear and vestibular toxicity caused by meglumine antimoniate, and it has been reported to

cause dizziness, tinnitus, and HL [46, 52]. Niclosamide and pentamidine thionate have been reported to cause dizziness [8].

Atovaquone is a hydroxynaphthoquinone analogue of ubiquinone. It is available as single or in combinations. It is an antimalarial agent and is also effective against several protozoan organisms. It is also used in the treatment of *Pneumocystis jirovecii*. The Federal Drug Administration (FDA) of the United States of America (USA) has approved atovaquone for prophylaxis and its fixed-dose combination with proguanil for the treatment of *P. falciparum* infections [19, 53]. The incidence of dizziness and vertigo with the atovaquone-proguanil combination was 2% [54].

Azithromycin, clarithromycin, and erythromycin are macrolide antibiotics. Azithromycin and clarithromycin are erythromycin derivatives used to treat community-acquired respiratory tract, mycobacterial and sexually transmitted infections, and *Helicobacter pylori* disease [55]. Azithromycin is used in combination with atovaquone to treat babesiosis [19]. Macrolide antibiotics can cause HL, tinnitus, and vertigo [16]. Sensorineural HL is a rare complication but is usually reversible [56]. However, irreversible SNHL due to azithromycin has also been reported [57]. Spiramycin is a macrolide antibiotic used to treat toxoplasmosis; HL has rarely been reported related to its use [58].

Amphotericin B is a polyene antifungal agent with in vitro activity against many fungi [59]. Although it is used to treat many serious and invasive fungal infections, its use successfully in the treatment of visceral leishmaniasis is also established. Liposomal amphotericin B, preferred in treating leishmaniasis in Europe and the USA, has an exceptionally high therapeutic effect and a suitable reliability profile [60]. Nephrotoxicity, infusion-related reactions, and electrolyte disorders are common side effects of amphotericin B. However, drug-related ototoxicity has rarely been reported in the literature. Reversible SNHL has been reported due to the use of liposomal amphotericin B in the treatment of visceral leishmaniasis and disseminated histoplasmosis [61, 62].

Clindamycin is a lincosamide antibiotic effective in treating anaerobic and gram-positive infections. Clindamycin is also in vitro active against *Toxoplasma gondii* and *Babesia* spp. It also has some activity against *P. falciparum* and *P. vivax* [63]. Although ototoxicity was reported due to clindamycin, limited information exists in the literature [6].

73.5 Conclusion

It has been necessary to monitor the ototoxic side effects of antiparasitic drugs since early diagnosis of HL with antiparasitic drugs is critical to initiate possible alternative treatments with less ototoxic drugs. Children's language and speech delays from HL can usually be prevented [64, 65]. Therefore, early diagnosis of temporary or permanent HL is the key to a child's successful communication [66].

More studies are needed to determine the risk of HL caused by ototoxic drugs while on antiparasitic therapy. When specific risk factors for ototoxicity are

identified, patients and their families can be appropriately counseled, which can help with early diagnosis and reduce the emotional impact of an HL diagnosis [12].

In clinical practice, the diagnosis of ototoxicity is often delayed and goes undetected until the communication problem becomes evident because of decreased hearing. The diagnosis is made according to the patient's history, symptoms, and hearing test results. Although it is ideal for assessing basal hearing status in ototoxicity, it is not always possible in practice.

It is essential to raise awareness about the symptoms that may occur due to the side effects of antiparasitic drugs on the audio-vestibular system. Healthcare professionals should be informed immediately when symptoms are recognized, such as tinnitus, fullness in the ear, decreased hearing, dizziness, or imbalance while on antiparasitic therapy. Early detection of HL is crucial. The causative drug should be stopped, and these symptoms should be addressed immediately.

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