Robin J. Green *Editor*

Viral Infections in Children, Volume II

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This book is dedicated to the many children who are sick with a viral infection. May I also dedicate it to my partner and best friend—Jessica.

Preface

This book is important. It is important not only because some of the world's leading authorities have summarized the evidence on each of these topics but also important because we live in a world where illness and infection are often perceived to be due to bacteria. This has led to an enormous increase in antibiotic use and, of course, the attendant increases in antimicrobial resistance. We need to know, and make our colleagues aware, of the enormous burden of viral infections in children, for which conventional antibiotics are redundant and unnecessary and even harmful. Knowing the burden may now save our world from the looming threat of "superbugs". We do of course need to work on dealing with the additional threat from viruses and much research and effective therapy is still needed. Hopefully some of us reading this book will be inspired to provide these outcomes.

This book attempts to summarize the known literature on each of the organ systems where viruses may cause disease. In addition, there are chapters on viral illnesses where the organisms produce more profound systemic pathologies. Since this book is inclusive, I have added a chapter on HIV and the problems caused specifically by the virus itself and another on the comorbid illnesses seen due to compromised immunity.

Each of the chapters contains the latest information on the pathobiology of viral infections, the clinical presentation and diagnostic pointers as well as management strategies. In this sense, the book should appeal to both non-clinicians and clinical specialists alike. I am particularly hoping that young doctors will find the book valuable in treating patients, because after all this should be our mandate—helping children in distress.

One word of explanation. Those of you who read the whole book may notice that some conditions and concepts are repeated in different chapters. This is for a number of reasons including emphasis on a different aspect of the disease, that repeating a certain topic may be required in order to introduce other concepts in that chapter, that the disease is common or currently making headlines and because the book is available on-line and some readers may elect to "pick-up" only selected chapters.

Enjoy the read!

Pretoria, ZA, South Africa — Robin J. Green

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Viral Upper Respiratory Tract Infections

1

George V. Guibas and Nikolaos G. Papadopoulos

Abstract

The upper respiratory system is one of the most common sites of infection for adults, but even more so for children. Several viruses, from variable families, cause upper respiratory infections which, although generally underestimated due to their typically self-limiting nature, underlie enormous healthcare resource utilization and financial burden. Such, otherwise "benign" infections, can have very significant sequelae both in the form of bringing about local complications but also inducing asthma attacks, thus greatly increasing morbidity. Their enormous prevalence also indicates that rigorous research should be undertaken in order to tackle them, in both the prevention and treatment field.

1.1 Introduction

The upper respiratory tract is the site of infection for several viral and bacterial pathogens. The term "upper respiratory tract infection" (URTI) encompasses a number of conditions that have a variable and diverse range of presentations, due to the

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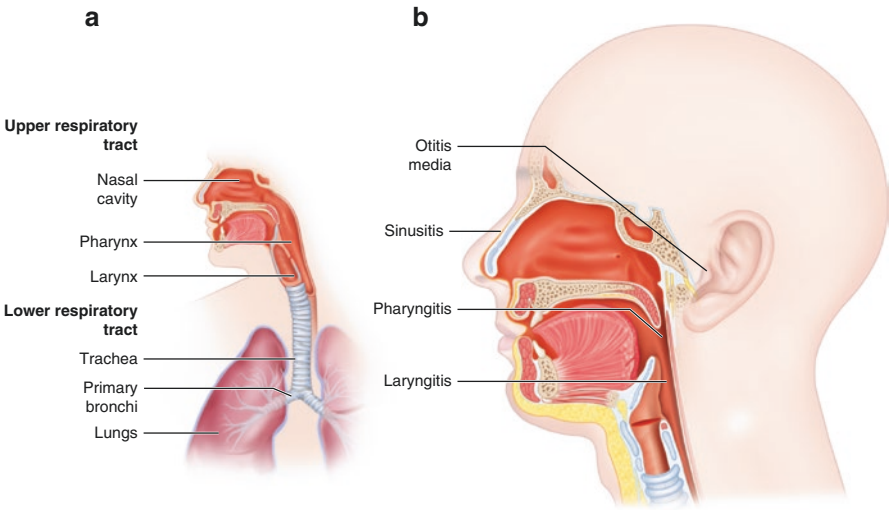

Fig. 1.1 (**a**) The nasal cavity, pharynx and larynx are part of the upper respiratory system. (**b**) Sinusitis (rhinosinusitis), pharyngitis, laryngitis and otitis comprise the URTIs

number of adjacent anatomical sites involved, causative organisms and several host and environmental factors. "*URTI*" is therefore a nonspecific term used to describe acute infections involving the upper respiratory tract (nose, paranasal sinuses, ear, pharynx, and larynx) (Fig. 1.1). It is, however, rather imprecise as it incorrectly implies an absence of *lower* respiratory tract pathology, when clearly such pathology may often co-exist with upper respiratory tract disease [1]. Acute URTIs are an important part of general practice visits: A national study suggested that they comprise roughly 10% of all GP consultations [2]. *Viral* URTIs cause considerable financial burden, also in association to their comorbidities [3]. Often regarded as trivial, URTIs do not receive the attention they merit if their enormous incidence, morbidity and occasionally serious sequelae are taken into consideration [4].

Most URTIs have viral origin, with human rhinoviruses (RV), parainfluenza viruses (PIV), coronaviruses, adenoviruses, respiratory syncytial virus (RSV), enteroviruses, human metapneumovirus, and influenza being the main culprits (Table 1.1) [5]. Human metapneumovirus (hMPV) has been recently identified in samples from RSV-negative children with bronchiolitis [6], while human bocavirus (BoV) was discovered by large-scale molecular virus screening of pooled respiratory tract samples [7]. The importance of each viral agent in early life is not clear but RSV, RV, PIV, and influenza virus are predominant in the literature. However, several factors limit our understanding regarding the relative importance of each pathogen, including differences in study design (e.g. PCR versus immunoassay or other detection methods [8]), in recruitment criteria, and in the investigated viruses (e.g. RSV has been considerably easier to detect *in-vitro*, as compared to RV).

Table 1.1 The viruses most commonly causing URTIs, their frequency and main months of their circulation in the community [8, 12, 13]

Virus	Proportion of URTI cases	Predominant months of circulation (temperate climates, Northern Hemisphere)
Rhinovirus	30–50% (adults) Up to 80% (children)	Year round with a peak in September and a smaller peak around April
Influenza viruses	5–15%	Winter months with a peak in February
Coronaviruses	5–15%	November to February
Respiratory syncytial virus	5%	Late fall and early spring, with a peak prevalence in winter
Parainfluenza viruses	5%	September to January
Adenoviruses	<5%	September to May
Respiratory enteroviruses	<5%	Winter and spring months
Metapneumovirus	Unclear	Late winter-early spring

Transmission of viruses causing URTIs occurs by dispersal of small-particle aerosols (droplets), large-particle aerosols that are briefly suspended in air, and by direct contact with infectious secretions on skin/environmental surfaces (e.g. direct hand-to-hand contact), with subsequent passage to the nares or eyes [9]. Hence, transmission occurs easier in crowded spaces. However, transmission dynamics are not identical between different viruses.

1.2 Viruses

Respiratory viruses are genetically and antigenically distinct. *Orthomyxoviridae* are enveloped, segmented viruses that include influenza and *Paramyxoviridae* are enveloped, non-segmented viruses that include parainfluenza [10]. The *Picornaviridae* are non-enveloped viruses with a single-stranded genome, and include rhinoviruses and enteroviruses (e.g. coxsackie virus). Viruses from the family *Coronaviridae are* single-stranded RNA, enveloped viruses including human coronaviruses [11]. DNA viruses include the family *Adenoviridae of* non-enveloped double-stranded DNA viruses (i.e. adenoviruses), and the recently-discovered family of single-stranded DNA viruses *Parvoviridae* (e.g. bocavirus). In this chapter focus will be on the agent that is by far the most common cause of URTIs in children, the human rhinovirus (Table 1.1). Other agents such as influenza and RSV are described in detail in other chapters.

1.2.1 Human Rhinovirus

Studies using molecular methods have shown that RV is behind up to 80% of common colds [14] The only known host of RV is human, although primates may also host the virus as a non-symptomatic infection [15]. Historically, enteroviruses (EVs) and RVs

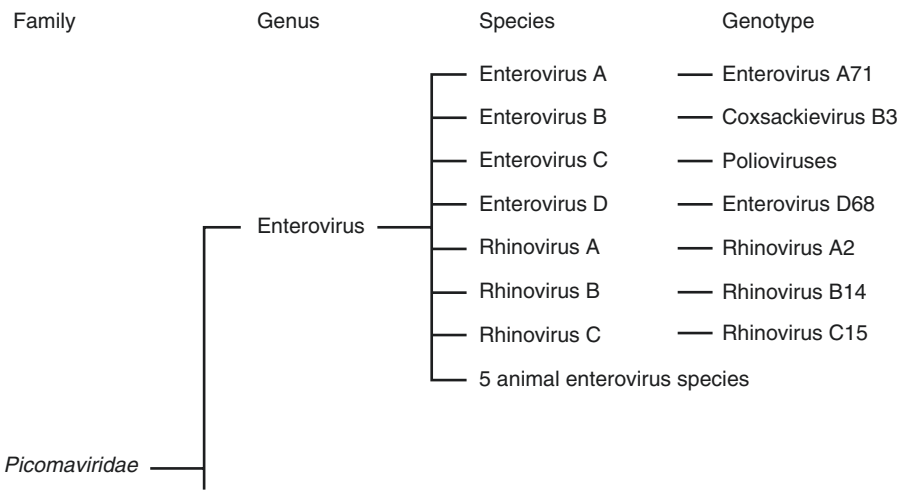

Fig. 1.2 Picornaviridae tree focused on rhinoviruses and enteroviruses. Enterovirus genus is divided into 12 species, based on genetic homology and similarity of pathophysiology

were classified into separate genera, but due to their related genome structure they were merged into a single genus, the *enteroviruses*, which include three RV species (RV-A to RV-C) and four non-RV EV species (EV-A to EV-D) [3] (Fig. 1.2). These viruses have different phenotypic characteristics, with RVs mainly being restricted to the respiratory system, whereas EVs cause diverse multisystem clinical manifestations (e.g. myopericarditis, encephalitis, and quite often viral meningitis [16]). However, some EVs cause RV-like respiratory symptoms (*respiratory* EVs, e.g. species C and D).

RVs and EVs are small, non-enveloped, RNA viruses with a genome of about 7.2–7.5 kb packed in a 30 nm icosahedric capsid which, in turn, is composed of 12 pentamers, each composed of 5 protomers. The protomers contain four capsid proteins: VP1, VP2, VP3 and VP4 [17]. The major group of RVs which includes RV-A and RV-B, typically needs intercellular adhesion molecule (ICAM)-1 as a receptor, whereas the minor group needs low density lipoprotein receptor (LDL-R) [18]; RV-C uses a different receptor (cadherin-related family member 3—CDHR3) [19]. Regarding recognition by the innate immune system, after ssRNA internalization the genome is recognized by endosomal toll-like receptor (TLR)7 and TLR8 [20]. Once double-stranded RNA is generated, the type I interferon (IFN) response ensues leading to pro-inflammatory cytokine gene expression, including RANTES, inducible protein (IP)-10, interleukin (IL)-6, and IL-8 [21, 22]. The latter (IL-8), is a potent neutrophil chemotactic/activation agent, and is an important determinant of the clinical outcome of RV infection. IL-8 production has been shown after RV infection in both upper and lower airway epithelial cells [23]. An antibody response to RV infection occurs after viral clearance, with the development of neutralizing serum antibodies (IgG) and secretory antibodies (IgA) in the respiratory tract. These are detectable 1–2 weeks after infection and maintained for at least 1 year [24], protecting from

reinfection from the same type of virus [25]. Although this humoral response appears to offer some cross-serotype protection [26], we have shown that, generally, protection is sub-optimal [27]. As opposed to influenza virus and respiratory syncytial virus, RV is rarely associated with significant cytopathology of the upper respiratory tract. The structure of the epithelial cell (EC) lining usually remains intact, and viral shedding is relatively limited when considering the severity of the symptoms [28]. However RVs do disrupt the function of the epithelium, facilitating exposure of epithelial cells to bacteria, allergens and irritants [29].

Children are considered as the major reservoir for RVs and could experience up to 12 common cold infections per year [30]. The average incubation period is 2 days with symptom duration of 7–10 days [31, 32]. There are two main peaks of infection, the first being around April/May and the second around September/October in the Northern Hemisphere, although infections can generally be seen all year round [33]. The RV URTI typically induces nasal congestion and rhinorrhea, cough, sneezing, sore throat and malaise, but no or low-grade fever.

1.2.1.1 Transmission

The airway epithelium is the primary site of infection of RV. Viral transmission occurs mainly via direct contact or through a fomite, typically with inoculation in the nasal mucosa or the eye conjunctiva, from where it is transported via the lachrymal duct to the nasal cavity; transmission by large particle aerosols is less common and probably less efficient [34]. RVs survive on surfaces and skin for several hours, which allows for easy transmission in the absence of adequate hygiene [35]. In one classic study, viral inoculum to the right conjunctival sac [36] led to positive cultures for RV initially from the nasopharynx and afterwards from the inferior turbinates, where it presumably spread via nose blowing.

1.2.1.2 RV in the Lower Airways

About two decades ago it was believed that RV could not infect the lower airways as it grows best at 33 °C (91.4 °F), hence virus replication was thought to be reduced at the core temperature found in the lungs [3]. However, we have shown that RV can replicate in lower airway epithelial cells [29], and that the difference in replication capacity at higher temperatures is minimal [37]. This was shown for eight different RV strains whose titers at 37 °C (98.6 °F) were significantly higher than those required to initiate infection [37]. This provided conclusive evidence to the infection-related mechanism underlying the epidemiological link between common colds and asthma exacerbations. Up to two-thirds of virus-induced asthma attacks are due to RV, probably as a result of local and systemic immune responses. Local cytopathology in bronchial epithelial cells can only be observed after the use of high viral inocula [29], suggesting a potential dose-response relationship, to which patients with asthma may be particularly susceptible. It is now well recognized that RV is not a strictly upper respiratory pathogen [38], but is in fact one of the most powerful early factors associated with asthma throughout childhood [39]. The dynamics of RV infection are affected in atopic individuals, although it is still not clear to what extent there is increased susceptibility to the virus and/or a differential response to it. In this

context we have shown that atopic children with asthma have a higher rate of symptomatic cold and asthmatic episodes than non-atopic children [40, 41].

1.2.1.3 RV Triggering Asthma Exacerbations

For a long time clinicians had suspected that upper respiratory infections were a major cause of asthma exacerbations. Their seasonality and the strong peaks in asthma morbidity in September in temperate climates, shortly after children returning to school, [42] corresponded closely to patterns of RV identification. In the mid-1990s, using the novel, at that time, PCR-based viral diagnostics, viral presence was detected in up to 85% of exacerbations of pediatric asthma, with approximately two-thirds of these associated with RV. Although normal steady-state viral presence—rather than infection—cannot be excluded for some of these cases, it was shown that 60–80% of children presenting with asthma exacerbations were positive for viral genetic material versus only 10–40% of healthy controls [43, 44]. RV was detected in 65% of cases, coronaviruses in 17%, influenza and parainfluenza viruses in 9%, and RSV in 5% [43]. It is now well established that RV is a potent trigger of asthma exacerbations. Reduced interferon responses in asthmatic children are thought to be a potential mechanism underlying RV-induced asthma attacks [21].

1.2.1.4 RV Causing Asthma

Numerous longitudinal studies have demonstrated that RV infections precede the development of asthma [45–47], and a birth cohort of high-risk infants (Childhood Origins of ASThma, or COAST) has shown that wheezing-associated illness with RV is probably the most important risk factor for future asthma [46, 48]. Other birth cohort studies also demonstrate a dose–response relationship between infant RTI severity and asthma risk [49]. Among infants with LRTI, the prevalence of RV was approximately 20–30% [50] and RV infection conferred a much higher risk for future asthma development than allergen sensitization or RSV infection alone [51]. Insofar as certain strains of RV can directly infect and activate $CD4^+$ and $CD8^+$ T cells, the early-life altered immune response to RV could be strain specific rather than illness severity specific [52].

Taken together, these data suggest that either early RV infections cause future asthma, or that they may simply reveal a pre-existing tendency for asthma. If the latter is true then early wheezing-associated illnesses due to rhinovirus are essentially viral-induced asthma exacerbations. In support of this hypothesis, it was recently shown that children with asthma at age seven had a lung function deficit and increased bronchial responsiveness as early as the neonatal age [53]. However, currently there is no consensus, and details are unclear regarding the direction of the relationship between early rhinovirus infection and future asthma [51].

1.2.1.5 RV-Induced Changes

It has been shown that RV is not considerably cytotoxic and, even though its replication causes cell lysis (which is the principal method for releasing progeny virus), most RVs Infect a small subset of cells and their lysis is not extensively damaging

of the epithelium [54]. There could instead exist mechanisms whereby early-life RV infections might permanently alter lung and immune development and airway physiology. RV infections appear to induce immune responses such as interferon release which can cause malaise and myalgia, neural activation which can promote sneezing/sore throat/cough as well as mediator release from infected cells and leucocytes. RV-infected epithelial cells release a variety of chemokines [21, 55], which promote the recruitment of neutrophils and mononuclear cells. In neonatal mouse models, RV infection resulted in prolonged asthma-like responses that were dependent on IL-13 and IL-25 [56, 57]. Furthermore, extracellular matrix collagen deposition was increased in RV-infected, cultured human bronchial ECs. We have shown local induction of proinflammatory mediators by RV infection [29], namely, an increase in mRNA expression and subsequent release of IL-6, IL-8, IL-16 and RANTES, a C-C chemokine with chemoattractant activity for eosinophils, monocytes, and T lymphocytes. Produced IL-1 can enhance airway smooth muscle contraction and attenuate smooth muscle dilation responses to bronchodilators [58].

Pre-existing asthma may hinder antiviral responses. Studies of experimental RV inoculation have demonstrated that asthma is associated with increased neutrophil production [59]. The asthma phenotype, which is associated with increased ICAM-1 expression, the principal receptor for RV, might also be associated with increased susceptibility and complications from RV infection [60]. Chronic allergen exposure can also increase epithelial ICAM-1 expression, as is also true for RV infection itself, through production of IL-1 [60, 61].

1.2.1.6 Prevention-Treatment

There are currently no approved antiviral agents for the prevention or treatment of RV infections. Vaccine development has been traditionally hindered by the existence of over 150 RV serotypes [62], while treatment remains primarily supportive and focused on symptom relief.

To date, no RV vaccines are being used in the clinic. Alongside the considerable serotype variability, vaccine development is hindered by the incomplete understanding of antigenic differences between the recently discovered RV-C species and the RV-A and -B species; It is also only recently that an animal model of experimental RV infection has been developed [18, 63], due to RV being a dedicated human pathogen in its wild form [64]. Recent research work has focused on deriving antigenic peptides to be recognized by cross-neutralizing antibodies from viral capsid proteins, VP1 [27, 65] and VP2 [66], but a clinically-applicable vaccine is still far down the road.

Regarding medication for prevention and treatment (as opposed to vaccination), investigational approaches to date have included interferons (IFNs), inhibitors of viral attachment and entry, and inhibitors of viral protease. Intranasal recombinant IFN-2b was used several decades ago, and modest efficacy was shown for prophylactic use [67], but safety-wise, long-term administration was associated with nasal irritation and mucosal histologic changes [68]. For treatment of already established infection, intranasal IFN was ineffective [69]. Regarding attachment and entry inhibitors, intranasal Tremacamra (Boehringer Ingelheim, Ridgefield, CT), a

soluble form of ICAM-1 designed to interfere with the attachment of RV on target host cells demonstrated small effects on symptom scores [70]. However, when given more than 12 hours after viral challenge, efficacy was unclear. Regarding capsid binding agents, Pleconaril (WIN63843) was developed and submitted for approval to the U.S. FDA after having succeeded in reducing symptom duration by 1.5 days. However, side effects and presumed drug resistance led the FDA to decline approval in 2002 [71]. Up to now none of the several agents investigated in research trials has found its way into the clinic [72].

1.2.1.7 RV-C

New molecular diagnostic tools allowed the discovery in 2006 of a new species of RV (RV-C) [73]. Since its discovery, RV-C is reported to have a high prevalence, resembling RV-A rather than RV-B [74]. Its seasonality seems to differ from the other RV species, with a peak during the winter months [75]. In temperate or subtropical countries it reaches its peak in the early fall and late spring, and in tropical countries in the rainy season [74]. Limited research has been conducted on RV-C so far, due to the lack of a human experimental model and the virus's inability to grow in standard cell lines. However the reports so far portray a predominant species with high virulence associated with acute, and occasionally severe, respiratory illness [74].

Young children who experience a wheezing illness due to RV-C are more likely to develop recurrent wheezing compared to other viruses [59]. Three types of RV-C (C2, C15, and C41) were shown to grow equally well at 33, 35, and 37 °C (91.4, 95, and 98.6 °F) [8]. This could facilitate development of lower respiratory tract infections (LRTI) and wheezing illnesses after RV-C infection [76].

1.3 Viral URTIs

Respiratory virus infections are often confined to the upper respiratory tract. Rhinitis and pharyngitis are frequently associated with some conjunctival and ear pathology. In infants, URTIs are often accompanied by fever and may lead to lethargy and poor feeding.

1.3.1 Diagnosis

Various techniques including nasal swab, aspirate, brush, and wash can be used to collect nasal specimens, and they are all effective [77]. Respiratory viruses are generally diagnosed by either of the following ways: virus culture, serology, immunofluorescence/antigen detection, and nucleic acid/PCR-based tests. In virus culture, cell lines are infected with viruses, whereas in serology, blood is tested for virus-specific antigen/antibodies [1]. Both methods are onerous and slow to produce results, therefore, they are not used in routine clinical work, but do have a role in an epidemiological context [1]. Antigen detection by antigen specific monoclonal

antibodies is the basis of a variety of rapid diagnostic tests. However, they demonstrate relatively low sensitivity in adults, where the viral load may be low [78]. Nucleic acid-based tests are increasingly being used and they have opened new avenues in research, especially for RV for which other methods were suboptimal [79]. Also, they are now being multiplexed, allowing the rapid concurrent detection of many viruses including RV, influenza virus, adenovirus, RSV, human metapneumovirus and PIV [8, 80–82]. Several rapid antigen tests have also been developed for certain viruses such as IFV [83], and RSV [84]. There are recommendations regarding the use of such tests, especially for influenza, where WHO has produced specific guidelines based on various criteria; e.g. for institutional outbreaks, for travelers, and when surveillance systems indicate that influenza is circulating in the community ("*WHO recommendations on the use of rapid testing for influenza diagnosis*"). URTIs are not an indication for the use of rapid antigen test in the clinic. Diagnostic tests for viral URTIs are generally not recommended in routine clinical practice unless there are special circumstances (e.g. complications, differential diagnosis issues, immunocompromised individuals etc.). We are currently developing a new chip to detect antibody responses to different RV subtypes in the context of the "PREDICTA" EU project. Such a tool may be able to be used for URTIs in the future. Although the role of radiologic studies in viral URTIs is limited, potential intracranial sequalae should be evaluated by computed tomography (CT) or magnetic resonance imaging (MRI).

1.3.2 Treatment

Currently, the only drugs for respiratory viruses used in everyday practice are for influenza, and only for lower respiratory infection. Several other drugs with antiviral activity, which mainly act as nucleoside analogues by inhibiting DNA/RNA polymerases, have been used up to now, but they are not generally used for URTIs. Brief mention will be made here of the most important of them, but not the detail as they are mainly being developed for lower respiratory tract infections, which is beyond the scope of this chapter.

Ribavirin was developed as an influenza drug with promising results in animal models several decades ago [85] but unclear results in humans [86], forcing the FDA to decline approval for influenza. It has been used off-label to treat RV and RSV infections in the immunocompromised host and hospitalized infants with severe lower respiratory infection [87], but because of its poor safety profile it's generally no longer used. For influenza infection of the lower airways Oseltamivir (Tamiflu) or zanamivir (Relenza), two neuraminidase inhibitors, have been historically used; currently, the former is the main medication used for influenza. They are active against both influenza A and B, and don't typically induce viral resistance. These agents have replaced the adamantanes (amantadine and rimantadine), M2 channel blockers only active against influenza A, which also caused widespread resistance and are not currently recommended for clinical use [88]. Currently, there are no licensed vaccines for parainfluenza, but various agents are

being evaluated in clinical trials (e.g. HPIV3 cp45 [89]). Regarding adenovirus, oral vaccines have been used for decades in USA military training installations [90]. Regarding treatment and/or prevention of RSV infection, several compounds are currently in clinical development: novel oral benzodiazepines, fusion inhibitors, F-protein inhibitors, siRNAs, and others [91, 92]. Furthermore, Palivizumab has reduced RSV hospitalizations by 50% in high-risk infants [93], and Motavizumab, was shown to be more effective [94, 95]. These agents are described in detail in other chapters of this book.

1.4 Specific Conditions

1.4.1 The Common Cold

The common cold is a mild, self-limiting illness of viral origin generally characterized by upper respiratory tract symptoms [31]. It is essentially a syndrome as it can be caused by several different viruses: most common culprit is RV, but it can also be caused by coronavirus, RSV, influenza virus, PIV, adenovirus, metapneumovirus and BoV. Occasionally, EVs are implicated in the summer. The common cold occurs year-round, but less so in warmer months. Cold temperatures may facilitate symptomatic presentation as has been shown in an important animal study where temperature changes directly impacted virus-host interaction and weakened the innate immune response to infection [96].

1.4.1.1 Symptomatology

The common cold is a clinical syndrome of rhinitis and other upper respiratory signs and symptoms, including rhinorrhea, sore throat, sneezing, cough, and watery eyes. Symptomatology is not pathognomonic for any specific viral agent, although there can be differences in the severity of specific symptoms between distinct viruses [10]; e.g. conjunctivitis is characteristically seen with adenovirus infections. Commonly, nasal congestion, sneezing and rhinorrhea form the initial presentation, while cough, sore throat and occasionally low-grade fever follow. Symptoms, usually peak at day 2–3 after the onset, decrease around day 5 and usually resolve spontaneously after 7–14 days. The incubation period could vary significantly depending on the virus: 1.5 days for influenza A, 12 hours for influenza B, 3 days for coronavirus, 4 days for RSV, 5.5 days for adenovirus, and 24–48 hours for RVs [31].

1.4.1.2 Diagnosis

Laboratory tests are not required for the diagnosis of the common cold: the clinical picture is diagnostic. Although large-scale PCR-based molecular screening for viral genome sequences continues to identify new causal agents, such testing is not needed in general practice as it does not alter management. Knowledge of the infecting agent does not offer significantly to treatment apart from potentially reducing excess use of antibiotics, and allowing more appropriate cohorting of hospitalized

patients to reduce nosocomial infection [1]. Rapid testing for bacteria may be, however, indicated when there is concern about differential diagnosis of microbial infection.

1.4.1.3 Treatment–Prevention

Generally, treatment is symptomatic only. Common cold is a syndrome and development of antivirals for specific viral agents will offer little relief to the majority of patients [10]. Furthermore, antibiotics have no role in treatment, consistent with the illness's viral etiology [97]. Increasing oral fluid intake does not appear to be of any benefit [98] and there is not sufficient evidence for the use of complementary or alternative therapies [99]. Anti-inflammatory drugs may relieve some of the discomfort but do not significantly control the symptoms or alter the course of the disease [100]. As opposed to second generation antihistamines which are ineffective, first-generation antihistamines improve rhinorrhea due to their antiholinergic properties, but should not be given to children [101]. In combination with decongestants, they are more effective, but with further compromise of the safety profile of the formulation [102]. Topical ipratropium reduces rhinorrhea and sneezing but has no effect on nasal congestion [103]. Probiotics have a marginal effect on prevention and duration of colds [104].

1.4.1.4 Sequelae

Common complications include acute otitis media and sinusitis due to the culprit virus or to bacterial superinfection which can occur in a range of up to 60% [105]. Patients with superimposed bacterial rhinosinusitis may experience symptoms for several weeks after a common cold including facial pain, headache and purulent nasal discharge [106]. In young children, viral pneumonia could be a severe complication of parainfluenza and RSV [105], bacterial pneumonia could be a sequela of influenza infection, while RVs have been isolated in up to 25% of children hospitalized with community-acquired pneumonia [107]. Also, laryngotracheobronchitis and bronchiolitis usually start with an URTI. Postviral olfactory disorders including parosmia, hyposmia, or anosmia are not frequently seen in children, but can be seen in around 10–40% of adult cases, presumably due to the increased impairment of olfaction that is seen with age [108]. Immunocompromised children with primary immunodeficiencies, organ transplantations, malignancies, HIV-infection, diabetes and auto-immune diseases are susceptible to increased morbidity (including ICU admission), and of increased mortality from viral URTIs [109].

1.4.2 Acute Viral Rhinosinusitis

Sinusitis is one of the three most common health care complaints and although it is typically a self-limiting disease, it ranks among the top 10 most costly conditions in the US [106]. It is defined as inflammation of the mucous membranes of the paranasal sinuses (Fig. 1.3), which may be triggered by viral, bacterial, or fungal infections, and often starts in, and always involves the nasal cavity [110]; hence the term *rhinosinusitis* is widely accepted and used. Acute rhinosinusitis (ARS) is divided

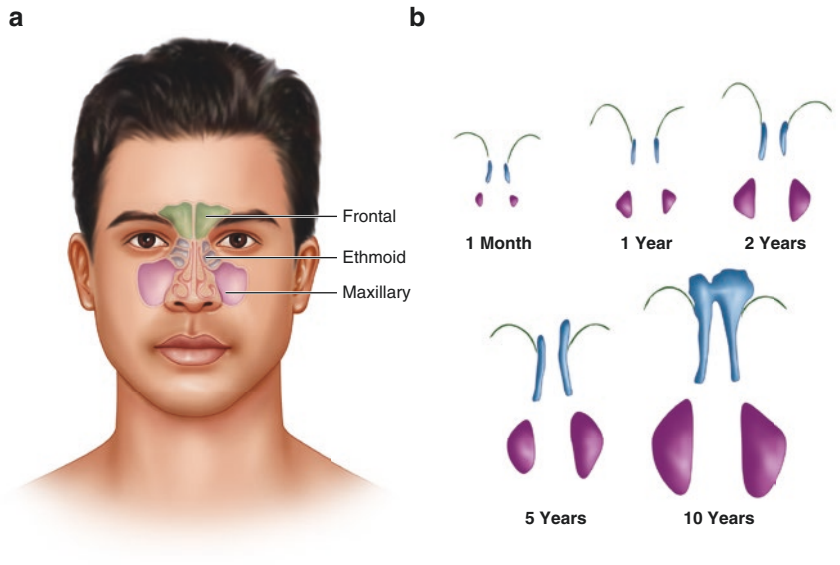

Fig. 1.3 The paranasal sinuses. (**a**) Formed in adulthood. (**b**) During development in childhood

into acute *viral* rhinosinusitis and acute *bacterial* rhinosinusitis although only about 2–4% of cases of community-acquired acute rhinosinusitis are due to bacteria, with the vast majority being of viral origin [111]. ARS is usually preceded by a viral rhinitis such as the common cold. In fact, the common cold would by itself often induce both rhinitis and sinusitis as detected by CT and MRI reports [112, 113].

1.4.2.1 Symptomatology

Common symptoms include nasal congestion, a reduced sense of smell, facial pressure/pain, rhinorrhea and fever/malaise. Symptoms peak within 2–3 days of onset, decline gradually thereafter, and resolve within 7–14 days.

1.4.2.2 Diagnosis

If symptoms of a common cold worsen after 5 days, or persist for longer than 10 days, and are more prolonged and/or severe than normally expected, the diagnosis of ARS, either viral or bacterial, is probable. The diagnosis of ARS is based on symptoms and their duration, and also on endoscopic or radiologic tests as seen in Table 1.2. Standard sinus radiographs may be useful for the diagnosis of acute frontal or maxillary sinusitis, but are not necessary.

Once ARS is diagnosed, the next step would be to distinguish acute bacterial rhinosinusitis from cases of viral rhinosinusitis, based on the patient's medical history and the physical examination [114]. In general, the illness course appears to be longer in bacterial RS [111]. Guidelines regarding the course of disease vary. The SAHP guidelines support the diagnosis of acute bacterial rhinosinusitis in a patient whose URI has not resolved after 10 days, or has worsened after 5–7 days [115].

Table 1.2 EPOS [111] guidelines for the diagnosis of rhinosinusitis

EPOS definition of rhinosinusitis
Inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which must be
i. **Nasal blockage/obstruction/congestion** *or*
ii. **Nasal discharge (anterior/posterior nasal drip)**
and any of:
iii. **Facial pain/pressure**
iv. **Reduction or loss of smell**
And one of the following
• **Endoscopic signs** (either of i. ***polyps,*** ii. ***mucopurulent discharge mainly from the middle meatus*** or iii. ***edema/mucosal obstruction primarily from the middle meatus***)
or
• **Computed tomography changes** (mucosal changes within: i. ***the ostiomeatal complex*** or ii. ***the sinuses***)

These guidelines are applicable both for adults and children. In *chronic* RS, symptoms last for >12 weeks (intermittently or continuously)

The AAAAI-ACAAI guidelines apply a longer time-frame for the persistence of URI symptoms, 10–14 days, before suspecting acute bacterial rhinosinusitis [114].

In clinical research, sinus puncture is used to confirm acute bacterial rhinosinusitis, but this procedure is not warranted in general practice except for patients with infections resistant to treatment, immunocompromised hosts and/or those with intracranial/orbital complications [116].

In chronic sinusitis, clinical manifestations generally are the same as in acute disease but last more than 12 weeks. Detailed discussion of chronic rhinosinusitis is beyond the scope of this chapter.

1.4.2.3 Treatment

Viral rhinosinusitis needs only support treatment focusing on symptom relief as the condition is self-limiting. Patients with symptoms persisting for ≥10 days without improvement, or those with severe symptoms (fever ≥ 39 °C (102.2 °F), purulent nasal discharge, facial pain), and those with a "double sickening" illness characterized by initial improvement of a typical viral URI, followed by deterioration, possibly have acute bacterial—rather than viral—rhinosinusitis [117]. Empiric antimicrobial therapy should be initiated. Treatment of acute bacterial sinusitis aims to eradicate bacterial growth in the sinuses, restore ventilation and drainage, and decrease the inflammatory process. First-choice antibiotics include amoxicillin, second- or third-generation cephalosporins, or amoxicillin plus clavulanic acid. The use of topical corticosteroids may be considered for better control of the symptoms in specific cases [118].

1.4.2.4 Sequelae

Viral rhinosinusitis induces local changes which increase the risk for bacterial superinfection (e.g. epithelial damage, mechanical/humoral/cellular alterations etc.). However, bacterial superinfection is seen in no more than 2% of cases of viral

rhinosinusitis. The bacteria usually involved are in descending order of frequency *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus and Moraxella catarrhalis* [119]. Other complications may rarely occur in nearby structures, such as the orbit, e.g. orbital cellulitis, or the brain, e.g. cerebral abscess. Persistent or repeated acute sinusitis may lead to chronic sinusitis (symptoms >12 weeks). CRS is often linked to chronic lung disease, especially severe asthma.

1.4.3 Pharyngitis-Tonsillitis

Acute pharyngitis is defined as an infection of the pharynx and/or tonsils and describes a syndrome of sore throat, fever and pharyngeal inflammation. It is very common among children and adolescents. Viruses cause most acute pharyngitis episodes with RV, coronavirus and adenovirus accounting for roughly 33% of pharyngitis cases, while Epstein-Barr, influenza and PIV for about 5% [120] (Table 1.3). Many microbes also cause pharyngitis, with group A Streptococcus (also known as *Streptococcus pyogenes*) causing 37% of total cases in children older than 5 years. Other culprit bacteria are Group C Streptococcus (5% of total cases), *Clamydophila pneumoniae*, (1%) and *Mycoplasma pneumoniae* (1%) (Table 1.3).

1.4.3.1 Symptoms

The disease is characterized by pharyngeal soreness, or irritation. Common symptoms are shown in Table 1.3. *Pharyngoconjunctival fever* can be seen in adenovirus cases, 35–50% out of which may present with conjunctivitis, a characteristic finding for this virus. *Acute lymphonodular pharyngitis* may be caused by coxsackie virus and is distinguished by characteristic nonvesicular eruption on the uvula, soft palate, anterior tonsillar pillars, and posterior pharynx. The lesions consist of multiple, raised, discrete papules surrounded by an erythematous halo. *Herpangina* is also caused by coxsackie viruses and is characterized by diffuse erythema and a vesicular eruption of the posterior oral mucosa and oropharynx which rupture, leaving painful ulcers. In young children, the typical *infectious mononucleosis* syndrome is caused by Epstein-Barr virus and is clinically characterized by sore throat, fever and lymphadenopathy, occasionally with characteristic palatal petechiae.

Table 1.3 Viruses and bacteria causing pharyngitis, and symptoms of each condition

Symptoms	Symptoms	
Viral etiology	*Strep. pyogenes*	
Conjunctivitis	Sudden onset	Vomiting
Cough	Sore throat	Patchy exudate
Coryza	Fever	Cervical lymphadenopathy
Diarrhea	Nausea	Winter presentation
Viruses	*Rhinovirus, coronavirus, adenovirus, herpes simplex virus types 1 and 2, parainfluenza virus, coxsackie virus A, Epstein-Barr virus, influenza A and B virus*	
Bacteria	*Strep. pyogenes, Streptococci group C and G, mixed anaerobes, Neissseria gonorrhoeae, Corynobacterium diphteriae, Arcanobacterium haemolyticum*	

1.4.3.2 Diagnosis

It is important to identify those cases of acute pharyngitis caused by *Strep. pyogenes* as this is the main agent that requires specific antibiotic therapy. Clinically, few signs can help tell apart a viral from a bacterial case, as they show considerable overlap and no single element of the patient's history or physical examination reliably detects etiology [121]. Subtle signs can help, however, including the diseases course, as onset of viral pharyngitis may be more gradual and symptoms more often include rhinorrhea, cough, diarrhea, and hoarseness. Bacterial culture of throat swabs is useful for the diagnosis of streptococcal pharyngitis but is not practical for routine use. Rapid antigen detection tests (RADTs) are highly specific, and provide an immediate result, thus being often used in routine daily practice. Where the clinical picture is suggestive of infectious mononucleosis (IM), diagnosis may be aided by a positive heterophile antibody test (Paul-Bunnell or "spot" test) which has a high sensitivity in the second week of illness. Investigations are rarely required for other causes of viral pharyngitis and the diagnosis is a clinical one.

1.4.3.3 Treatment

There is no management required for viral pharyngitis other than supportive measures. For *Strep. pyogenes* pharyngitis, penicillin V. and amoxycilin are the treatment of choice [122].

1.4.3.4 Sequelae

Complications can be distinguished in suppurative and nonsuppurative. Suppurative complications are mainly due to the spread of the culprit agent to adjacent tissues: In the case of *Strep. pyogenes* this can include peritonsillar/retropharyngeal abscess, cervical lymphadenitis, otitis media, mastoiditis and sinusitis [123]. All these complications except for the abscesses can be seen with viral pharyngitis as well. Nonsuppurative, immune-mediated sequelae are mainly associated with *Strep. pyogenes* rather than viruses, and include acute rheumatic fever (ARF), and acute poststreptococcal glomerulonephritis [123].

1.4.4 Otitis Media

Acute otitis media (AOM) is pathology of the middle ear and mucosa of the tympanic membrane (behind the ear drum), which complicates approximately one third of cold-like viral URTIs in early childhood. In other cases RSV, adenovirus, cytomegalovirus, PIV, adenovirus, enterovirus, and influenza virus [124] are identified. RVs have been increasingly appreciated as causes of the condition, as otologic manifestations of RV infection include eustachian tube dysfunction and abnormal middle ear pressure [125, 126], the main causes thought to underlie AOM. RV was detected by real-time PCR in nasopharyngeal aspirate or middle ear fluid specimens in 41% of episodes of AOM in children nasally inoculated with the virus [47]. RSV is the cause of acute otitis media in approximately 15% of cases, and it accounts for one-third of viral causes [127].

Otitis media with effusion (OME) is a condition, which often follows a slowly resolving AOM. There is an effusion of glue-like fluid behind an intact tympanic membrane in

the absence of signs of acute inflammation. RV was the predominant virus recovered by our team in the middle ear cavities of children with asymptomatic OME [128].

1.4.4.1 Symptoms

AOM typically has a short history, and is commonly associated with fever, otalgia, irritability, otorrhea, lethargy, anorexia, and vomiting; the symptoms alone lack sensitivity and specificity for diagnosis.

1.4.4.2 Diagnosis

Otoscopy is vital in making the diagnosis, with sensitivity and specificity being 90% and 80%, respectively; this may be increased by using pneumatic otoscopy [129]. The clinical findings are variable, and include abnormal color (e.g. yellow/amber/blue), retracted/concave tympanic membrane, and air–fluid levels. Additional tests such as audiometry and tympanometry could be used, but are not necessary to set the diagnosis of AOM.

1.4.4.3 Treatment

Viral AOM does not need any specific treatment. Bacterial AOM generally follows a mild course without antibiotic treatment. Supportive measures (analgesia and antipyretics) are important in both cases. Approximately 80% of children have spontaneous relief of AOM within 2–14 days [130, 131] suggesting that simple monitoring may be sufficient. However this is not always the case and different societies have produced guidelines regarding when antibiotics should be administered [129, 132]. Acute mastoiditis is more serious than uncomplicated AOM, typically requiring hospital admission, intravenous antibiotics, and surgery if abscess has formed or mastoiditis has not responded to initial therapy [129].

1.4.4.4 Sequalae

Coinfection with bacterial pathogens is common during viral AOM episodes. In one study, bacterial-viral coinfection occurred in 66% of patients, with picornaviruses accounting for two-thirds of cases [133]. A relatively common complication of AOM is acute mastoiditis, defined as acute inflammation of the mastoid periosteum [134]; Patients usually present with the symptoms of AOM plus post-auricular swelling and mastoid tenderness. Other more severe complications are usually seen more often in microbial otitis and include meningitis, epidural/brain abscess, thrombosis of the lateral/cavernous sinus and others.

1.4.5 Obstructive Conditions of the Upper Respiratory Tract

Acute obstructions may present in the supraglottic, glottic, or subglottic regions. Edema developing in this area will reduce the radius of the airway lumen and, subsequently, the airflow. Because of their similar pathophysiologic background and the confined anatomical space wherein these conditions develop (Fig. 1.4), they share several signs and symptoms, regardless of the underlying cause [135]. Viral tracheitis (viral croup) is by far the commonest of these conditions.

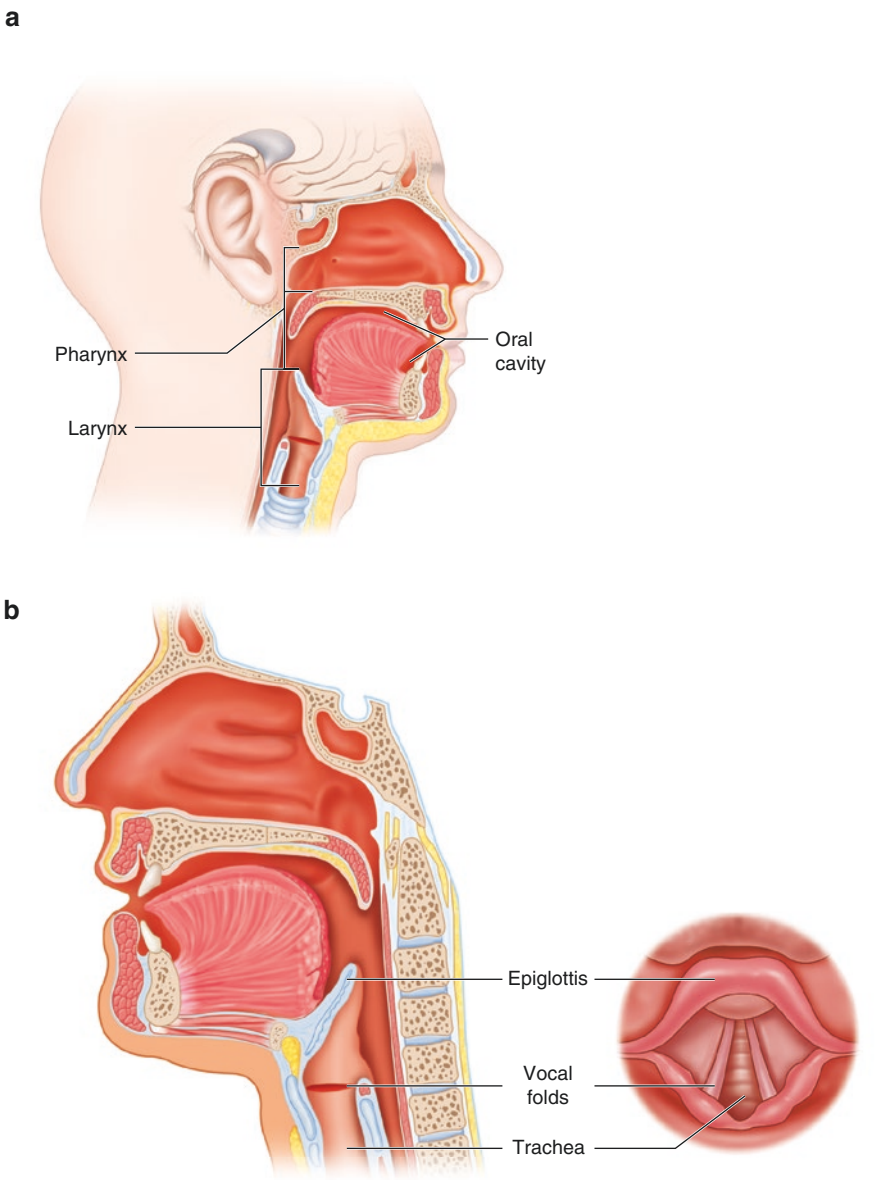

Fig. 1.4 (**a**) Anatomy of the wider site, and localization of the larynx in relation to other landmarks. (**b**) More detailed description of the laryngeal site, where the obstructive conditions develop

1.4.5.1 Acute Viral Laryngotracheitis (Viral Croup)

Viral croup is a common illness characterized by inflammation of the larynx. It is defined as an acute clinical syndrome with inspiratory stridor, a barking cough, hoarseness and variable degrees of respiratory distress. About 12 million cases are diagnosed annually, accounting for one third of patients presenting with acute cough. Viral croup is the commonest form of croup and accounts for over 95% of laryngotracheal infections. Peak incidence is in the second year of life and most affected children are aged between 6 months and 5 years. Although typically caused by PIV (and especially type 1 PIV [136]), all respiratory viruses can cause croup: RV [137], RSV, adenovirus, hMPV, influenza virus [138], CoV NL63 and HBoV have been described as causes of croup with variable incidence [139]. RV is detected more often in samples obtained during the fall whereas influenza A and RSV are more common in the winter, and PIVs are mainly found in winter and spring [20].

1.4.5.2 Symptomatology

Symptoms develop mainly due to airway obstruction. After a short history of preceding viral illness (sore throat, coryza, and fever) the patient will present with characteristic "barking" cough, harsh inspiratory stridor and occasionally, variable degrees of respiratory distress as evidenced by increased effort of breathing (intercostal/subcostal recession, grunting, nasal flaring, etc.) [135]. Most often, however, the presentation is mild [20].

1.4.6 Diagnosis

Viral croup is a clinical diagnosis and no tests need to be conducted to diagnose uncomplicated croup. If undertaken, lateral neck films may show subglottic narrowing and the classic "steeple sign" (Fig. 1.5). Plain neck radiographs could help to differentially diagnose retropharyngeal abscesses, epiglottitis, and foreign body aspiration. Direct laryngoscopy is rarely indicated.

1.4.6.1 Management

The episodes are usually self-limiting. Racemic epinephrine nebulizations to reduce subglottic edema are helpful However, it should be noted that the beneficial effect of nebulized epinephrine is transient. Current treatment is systemic dexamethasone preferably via the oral route [140]. Fewer than 5% of hospital admissions for croup will require intubation.

1.4.6.2 Spasmodic Croup

Spasmodic croup is not caused directly by viruses or bacteria and almost always occurs at night in children that were previously well, or had a mild URTI. It is occasionally indistinguishable from viral croup and possibly represents a condition within the same spectrum [135]. Classically, the child awakens with, a "barky" cough and inspiratory stridor; Fever is not present and exposure to the moist night air typically helps resolve the symptoms. The etiology of the airway edema is

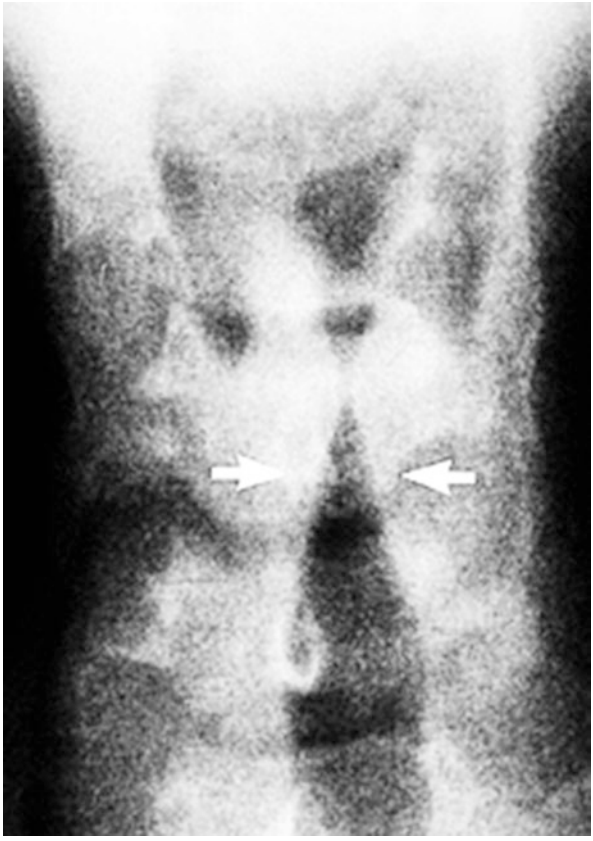

Fig. 1.5 "Steeple sign"

unclear but it may be caused by an allergic reaction to viral antigens. However, there is no direct viral involvement and usually patients have a history of allergic diseases. Treatment is identical to that of viral croup.

1.4.7 Epiglottitis (Supraglottitis) and Bacterial Tracheitis

Acute epiglottitis (supraglottitis) is an infection of the epiglottis. This is a disease that was historically caused by *Haemophilus influenzae* type b (Hib); however the development of the Hib vaccine has altered this trend, and now the rare cases of epiglottitis in an immunized child are mostly due to *Haemophilus parainfluenzae*, *S. aureus*, and *Streptococcus pneumoniae*. This is a condition caused by bacteria rather than viruses and its detailed description is beyond the scope of this chapter. It is briefly discussed in this section, alongside bacterial tracheitis for purposes of differential diagnosis [135]. This is a condition that can easily escalate to complete airway obstruction. The classic clinical presentation is of a toxic-looking child with severe anxiety and sore throat, soft inspiratory stridor, dysphagia, high fever and drooling. There is usually minimal or no

cough. Radiology is not required to set the diagnosis but if undertaken, the inflamed and swollen epiglottis gives the characteristic "thumb" sign [135]. Antibiotics (usually cefotaxime or ceftriaxone) must commence promptly [135]. This condition can be easily told apart from viral coup because of the toxic appearance of the child, the high fever, the lack of cough, and a history of severe sore throat with dysphagia. Bacterial tracheitis, or pseudomembranous croup, is another condition characterized by bacterial inflammation. The tracheal mucosa is infected by *Staphyloccocus aureus*, streptococci or *Haemophilus influenzae* B (HiB) and the patient appears toxic with a high fever and progressive upper airway obstruction [135]. As opposed to epiglottitis, the characteristic barky cough is prominent and there is typically no drooling. Intravenous antibiotics (typically flucloxacillin and cefotaxime) should be given.

1.5 Conclusions

URTIs are some of the most prevalent pathologic conditions, and a considerable cause of morbidity and increased financial burden to health systems and the society. Their most severe sequalae, although rare, could be a cause of mortality and significant disability. The importance of these conditions is grossly underestimated, and they need to be acknowledged as a significant health problem, especially since the over prescription of antibiotics is steadily leading to dangerous, treatment-resistant forms of disease.

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Viral Lower Respiratory Tract Infections

2

Robin J. Green, Heather J. Zar, Debbie A. White, and Shabir A. Madhi

Abstract

Lower respiratory tract infections in children are often viral in origin. Unfortunately in this time of significant antimicrobial resistance of infectious organisms, especially bacteria, there is still a tendency for clinicians to manage a child who coughs with antibiotics. In addition, the World Health Organization (WHO) has defined "pneumonia" as a condition that only occurs in children who have "fast breathing or chest wall indrawing". That would delineate upper respiratory tract infections from those in the lower airway. However, in addition to pneumonia another important entity exists in the lower respiratory tract that is almost always viral in origin. This condition is acute viral bronchiolitis. The concept of "acute lower respiratory tract infection" (ALRTI) has emerged and it is becoming increasing evident from a number of studies that the infectious base of both acute pneumonia (AP) and acute bronchiolitis in children has a mixed etiology of microorganisms. Therefore, whilst certain clinical phenotypes do not require antibiotics the actual microbial etiology is much less distinct.

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2.1 Introduction

Lower respiratory tract infections in children are often viral in origin. Unfortunately in this time of significant antimicrobial resistance of infectious organisms, especially bacteria, there is still a tendency for clinicians to manage a child who coughs with antibiotics. In addition, the World Health Organization (WHO) has defined "pneumonia" as a condition that only occurs in children who have "fast breathing or chest wall indrawing" [1]. That would delineate upper respiratory tract infections from those in the lower airway. However, in addition to pneumonia another important entity exists in the lower respiratory tract that is almost always viral in origin. This condition is acute viral bronchiolitis. The concept of "acute lower respiratory tract infection" (ALRTI) has emerged and it is becoming increasing evident from a number of studies that the infectious base of both acute pneumonia (AP) and acute bronchiolitis in children has a mixed etiology of microorganisms. Therefore, whilst certain clinical phenotypes do not require antibiotics the actual microbial etiology is much less distinct.

Both pneumonia and acute viral bronchiolitis are major cause of health care utilization and hospitalization in higher socio-economic regions of the world and pneumonia is the leading cause of death in children, under 5 years of age, in developing countries [2–5]. The HIV epidemic has contributed enormously to more severe AP and thus increased the mortality [3, 5]. ALRTI accounts for between 30 and 40% of hospital admissions, with associated case fatality rates of between 15 and 28% in developing countries but death is less common in the developed world [5, 6]. Despite the provision of effective and affordable vaccines and antibiotics that have reduced pneumonia mortality from four million in 1981 [7] to just over one million in 2013 [8], pneumonia still accounts for nearly one-fifth of childhood deaths worldwide. Risk factors for AP are reflected in Table 2.1.

2.2 Definitions

AP is usually community acquired, although children in hospital and in long-term health and social facilities are at risk of hospital acquired infections. Community acquired pneumonia (CAP) can be defined as an acute infection (of less than 14

Table 2.1 Risk factors for acute pneumonia in children

Young children
Prematurity
Malnutrition
Immunosuppression (including HIV)
Poor social/environmental circumstances (including household crowding)
Passive tobacco smoke exposure
Indoor fuel exposure
Inadequate vaccine administration
Winter season

days' duration), acquired in the community, of the lower respiratory tract leading to cough or difficult breathing, tachypnoea or chest-wall in-drawing [9]. For the purposes of this chapter AP will be assumed to be community acquired.

Bronchiolitis is a viral-induced lower respiratory tract infection (LRTI) that occurs predominantly in children <2 years of age, particularly infants [10].

2.3 Etiology of ALRTI in Children

AP is caused mostly by viruses and bacteria. Not only is it clinically impossible to distinguish viral from bacterial pneumonia, new evidence suggests that most cases of AP in children have a mixture of micro-organisms in the airway and that both bacteria and viruses occur in combination [11]. In addition, finding an organism on the common tests employed (of airway secretions) does not prove that organism is causing the LRTI. In addition, the problem is compounded by the fact that many healthy children harbor both viruses and bacteria in their airways [11]. These findings suggest that the management of a LRTI in children requires choosing therapies based on clinical findings rather than on special investigations. The possible causes of pneumonia in children are listed in Table 2.2.

Bacteria are the important organisms causing pneumonia-related death [1, 3, 4]. *Streptococcus pneumoniae* is the commonest cause of bacterial pneumonia, but with the introduction of vaccination against pneumococcus around the world, this cause of pneumonia is becoming less common. Other bacteria that remain a cause

Table 2.2 Common causes of AP in infants and children

Viruses
Respiratory syncytial virus
Human metapneumovirus
Parainfluenza virus types 1 and 3
Adenovirus
Influenza A and B
Rhinovirus
Other viruses - measles, boca and corona virus
Bacteria
Streptococcus pneumoniae
Haemophilus influenzae
Staphylococcus aureus
Mycobacterium tuberculosis
Moraxella catarrhalis
Bordetella pertussis
Mycobacterium tuberculosis
Atypical bacteria
Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydophila pneumoniae

of pneumonia include *Staphyloccocus aureus* and *Haemophilus influenzae*, both type b (Hib) and non-typeable disease. The routine immunization of children against Hib has decreased the incidence of pneumonia due to this bacterium, although non-typeable strains are still responsible for a significant proportion of pneumonia.

In addition pathogens vary by age and neonates and children younger than 2 months of age Gram-negative bacteria, Group B streptococcus, *S. aureus*, and *C. trachomitis*, are important causes. Atypical bacteria are said to be more common in children older than 5 years of age, but may occur at any age.

Mycobacterium tuberculosis (TB) has been recognized as an important cause of AP in both HIV-infected and HIV-uninfected children [12]. In Uganda 20% of 270 children with severe AP had clinically suspicious TB and 10% had a culture confirmed diagnosis [13].

Respiratory syncytial virus (RSV) is the commonest cause of viral AP, especially in the first year of life. RSV causes significant mortality and morbidity, especially in children born prematurely and who have other risk factors (Table 2.5). HIV-infected children with RSV are more likely to develop pneumonia rather than bronchiolitis compared with HIV-uninfected children. Other important respiratory viruses include human metapneumovirus, parainfluenza virus types 1 and 3, adenovirus, influenza A and B, rhinovirus, bocavirus, coronavirus and measles virus.

The most frequent cause of bronchiolitis is human rhinovirus (RV) and of severe bronchiolitis, respiratory syncytial virus (RSV) infection, with other respiratory viruses (para-influenza virus (PIV), influenza virus, human metapneumovirus (hMPV), measles virus, bocavirus and coronavirus) being less common.

RSV is an RNA virus. The two major RSV subgroups are A (RSV-A) and B (RSV-B), which are further characterized into several genotypes, based on antigenic and genetic variability of the G-protein. A number of genotypes can produce disease at the same time in a single season, and genotypes often vary from year to year.

Human RV is a Picornavirus, a small RNA virus of which there are 100 serotypes. The major group (90% of serotypes) use ICAM-1 as the cellular receptor, the minor groups use, amongst others, the LDL receptor. RV replicates in the nose and LRT.

Influenza and parainfluenza (1–4) are also RNA viruses. PIV 1 and 2 (Respirovirus genus) produce URTI's and laryngo-tracheo-bronchitis in children 2–5 years of age. PIV 3 (Rubulavirus genus) is responsible for bronchiolitis in infants. PIV 4 rarely causes disease. Human coronavirus produces 15% of the common colds and ocassional bronchiolitis. HMPV is a common cause of bronchiolitis.

Adenovirus is a large naked DNA virus, which inhibits the expression of host messenger RNA, inducing excessive production of adenoviral proteins. It is responsible for prolonged replication and thus severe disease.

2.4 Epidemiology of ALRTI

Epidemiological studies on pneumonia and bronchiolitis often include all children presenting with a clinical diagnosis of LRTI, and may overestimate the true incidence of each entity (AP or bronchiolitis) alone. In one study of LRTI, in South

Africa (SA), the respiratory viruses were detected in 78% of cases. The viruses that were isolated included RV in 37%, RSV in 26%, adenovirus in 26%, influenza virus in 7% and hMPV in 5% [14]. In 2009 and 2010, this surveillance study evaluated respiratory viruses by a 10-plex real-time reverse-transcription polymerase chain reaction (rRTPCR) [15]. Respiratory viral co-infections were common and 17.4% of cases had more than two viral coinfections [15].

A number of studies have found that RV is identified in children with bronchiolitis; however, this virus is also commonly identified in healthy children without symptoms and this makes it difficult to definitively link RV to etiology of bronchiolitis. Early studies have suggested that oxygen saturation is generally not as low in children with RV-associated bronchiolitis as in those with RSV-associated bronchiolitis [16]. However, more recent studies suggest that RV may be more sinister [17]. All three types of RV have been identified in LRTI, although RV-A and RV-C are more common than RV-B. RV is associated with symptomatic respiratory illness; however, there is no association between RV type and disease severity [18]. RV-D has subsequently been identified [19].

RSV is the most common cause of moderate to severe bronchiolitis and a leading cause of ALRTI among young children. RSV-associated bronchiolitis occurs most frequently in infancy, being 2–3 times more likely to occur then, than in older children. Within RSV disease, genotypes differ in different studies [20] and these differences could be related to the extent of community immunity to the specific genotype, with more severe disease observed in the presence of lower community immunity to that strain.

Infection with RSV does not result in permanent or long-term immunity, as reinfections, usually of lesser severity, are common and may be experienced throughout life [21]. An estimated 33.8 million new episodes of RSV-associated acute lower respiratory tract infection (ALRTI) occurred worldwide in 2005 in children under-5 (22% of episodes), with at least 3.4 million episodes necessitating hospital admission. An estimated 66,000–199,000 children under-5 died from RSV-associated ALRTI in 2005, with 99% of these deaths occurring in developing countries [22]. In SA, for example, the prevalence of RSV among 4293 LRTI hospitalizations in under-5 children was 27%, including 863 of 1157 (75%) less than 12 months of age, of whom 637 (74%) were less than 6 months old. Nine of 1153 children with RSV-associated ALRTI died (case fatality proportion 1%). Children admitted with RSV-associated ALRTI were younger than those who tested RSV negative [23].

RSV-associated severe ALRTI occurs in all children from both developing and developed countries roughly to the same extent. However, the case fatality rate is higher in developing areas (2.1% vs. 0.3–0.7%) [22]. The case fatality rate for individual risk factors for RSV-associated disease among children with chronic lung disease, congenital heart defects (CHDs), nosocomial infection, intensive care unit admission and prematurity is significantly higher [24, 25]. HIV is associated with a two to three fold greater risk of RSV pneumonia, but seemingly not bronchiolitis [11]. In addition mortality is higher in HIV-infected children (12% vs. 2% in HIV-uninfected children) [23].

2.4.1 Bacterial-Viral Interactions

Bronchiolitis is a disease caused by respiratory viral infections, with little evidence of bacterial coinfection [26]. There may however, be important viral-bacterial co-infections [27]. Bacterial infections may complicate cases of respiratory viral infections but these children usually present with the more classic signs of AP, including alveolar consolidation on chest radiographs, raised C-reactive protein (≥40 mg/dL), temperature ≥ 38 degrees centigrade (°C) (100.4 °F), chest crackles and bronchial breathing on chest auscultation. The role of bacterial co-infections in children with a respiratory virus-associated pneumonia is frequently under emphasized owing to limited tools for diagnosing bacterial pneumonia, with blood culture sensitivity ranging from 3 to 18% for detecting pneumococcal pneumonia [28]. However, epidemiological studies have identified a strong temporal association between some respiratory viruses and invasive pneumococcal disease. Included among these are studies on the temporal association of the influenza virus and RSV epidemics and invasive pneumococcal disease [29]. Further evidence for this association was observed in an randomized controlled trial of an investigational 9-valent pneumococcal conjugate vaccine (PCV), in which children vaccinated with PCV had a 32% lower risk of being hospitalized for a viral-associated pneumonia compared with placebo recipients [30]. This lower risk of respiratory virus-associated hospitalization was evident for influenza virus, hMPV and RSV-associated pneumonia [31]. The biological rationale for the reduction in respiratory virus-associated pneumonia among the PCV-vaccinated children in this study, was attributed to vaccination having prevented the superimposed vaccine-serotype pneumococcal co-infection, which would have led to progression to more severe disease, culminating in hospitalization among the placebo recipients. Notably, there was no reduction in hospitalization for bronchiolitis among the PCV9 vaccinated children, corroborating that pneumococcal co-infection was unlikely to have played a role in the pathogenesis of bronchiolitis.

The pathogenesis of increased susceptibility to pneumococcal infection following RSV infection in mice-model studies has been attributed to RSV G glycoprotein-binding penicillin-binding protein 1a increasing pneumococcal virulence owing to up-regulation of virulence genes, pneumococcal toxin and pneumolysin. This could lead to an increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures [32, 33]. This again is corroborated by studies in children with alveolar pneumonia associated with RSV or RV infection, among whom higher pneumococcal bacterial load was observed in the nasopharynx than in children with RSV or RV in the absence of alveolar consolidation [34].

Evidence from an epidemiological study in the USA, revealed that RSV AP and pneumococcal pneumonia tended to occur together over similar time periods, with RSV associated with a significant increase in the incidence of pneumococcal pneumonia in children less than 1 year of age (attributable percent 20.3%) and among children aged 1–2 years (attributable percent 10.1%). Similarly, influenza was associated with an increase in pneumococcal pneumonia among children aged 1–2 years. After the introduction of PCV7 into the USA there was an observed decline

in RSV-coded hospitalizations for children <1 year old (attributable percent −18.0% for 2004/2005–2008/2009 vs. 1997/1998–1999/2000) [35]. Although the above mentioned data support an interaction between RSV and pneumococcal superimposed infections, these specifically refer to children who are hospitalized with RSV-associated pneumonia and not to those with bronchiolitis or milder outpatient RSV-associated illness. As such, empiric antibiotic treatment against pneumococcus with RSV-associated pneumonia is only warranted in a child who is hospitalized and whose clinical syndrome is more in keeping with AP rather than uncomplicated bronchiolitis.

There are a number of factors that create circumstances in which RSV and subsequent infection, occur. These include geographical locations (latitude and altitude) and climatic factors (temperature, barometric pressure, relative humidity, vapor tension, hours of light, precipitation, dewpoint). In most temperate regions, such as the USA and Europe, RSV outbreaks last an average of 3–4 months, with a peak incidence during winter, although the exact timing of onset of the outbreak is uncertain. In tropical regions, RSV outbreaks are not distinctly related to season, but often occur during the hottest rainy season [36].

RSV disease is not distinctly seasonal in HIV-infected children and often occurs throughout the year because the virus is shed over a longer period (up to 100 days post infection) compared with 5–7 days in HIV-uninfected children [37]. Although HIV-infected children with RSV-associated ALRTI are at increased risk of hospitalization and death, this could be due to greater susceptibility to co-infections. The increased risk of RSV-associated ALRTI hospitalization in HIV-infected children is greatest during infancy, but remains high even into toddlers [23].

2.5 Pathophysiology of Disease

Immunologically children at risk of bronchiolitis often have an abnormal inflammatory response to infection [38]. Conflicting results from different studies of children with bronchiolitis make definitive conclusion about which cellular regulation and cytokines are at play. One study has documented that nasopharyngeal cytokines interleukin (IL)-6, IL-1B and IL-8 are more significantly elevated in more severe RSV-related disease [39], whilst another study revealed that the T helper (Th) 17 related cytokines IL-1B, IL-17A and IL-23 were associated with a reduction in clinical symptoms [40]. Certainly it seems likely that an uncontrolled or abnormal host response to viruses determines clinical outcome. It is also likely that the inflammatory cellular response influences disease severity, with for example, formation of neutrophil extra-cellular traps (NETs) in abundance in more severe disease that occlude small airways [41]. Whilst the role of vitamin D in disease association has been demonstrated for a host of acute and chronic inflammatory conditions at least one study suggest that vitamin D insufficiency is not characteristic of more severe bronchiolitis [42].

The viral infection starts in the upper respiratory tract and spreads to the lower tract within a few days, resulting in inflammation of the bronchiolar epithelium and

edema of the submucosa and adventitia [43]. Plugs of sloughed, necrotic epithelium, fibrin and excessive mucus secretions add to airway obstruction, causing partial or total obstruction to airflow [44]. A "ball-valve" mechanism can result in trapping of air distal to obstructed areas, with subsequent absorption, atelectasis, and a mismatch of pulmonary ventilation and perfusion that may lead to hypoxemia. Smooth-muscle constriction does not contribute significantly to airway obstruction. Although these mechanisms are known for RSV bronchiolitis, it is assumed that other viruses produce similar pathological conditions. In AP the pathology is centered on the alveolus with neutrophil driven inflammation.

2.6 Diagnosis of an ALRTI

The diagnosis of a LRTI should be considered in any child who has an acute onset of respiratory symptoms, particularly cough, fast breathing or difficulty breathing. Diagnosis includes clinical evaluation, radiographic evaluation and etiological investigations to distinguish between pneumonia and bronchiolitis; decide on management based on the severity; and determine the causative organism where possible and necessary (hospitalized children).

2.7 Clinical Diagnosis of ALRTI

A history and clinical examination are the basis for diagnosing AP and evaluating the severity of illness. The physical examination should include assessment of the child's general appearance, measurement of the respiratory rate, evaluation of the use of accessory muscles and assessment of oxygenation. Auscultation of the chest is an important step.

The principal symptoms of pneumonia are cough, dyspnea or tachypnea (fast breathing). For diagnosis of pneumonia and assessment of the severity of respiratory illness simple clinical signs (respiratory rate and lower chest-wall indrawing) are recommended. WHO guidelines [1] recommend the following:

- That pneumonia be diagnosed when a child older than 2 months has a cough or difficult breathing with tachypnea defined as: (1) more than 50 breaths per minute (bpm) for infants 2–12 months of age; and (2) greater than 40 bpm for children 1–5 years of age.
- That severe/very severe pneumonia be diagnosed when a child has lower chest wall retractions or a general danger sign (Fig. 2.1). The presence of wheezing and clinical chest hyperinflation, without bronchial breathing, on auscultation is suggestive of bronchiolitis as the cause of the lower respiratory tract illness [10].

The presentation of AP can range from mild to severe life threatening illness. It is essential to ensure children with severe disease are hospitalized (Table 2.3) and children with less severe AP are managed as outpatients. Assessment of the general

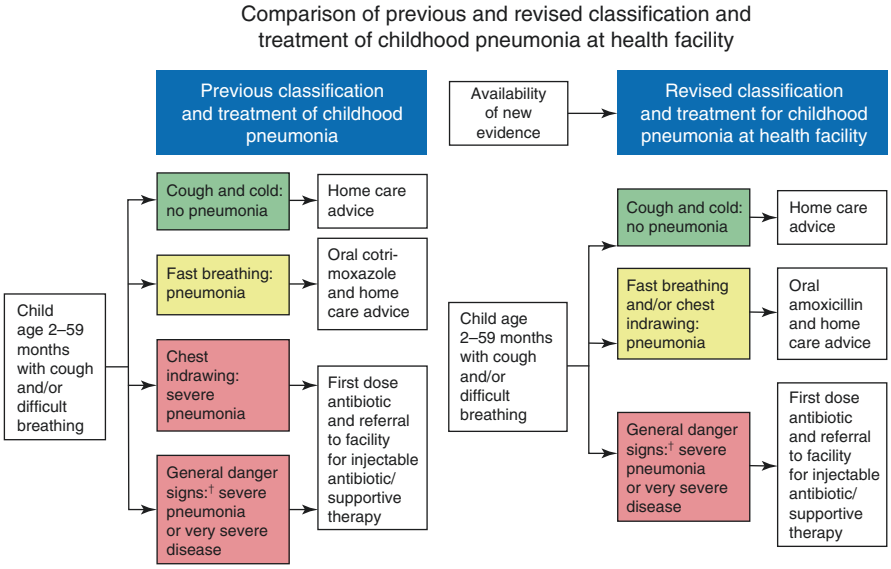

Fig. 2.1 WHO recommendation for management of acute pneumonia. Reprinted with permission from [1]

Table 2.3 Indications for admission to hospital for a child with AP

All children younger than 2 months
Children older than 2 months with:
Impaired level of consciousness
Inability to drink or eat
Cyanosis
Stridor in calm child
Grunting
Severe chest-wall indrawing
Room air SaO2 ≤ 92% at sea level or <90% at higher altitudes
Severe malnutrition
Family unable to provide appropriate care
Failure to respond to ambulatory care or clinical deterioration on treatment

appearance of the child is helpful in determining the severity of illness. The WHO guidelines [1] define specific "danger signs" that indicate severe disease requiring referral to hospital including inability to drink, convulsions, abnormal sleepiness, or persistent vomiting. All children with pneumonia under the age of 2 months require admission to hospital (Table 2.3).

Assessment of oxygenation is important in the evaluation of a child with pneumonia and pulse oximetry should be performed on all children seen at a hospital. To ensure an accurate reading, a pediatric wrap around probe should be used. Children

with a saturation of less than 92% at sea level or less than 90% at higher altitudes should be considered for hospital admission and supplemental oxygen [9].

Clinically AP presents in a similar way in HIV-infected and HIV-uninfected children [45]. However, pneumonia resulting from opportunistic pathogens should also be considered in HIV-infected children. Of these, *Pneumocystis jiroveci* and cytomegalovirus (CMV) are the most common and serious infection among infants, occurring commonly at 6 weeks–4 months of age. These infections are frequently the initial presenting feature of AIDS in HIV-infected children not taking cotrimoxazole prophylaxis [46, 47]. Clinical features include cough, dyspnea and relatively few crackles on chest auscultation. Hypoxia is prominent and often severe. These infants often require ventilator support for the severity of pneumonia and multiple antibiotic strategies [46].

Bronchiolitis may be diagnosed on the basis of clinical signs and symptoms. In a young child, the diagnosis can be made on the clinical pattern of wheezing and hyperinflation. Bronchiolitis follows an upper respiratory tract infection with low-grade fever and cough and 1–2 days later the infant develops fast breathing, hyperinflation and wheeze as a consequence of lower airway inflammation and air trapping [10]. The illness is generally self limiting, but may progressively become more severe and include signs such as grunting, nasal flaring and hypoxemia [21]. The most reliable clinical feature of bronchiolitis is hyperinflation of the chest, evident by loss of cardiac dullness on percussion, an upper border of the liver pushed down to below the 6th intercostal space, and the presence of a Hoover sign (subcostal recession, which occurs when a flattened diaphragm pulls laterally against the lower chest wall) (Fig. 2.2).

Measurement of peripheral arterial oxygen saturation is important to indicate the need for oxygen therapy. As with AP, hypoxia indicates that the child requires hospital admission for oxygen therapy.

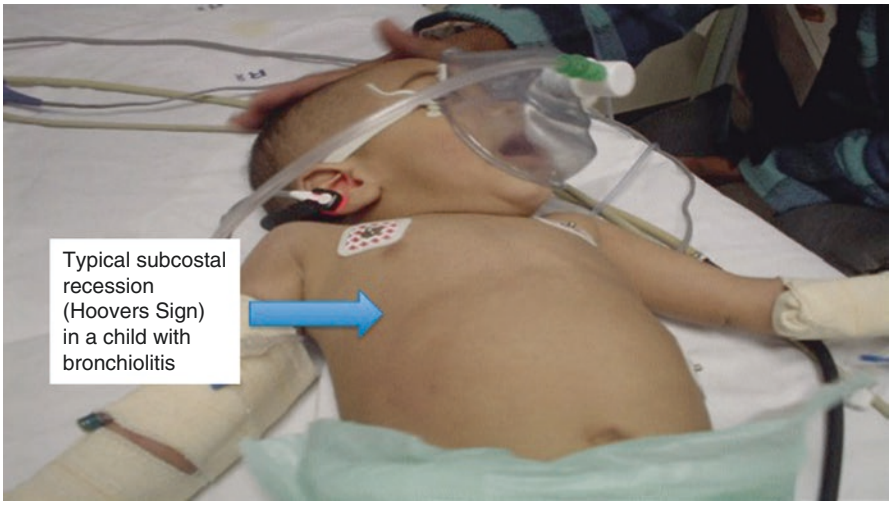

Fig. 2.2 A child with clinical hyerinflation of the chest and a "Hoovers Sign"

2.8 Radiological Diagnosis of ALRTI

A chest radiograph (CXR) may be useful for confirming the presence of pneumonia and detecting complications such as a lung abscess or empyema. CXRs are not useful for distinguishing between viral and bacterial etiologies [48]. Studies have demonstrated that a CXR does not result in improved outcome or change of treatment in an ambulatory setting [49]. The cost, radiation exposure, need for infrastructure, staffing and wide observer variation in interpretation all suggest that routine use of CXRs is not required. There is also no evidence that a routine lateral CXR improves the diagnostic yield in children with AP, except if tuberculosis (TB) is suspected [50].

Definite indications for a CXR include:

- Clinical pneumonia not responding to initial antibiotic therapy
- Unusual clinical presentation or resolution
- When TB is suspected
- Suspected foreign body aspiration
- Hospitalized children to detect complications.

CXRs may also be considered in children presenting with high fever, leukocytosis and no obvious focus of infections, since roughly a quarter of pyrexial children without obvious clinical source may have pneumonia [51].

The interpretation of CXR changes is even more difficult in HIV-infected children as chronic radiological lung changes are common, especially with increasing age [52].

CXRs are generally unhelpful when bronchiolitis is the clinical diagnosis in a child and not required if the clinical diagnosis is obvious. Risk of pneumonia is low in children with saturation greater than 92% and with only mild respiratory distress [53]. Pneumonia is more likely with associated fever [54].

CXRs in bronchiolitis show signs of hyperinflation (Fig. 2.3). The additional features of airway inflammation (peribronchial thickening or sub-segmental

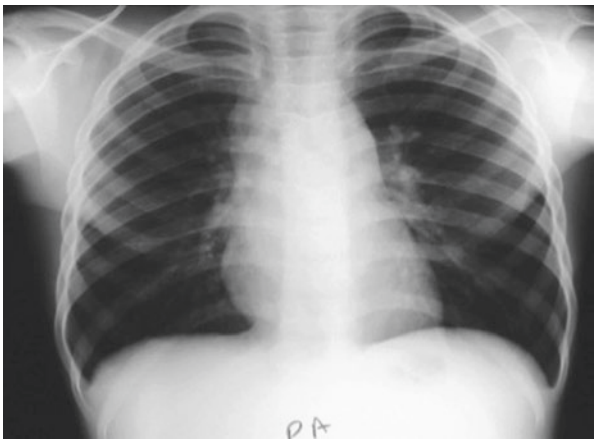

Fig. 2.3 CXR demonstrating marked hyperinflation in acute bronchiolitis

atelectasis) are often misinterpreted as pneumonia. A CXR should only be performed in the following instances [53–55]:

- If complications are suspected, e.g. pleural effusion or pneumothorax
- Severe cases
- Temperature ≥ 38 °C (100.4 °F)
- Uncertain diagnosis
- If the child fails to improve or if their condition deteriorates.

A new modality that is emerging as a diagnostic tool for AP is clinical lung ultrasound and especially point-of-care lung ultrasonograpy (POCLUS). In one study this form of testing revealed a sensitivity of 87.1% and specificity of 94.8% against CXR interpretation of experienced radiologists [56]. The value of this modality is the lack of ionizing radiation exposure and potential use even in developing nations.

2.9 Investigations for ALRTI

The clinical and radiographic features of AP cannot reliably determine the etiology of pneumonia. However, additional tests to help identify a causative agent should be sought in hospitalized children as identification of a pathogen may allow for more directed therapy, provide important epidemiological data and allow for the implementation of infection control measures to reduce the risk of nosocomial transmission of specific pathogens (Table 2.4). However, identifying a specific etiological agent is difficult and may not be possible in most children. Diagnostic testing should not lead to delay in initiation of therapy as this may adversely affect outcome. Empirical treatment should be commenced based on the most likely pathogen and modified according to microbiological results. The following points should be considered when investigating the etiology:

- General tests of infection including acute phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), white cell count (WBC), neutrophil count and procalcitonin will not differentiate between bacterial and viral pneumonia [57–59]
- Blood culture may be useful to identify bacterial pathogens and their antimicrobial sensitivity, but only about 5% of blood cultures are positive in HIV-uninfected children with bacterial CAP. The sensitivity of blood cultures is greater in HIV-infected children, in whom approximately 18% of cultures are positive [28]

Table 2.4 Investigations in children hospitalized for acute pneumonia

Pulse oximetry/arterial blood gas
Chest radiograph
Blood culture (recognizing the limited value)
Induced sputum for TB testing (where appropriate)
Tuberculin skin testing (where appropriate)
NPA for viral detection
Aspiration of pleural fluid

- Pleural fluid, if present, should be aspirated and sent for culture and sensitivity testing
- Specimens for culture from the lower respiratory tract can be obtained using sputum induction [60], endotracheal aspiration in intubated children and bronchoalveolar lavage (BAL). The isolation of bacteria from these samples (either on culture or using new PCR techniques) may, however, represent contamination with bacteria that normally colonize the nasopharynx
- Tuberculin skin testing (Mantoux method) and induced sputum or gastric lavage are indicated when TB is suspected [61].

Blood tests are not needed routinely for children with definitive clinically diagnosed bronchiolitis. Risk factors in patients with severe bronchiolitis that require hospitalization and may even cause death, include prematurity, congenital heart disease and congenital lung malformations.

Hematological testing (including complete blood counts and C-reactive protein) does not provide additional information in managing bronchiolitis [14, 62]. If the infant appears severely ill, consider alternative diagnoses (bacterial co-infection and other causes of airway obstruction). Clinical signs of concern include pallor, lethargy, severe tachycardia, high temperature, hypotonia or seizures. In cases of serious sepsis investigations may include a CXR, blood culture, and urinary and cerebrospinal fluid analysis [17].

Nasopharyngeal aspirates (NPAs) are not usually taken and viral testing does not assist in the management of bronchiolitis. However, NPAs may be helpful for purposes of disease surveillance, and also in the following cases [17, 43]:

- Neonates
- Where apnea is a prominent feature
- Isolation of patients.

The correct procedure for a NPA should be followed in order to achieve best results. NPAs should be placed in viral transport medium at 4–8 °C (39.2–46.4 °F) and transported to an appropriate laboratory within 72 hours of collection. Specimens should be tested by multiplex real-time reverse-transcription polymerase chain reaction (rRT-PCR) assay for respiratory viruses. Comparative studies have shown that rRT-PCR assays are more sensitive than viral culture and immunofluorescence assays [63]. Multiplex PCR testing has been documented to allow testing for a number of viruses in one assay and is thus more cost-effective [63].

2.10 Severe and Chronic Disease

In infants certain factors predispose to more serious lower respiratory tract illnesses, bronchiolitis and pneumonia. Infants less than 1 year of age are at greatest risk of bronchiolitis, and more severe when additional risk factors are present (Table 2.5) [64–69]. Debate about the importance of RSV infection as a cause of hospitalization in late preterm infants has raged because of the cost of prophylactic therapy. Recent

Table 2.5 Risk factors for more severe bronchiolitis

Age under 1 year
Male sex
Day care attendance
Prematurity
Congenital heart disease
Chronic lung disease
Immunodeficiency
Household smoker

reports have suggested that these infants are at equal risk and require prophylaxis [70, 71]. Studies have revealed that the mean duration of symptoms following bronchiolitis was 12 days. After 21 and 28 days, 18% and 9%, respectively, were still ill. Many infants require additional follow-up visits to a doctor [72].

Many studies have concluded that the respiratory viruses, especially RSV and RV, may predispose to recurrent wheezing in early life and possibly asthma [73–76]. There is now increasing evidence that the asthma phenotype expression is strongly influenced by respiratory viral infection. Whilst allergy may contribute to asthma initiation, viruses and recurrent viral infections are now understood to be equally important. The effect on asthma, however, is strongest when both factors (allergy and infection) operate in synergy [77]. New evidence suggests that susceptibility to recurrent viral infections, failure to generate protective immune tolerance to aero-allergens, and the interaction of these factors with airway inflammation may result from innate immune defects of respiratory epithelial (including mucosal dendritic) cells [77–80]. The resultant viral interaction with airway cells produces upregulation of high-affinity IgE receptors on myeloid precursor cells, amplifying local airway inflammation. The genetic profile and polymorphisms of these associations are now being discovered [81]. Toll-like receptor 1 single nucleotide polymorphisms (TLR1 SNPs) has been associated with both atopy and multiple viral presence in host airways [81].

2.11 Differential Diagnosis of Viral LRTI

The differential diagnosis of acute and chronic respiratory symptoms is a long one, however, some of the conditions listed in Table 2.6 should be considered.

2.12 Management of ALRTI

AP is always treated with an antibiotic, even though many are viral, or mixed infection, in etiology [9]. The actual antibiotic/s used depend on the local microbial epidemiology drug resistance patterns, confounding factors such as comorbid disease and availability of antibiotics in the region. In most regions of the world the common causative organisms are sensitive to amoxicillin, and hence most

Table 2.6 Differential diagnosis of LRTI

Acute symptoms
Bronchopneumonia or bronchiolitis—other etiology
Pertussis
Foreign body
Myocarditis
Recurrent wheeze or cough
Cystic fibrosis
Cardiac disease
Gastro-esophageal reflux
HIV/tuberculosis

studies and local guidelines recommend amoxicillin as the antibiotic of choice [82–84]. In addition the dosing recommendation is now **40 mg/kg/dose twice daily (80 mg/kg/day) for three to 5 days** [1]**. Three days of therapy is recommended for AP without chest in-drawing and 5 days for AP with chest in-drawing** [1]**.** It must be noted that the etiology of pneumonia in children differs with age. Children younger than 2 months of age are more likely to harbor a Gram-negative infection and they usually require Gram-negative cover with an aminoglycoside or a cephalosporin. It is always claimed that children older than 5 years of age are more likely to have pneumonia caused by *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, and may therefore require a macrolide [85, 86]. it is also true that such infections may occur at any age and any child who does not respond to first line antibiotics or who has an atypical presentation should be considered for a macrolide [85].

HIV-infected children, with more severe pneumonia or who are malnourished should have the possibility of a Gram-negative organism covered with appropriate antibiotics [87, 88]. In addition in HIV-infected young infants PCP should be considered and co-trimoxazole added [1].

When *S. aureus* is suspected, cloxacillin is the drug of choice. This should be considered if there is clinical evidence of skin lesions and abscesses and radiological evidence of pneumatocele, empyema or abscess formation or if the child remains pyrexial 48 hours after starting amoxicillin. In HIV-infected children, approximately 60% of community acquired *S. aureus* may be resistant to cloxacillin and require treatment with vancomycin [89].

World-wide there is an increase in the incidence of *S. pneumoniae* resistance to the beta-lactam antibiotics, as well as other classes of antibiotics [1, 84]. However, the benefits of amoxicillin when used in the treatment of pneumonia still makes it the preferred antibiotic [1, 84]. In children with pneumonia, the increasing resistance of pneumococcus to penicillin can be overcome by giving a higher dose of amoxicillin. The use of high-dose amoxicillin (40–45 mg/kg/dose twice a day) is advocated. Antibiotic recommendations are summarized in Table 2.7.

Intravenous and intramuscular administration of antibiotics is traumatic to children, expensive and does not improve outcome in uncomplicated pneumonia. Oral amoxicillin has similar efficacy to parenteral penicillin in treatment of severe

Table 2.7 Empirical antimicrobial therapy for pediatric pneumonia [1]

0–2 months of age	– Recommend admission to hospital
	– Ampicillin/penicillin + gentamicin/aminoglycoside iv
3 months–5 years	– Oral amoxicillin po high dose for ambulant children
	– Ampicillin/penicillin iv + aminoglycoside iv for hospitalized children
	– Add: cloxacillin if suspect *Staphylococcus aureus*
Older than 5 years	– Amoxicillin po high dose or
	– Macrolide po (erythromycin/clarithromycin/azithromycin) if suspect *Mycoplasma pneumoniae* or Chlamydophila spp.
	– Ampicillin or 3rd generation cephalosporin (Cefuroxime, Cefotaxime, Ceftriaxone) iv for hospitalized children
	– Add: cloxacillin if suspect *Staphylococcus aureus*

po oral, *iv* intravenous

pneumonia [84]. Parenteral administration should only be given to those children who are severely ill and those with gastrointestinal disturbances (vomiting and diarrhea) in whom absorption may be problematic.

It is generally recommended that 3–5 days of therapy is sufficient for uncomplicated pneumonia. A Pakistan study of HIV-uninfected children with uncomplicated pneumonia reported that the clinical efficacy of 3 days of oral amoxicillin was similar to 5 days for outpatient therapy [90]. Children with *S. aureus* pneumonia should be treated for 14–21 days and children infected with *M. pneumoniae* or *C. pneumoniae* require erythromycin for 10 days or a newer macrolides such as azithromycin for 3–5 days.

In addition to antibiotics, supportive management is essential for children with AP.

Hypoxemia must be accurately assessed with a pulse oximeter. Oxygen therapy should be used to treat hypoxia. When pulse oximetry is available oxygen therapy should be administered when transcutaneous saturation is less than 90–92% in room air. When pulse oximetry is not available, oxygen should be administered when there is central cyanosis, lower chest indrawing, grunting, restlessness, inability to drink or feed or respiratory rate more than 70 breaths per minute [9]. Nasal prongs are recommended for most children who require oxygen. Humidified low-flow oxygen (0.5–3.0 L/min) applied by nasal prongs is effective for hypoxic children. Nasal prongs give a maximum inspired oxygen of 28–35% except in small infants, when higher oxygen concentrations may be obtained. Oxygen should be weaned when the child improves clinically and as hypoxia resolves. Oxygen should be stopped when the transcutaneous saturation is above 90% in room air.

A fever is a useful response of the host in immunological response to infection and does not necessarily require antipyretics [91]. However, pain associated with pneumonia may be due to pleurisy or to pathology involving the upper airways. Pain or discomfort should be treated as it may severely compromise respiratory function and adequate clearance of secretions. The most appropriate agent is paracetamol at

a dose of 15 mg/kg/dose given four to six hourly. Aspirin is contraindicated in most children because of the association with Reye's syndrome.

Children with uncomplicated pneumonia should receive normal maintenance fluids and usually orally. Appropriate rehydration is required in children who are dehydrated.

Children with pneumonia should be encouraged to feed orally and breastfeeding is best in infants, unless they are:

- Too distressed to drink or swallow safely
- Having frequent severe coughing episodes that may be associated with vomiting and possible aspiration of gastric contents
- Dehydrated or shocked.

If children are too distressed to take fluid and feeds orally, continuous enteral feeds via a nasogastric tube may be provided. Ensuring adequate caloric intake is essential as there is an excessive demand on the energy reserves in children with pneumonia, in whom the work of breathing is increased. Children in hospital or pediatric intensive care units (PICU) should not be starved for more than 24 hours.

Intravenous fluids must be used with great care and only if there is adequate monitoring available.

Vitamin A should be given to children with measles to prevent pneumonia [92, 93]. For measles, 200,000 IU vitamin A given daily for 2 days substantially reduced overall and pneumonia-specific mortality [92]. There is no evidence that vitamin A improves outcome in non-measles pneumonia [93].

In children with AP, and especially who are malnourished, adjuvant treatment with 20 mg zinc per day until discharge was found to accelerate recovery from severe pneumonia, reducing the duration of hypoxia [94–96].

A very small proportion of children will require ventilator support for severe ALRTIs. Indications for ventilator support include children who cannot maintain normal oxygen saturations on nasal prong oxygen who are in respiratory failure or who are tiring from excessive work of breathing.

There are a number of therapies that have no proven benefit in the management of children with AP:

- Chest physiotherapy
- Mucolytic agents
- Postural drainage
- Nebulized bronchodilators or saline
- Oral or inhaled corticosteroids.

Because acute bronchiolitis is viral in etiology, most therapies used for other forms of airway inflammation, such as asthma, have no proven value [97]. There is currently no proven effective therapy, other than oxygen, for hypoxic children [98, 99].

Rapid, short-acting inhaled or nebulized bronchodilator therapy such as albuterol or salbutamol has not been documented to be of benefit in the treatment of bronchiolitis [100]. A Cochrane review of 30 trials, including all severities of disease, reported no change in any end points, from nebulized bronchodilators [100]. In addition, bronchodilators cause adverse events in infants and therefore, bronchodilators should not be recommended for the routine treatment of bronchiolitis. Adrenalin too, has not been documented to provide clinical benefit. A Cochrane review suggested a short-term benefit from adrenaline, especially in the first 24 hours of the illness [101], however, no differences were found for length of hospital stay. There was some evidence that adrenaline combined with steroids was effective for reducing the number of hospital admissions [101]. However, despite some benefit, most guidelines state that "there is currently insufficient evidence to support the use of adrenalin for the treatment of bronchiolitis among children admitted to hospital". Inhaled ipratropium bromide has also not been shown to be effective [102].

There is inconsistent data regarding the efficacy of hypertonic saline nebulization (3 or 5%) in the treatment of acute bronchiolitis. A 2013 Cochrane review reported a reduction in duration of hospital stay and improvement in clinical scores in children who were inpatients, but no short-term effects in children in four trials conducted in an emergency unit setting [103]. However, recently the largest reported randomized controlled study of nebulized hypertonic saline in acute bronchiolitis in hypoxic children, found no difference in outcomes between children who received hypertonic saline compared with those who received standard care [104]. Other recently published randomized trials have also added to the evidence against the use of hypertonic saline in bronchiolitis, showing no difference in length of hospital stay, clinical scores or improvement in oxygenation compared with children receiving normal saline nebulization or salbutamol [105–108]. Because current evidence does not demonstrate important benefits with the use of hypertonic saline, it is therefore not be recommended.

Systemic or inhaled corticosteroids have been shown not to be effective in reducing hospital admission or improving clinical scores in ambulatory patients [97, 109]. However, among inpatients, corticosteroids improved clinical scores within the first 12 hours, but did not have any effect on length of stay. Therefore, corticosteroids should not be routinely recommended [109].

Five randomized controlled trials have shown no evidence of benefit for inhaled corticosteroids started in the acute phase of bronchiolitis for prevention of post-bronchiolitic wheezing [110]. Routine use of systemic or inhaled steroids in the management of bronchiolitis is therefore not indicated.

Montelukast is not effective in the management of bronchiolitis. A study of montelukast (4 mg daily until discharge) found that it demonstrated no improvement in the clinical course of the disease [111]. In a study of post-bronchiolitis wheeze, montelukast did not improve respiratory symptoms of post-RSV bronchiolitis in children [112]. In addition, aerosolized ribavirin has been reported not to have any significant consistent beneficial effect in the management of bronchiolitis [97, 113].

Chest physiotherapy (using vibration and percussion techniques) does not contribute to resolution or reduction in severity of disease in infants with acute bronchiolitis [114].

In acute bronchiolitis antibiotics are seldom required. A Cochrane review of antibiotics compared with placebo for bronchiolitis, including two studies of azithromycin compared with placebo, found no difference in duration of illness [115]. Antibiotics should therefore not be used routinely in bronchiolitis, except in children with severe disease in whom bacterial lower respiratory tract infection is suspected [116].

An example of am algorithm to manage acute viral bronchiolitis is provided in Fig. 2.4 [117].

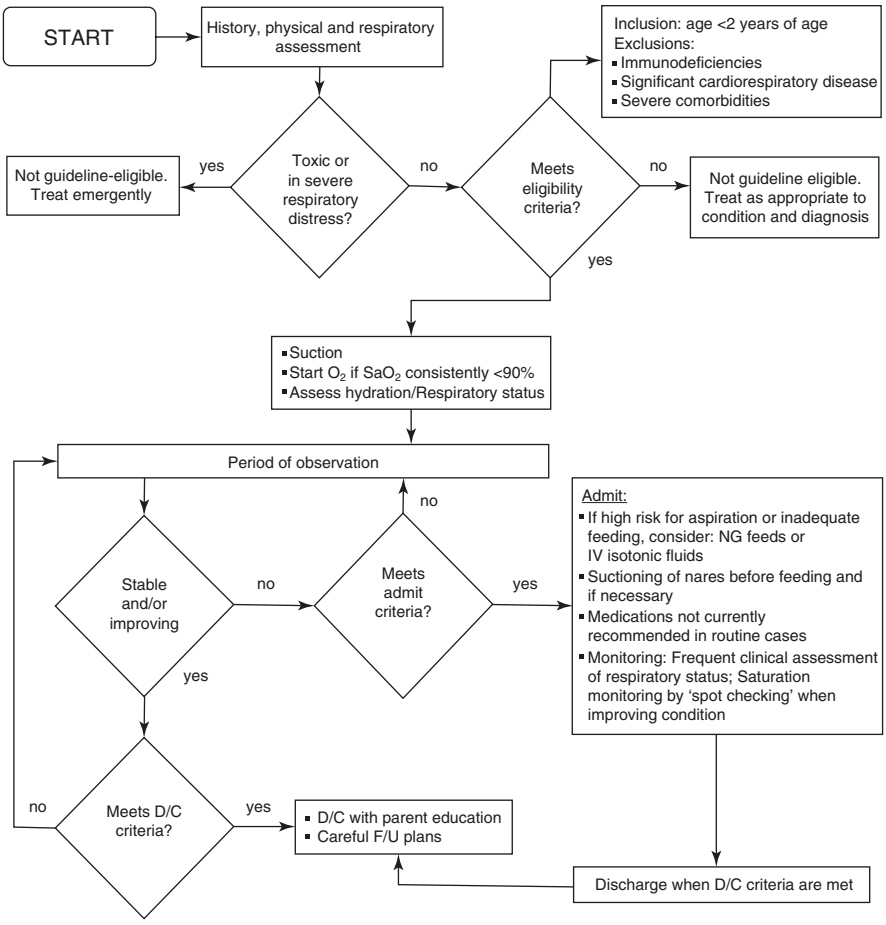

Fig. 2.4 Canadian acute viral bronchiolitis management algorithm. Source: Adapted with permission from [117]

2.13 Prevention of Childhood ALRTI's

Attention to adequate nutrition and growth monitoring should be encouraged as malnutrition frequently predisposes children to pneumonia. Breastfeeding has been documented to decrease the risk of pneumonia in young children by up to 32% [118]. Breastfeeding should be encouraged for the first 6 months of life.

HIV-infected or malnourished children should receive micronutrient supplementation (Vitamin A and zinc) [119, 120], as part of routine care.

Exposure to passive environmental tobacco smoke, indoor cooking fumes and smoke should be avoided.

Vaccines should be considered the most effective form of prevention of AP and every child should receive primary and booster immunizations to BCG, diphtheria-pertussis-tetanus (DPT), Hib conjugate vaccines, pneumococcal conjugate vaccines and measles. Pneumococcal vaccination is specifically relevant, reducing pneumococcal pneumonia by up to 80%, even with the 7-valent vaccine [121]. Additional vaccines may be available in some regions of the world.

Influenza vaccine may be considered appropriate for all children, however, most guidelines advocate mandatory vaccines for children with chronic diseases (pulmonary, cardiovascular or immunosuppressive) and those on long-term aspirin therapy. Children should be vaccinated annually, with influenza vaccine, before the start of the influenza season. Evidence suggests that influenza vaccination is safe in HIV-infected children, especially those with restored CD4 counts on therapy.

Co-trimoxazole prophylaxis for *Pneumocystis jiroveci* is indicated for HIV-infected infants as per local guidelines (see Vol. 1, Chap. 5).

All children under 5 years of age exposed to a household TB contact should be given INH prophylaxis (10 mg/kg) daily for 6 months once active TB disease has been excluded. HIV-infected children exposed to a household contact should be given prophylaxis for 6 months irrespective of their age. Prophylaxis should also be given to HIV-infected tuberculin skin test-positive children even in the absence of a known household contact.

The use of HAART to reconstitute immunity is very effective for decreasing the incidence of pneumonia and opportunistic infections in HIV-infected children (see Vol. 1, Chap. 4).

2.14 Prevention of RSV Disease in High-Risk Children

A specific RSV monoclonal antibody, palivizumab, is available for children at risk of severe ALRTI. RSV-associated risk of hospitalization is 5.2/1000 cases [122]. However, hospitalization becomes more likely with prematurity. Hospitalization for RSV-related disease is more common in young infants and infants with chronic lung disease [122].

Palivizumab has been effective in reducing RSV-related hospitalization and epecially more severe disease resulting in the need for PICU admission among premature infants and those with chronic lung disease [123]. Meta-analysis has confirmed

this across all populations of preterm infants [124]. Palivizumab is also effective in reducing duration of hospitalization and severity of disease in infants with congenital heart defects [125]. In most countries of the world health regulators and managed health care organisations have restricted the use of palivizumab to high risk groups because of the cost of the product [126].

For the prevention of RSV-associated ALRTI, most guidelines for the use of palivizumab recommend that it should be restricted for use in the first 6 months of life in high risk children, defined as premature infants [123, 124]. Furthermore, infants with chronic lung disease of prematurity or those with congenital heart defects with significant haemodynamic instability (complex lesions with pulmonary hypertension) should be covered during the first 24 months of life and during the RSV season. RSV prophylaxis may be considered in children with profound immunocompromise or pulmonary neuromuscular disease. The value of palivizumab is uncertain in children with Down syndrome, cystic fibrosis, recurrent wheeze and in nosocomial outbreaks. Some national bronchiolitis guidelines advocate the use of Palivizumab against a set of scored points to adjudicate risk [126], whist some controversially recommend Palivizumab prophylaxis only in very young premature infants [21].

Palivizumab treatment should commence before start of the RSV season in infants identified to be most at risk. The standard dose of 15 mg/kg is given monthly and in most guidelines advocated for 5 months of use. Where the premature infant is still in the hospital environment at the time of dosing requirement, Palivizumab should be iniated there.

2.15 New RSV Vaccines and Maternal Vaccination

RSV was first identified in 1956 as causing human LRTI. Since the 1960s many efforts have been made to develop an effective and safe vaccine. One of the first attempts (a formalin-inactivated vaccine) led to significant mortality and further research efforts were put on hold for many years. In the early 1980s alternative vaccine candidates were explored. However, attempts at attenuation of the RS virus, resulted in vaccine candidates that were either too reactogenic or inadequately effective.

The F-protein on the surface of RSV was utilized as a target to develop palivizumab, a humanized monoclonal antibody that has been shown—since the mid-1990s—to prevent RSV lower respiratory tract infection in young children with underlying risk factors. This monoclonal antibody, however, requires monthly intramuscular injections for 4–5 months of the year and is substantially costly. For these reasons it is currently advocated only for premature infants and those with chronic conditions who are at substantive risk. The majority of children, in whom disease is common and severe, are thus not protected.

In the last few years a number of advances have been made. This includes the successful development of a re-engineered F-protein monoclonal antibody that has an extended half-life, which would allow for a single dose to provide protection

Table 2.8 Key elements of an educational message for parents of children with ALRTI

The condition may start as an upper respiratory tract infection with low-grade fever
Symptoms are cough and fast breathing and/or wheeze
When a child has fast breathing, additional medical help should be sought
Bronchiolitis is caused by a virus; antibiotics are not needed
Bronchiolitis is usually self-limiting, although symptoms may occur for up to 4 weeks in some children
AP requires antibiotic treatment but the dose and duration are important

against RSV illness for the duration of the RSV season (4–5 months). There are a number of other candidate vaccines in development [127]. These include live attenuated RSV vaccines, vector-based vaccines, F-protein-based subunit vaccines, including the use of nanoparticle technology or targeting the prefusion epitopes of the F-protein [128, 129].

Since RSV disease begins in very early life the ultimate value of vaccination may lie in targeting pregnant mothers. Accordingly, the first studies of the nanoparticle RSV F-protein vaccine candidate in pregnant women were recently completed, and a multicenter safety and efficacy trial is currently underway in pregnant women. Other vaccines, also targeted at the F-protein, are in development.

Vaccine targets for RSV are critical for all children. This includes affordable vaccines in developing countries.

2.16 Parent and Caregiver Education

As doctors it behoves us a clinicians to ensure that parents of sick children are knowledgeable about the condition, its symptoms, management and expected outcome. This is critical for children who are not admitted to hospital, and for those who leave hospital. The important messages that should be conveyed are listed in Table 2.8.

2.17 Severe Respiratory Syndromes

2.17.1 Severe Acute Respiratory Syndrome (SARS)

SARS is a more severe respiratory tract infection caused by infection with the SARS-associated coronavirus. During 2003 there was a global outbreak with significant mortality, however, children were less affected and the disease, in children, was significantly milder [130]. Fever is a prominent feature of the condition and 60% of children had a cough. All had clinical and radiographic features of pneumonia. No deaths were reported among children with SARS, and at 6 months after illness only mild residual changes were reported in exercise tolerance and pulmonary function [130].

2.17.2 Middle East Respiratory Syndrome (MERS)

MERS is a similar severe acute respiratory tract condition caused by a MERS coronavirus. There have been very few pediatric cases reported, most from the Kingdom of Saudi Arabia [131]. Once again the condition is less severe in children.

2.17.3 Hantavirus Pulmonary Syndrome (HPS)

HPS is a severe respiratory illness transmitted by rodents. The highest number of cases are reported in central and south America and in the southwestern USA [132, 133]. The overall case-fatality rate was 35%, however this was mostly in adults [132].

Most persons had chest radiographs showing unexplained bilateral infiltrates (often labeled as interstitial pneumonia) and required supplemental oxygen. Fever, thrombocytopenia and renal dysfunction are common [132].

2.17.4 Enterovirus D68 (EV-D68) Acute Respiratory Illness

In 2014 there were reports of respiratory infections caused by EV-D68 in the USA. Most individuals affected were children [134]. Many children were hospitalized with severe lower respiratory symptoms and asthma. Investigators noted an association between EV-D68 infection, polio-like acute flaccid paralysis, and cranial neuropathy in children [135].

2.17.5 Avian Influenza

Avian influenza viruses A (H5N1) is significantly more common in children than A (H7N9) [136]. Lower severity and greater transmission is found in the H7N9 childhood cases than in the H5N1 childhood cases [136]. Respiratory disease is an invariable finding.

2.18 Other Respiratory Virus Associations

New evidence is emerging that respiratory viruses may play an important role in hospital-acquired infections, including in the PICU. They often cause pneumonia or even sepsis-like clinical disease. Nosocomial transmission of viruses is an important source of such infections. Viruses play an important role in severe infections in transplant recipients and here CMV is an important organism. Finally, viruses are now being understood to cause important acute exacerbations of chronic illnesses, including cystic fibrosis and other chronic lung diseases.

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Viral Exanthems

3

Adrianne Eyman and Joseph M. Lam

Abstract

Viral skin diseases can range from benign self-limited conditions to more serious infections that can manifest with local or systemic complications. While viral exanthems can occur at any age, they are most common in childhood. Although not always diagnostic, certain features of viral exanthems, such as the morphology, distribution, and clinical course of the cutaneous eruptions can give key clues to the origin of a patient's particular viral exanthem.

This chapter will review common and uncommon viral exanthems that present in the pediatric age group.

3.1 Introduction

Viral exanthems can be a sign of a benign self-limited condition, or they may herald more serious infections with local or systemic complications. The term exanthem originates from the words "exanthema" and "anthos", which mean "breaking out" and "flower" in Greek, respectively [1]. Similarly, a child with a viral infection may often have an eruption that appears to break out like a flower in bloom.

Certain features of viral exanthems, such as the morphology, distribution, and clinical course of the cutaneous eruptions can give key clues to the origin of a patient's particular viral exanthem.

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This chapter will discuss manifestations of common classic viral pathogens such as herpes simplex virus 1 and 2, varicella, Epstein Barr virus, human herpes virus 6 and 7, measles, rubella, parvovirus, coxsackie and molluscum contagiosum virus. Some of the cutaneous features result from direct viral activity, such as the vesicles seen in varicella and the herpes simplex viruses. Other manifestations can result from interactions with medications, such as the classic maculopapular eruption with concomitant Epstein Barr virus infection and exposure to aminopenicillins or the eruption of DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) which occurs with reactivation of human herpes virus 6 or 7. Similarly some cutaneous eruptions occurs as a result of the interplay between the body's host immune response and the infectious pathogen. Examples of these include erythema multiforme and papular acrodermatitis of childhood (Gianotti-Crosti syndrome). Finally, we touch on emerging manifestations of old diseases, such as the recent serotypic change of the hand, foot and mouth disease pathogen in North America from coxsackie virus A16 to coxsackie virus A6 and its altered manifestation as the more severe and widespread eczema coxsackium.

3.2 Herpes Viruses

The *Herpesviridae* family is a group of enveloped, icosahedral double-stranded DNA viruses. There are eight members of the *Herpesviridae* family known to be human pathogens, dubbed human herpes virus (HHV) 1–8. Once infection of a host organism is achieved, all members of the Herpesviridae family are capable of remaining latent within the body and potentially causing disease reactivation at a later date. Different subfamilies of the virus establish latency in different types of tissue [2].

3.2.1 HHV 1 and 2

Herpes simplex virus 1 and 2 (HSV 1 and 2) are the two major types of herpes simplex virus. They are members of the alphaherpesvirinae subfamily which establishes latency in sensory ganglia. This family is characterized by a short reproductive cycle and rapid spread between cells in viral culture [2]. HSV 1 typically infects the oral mucosa and the trigeminal nerve while HSV 2 is typically found in the sacral ganglia after genital infection. However, both viruses can infect either location. Primary infections can present with fever, myalgia, and malaise, but recurrences are not typically associated with systemic symptoms in immunocompetent patients. Neonates can be exposed to HSV at the time of delivery, leading to dermatologic, central nervous system (CNS), or systemic disease [3].

Oral HSV 1 infection is either asymptomatic or associated with a discrete episode of gingivostomatitis. In children, most initial infections go unnoticed [4].

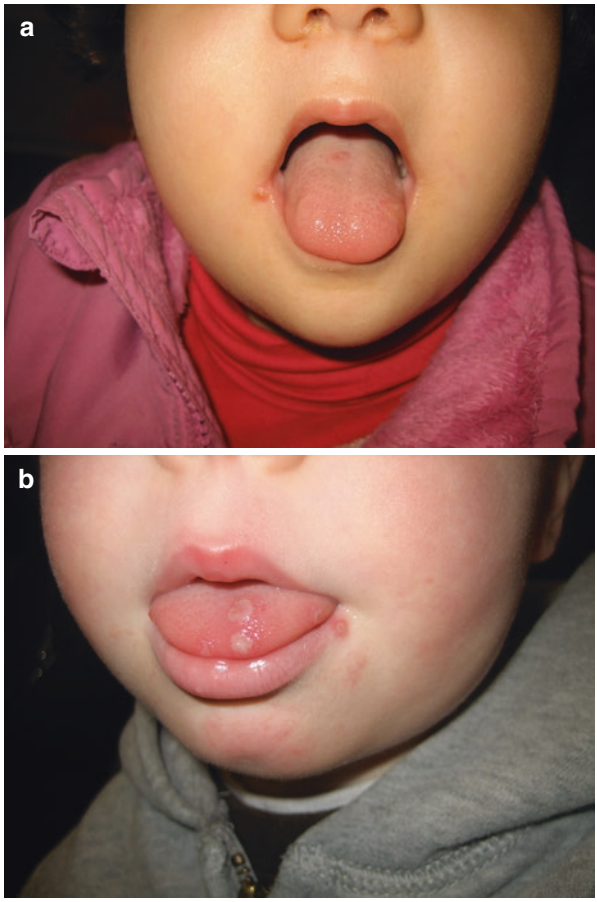

Fig. 3.1 (**a**, **b**) Herpes labialis

Disease recurrence can be triggered by physiologic or emotional stress and the eruption is usually preceded by itching, burning, or paresthesias on the face. Lesions usually appear on the lips (Fig. 3.1a, b), and progress from red macules to vesicles, pustules, ulceration, and ultimately scabbing [5]. Healing occurs within 1–10 days of onset [4]. Herpetic whitlow occurs when HSV-1 or -2 infects a digit, leading to swelling, erythema and tenderness of the affected digit (Fig. 3.2).

Herpes genitalis typically presents with severe, painful genital ulcers and non-specific symptoms including dysuria, cervicitis, and inguinal adenopathy, although the initial infection can be clinically silent. The initial outbreak generally resolves within 3 weeks. As in herpes labialis, recurrence is often accompanied by a prodrome of burning or tingling. Secondary outbreaks are generally less severe than the primary infection and typically resolve within 3–5 days. During recurrent episodes lesions can occur in any regions innervated by the sacral nerve, including the rectum, buttocks, and thigh [6].

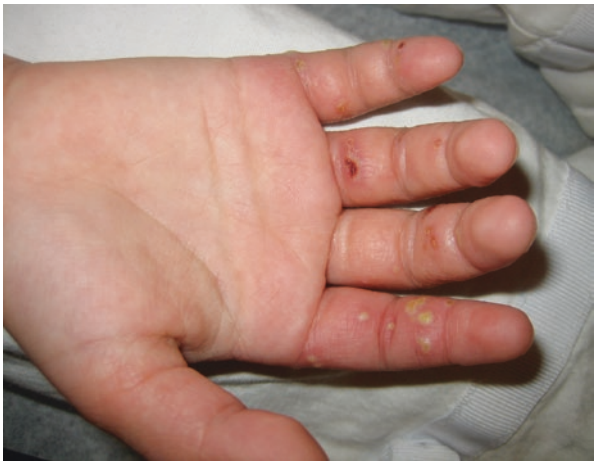

Fig. 3.2 Herpetic whitlow

3.2.1.1 Herpes Gladiatorum

Herpes gladiatorum is a cutaneous HSV infection typically seen in wrestlers and other athletes. Transmission of the virus occurs by direct contact between infected skin or secretions of the host and abraded or otherwise compromised skin of the recipient, or less commonly thorough fomites [7]. One to two days following a prodrome of burning or tingling, painful, clustered vesicles on an erythematous base appear on the skin. Lesions evolve into moist ulcerations and then to crusted plaques, and resolve within 10 days without scarring [8]. After initial infection, the virus establishes latency within the host and recurrence is possible. Recurrent lesions present at the site of the initial outbreak and are shorter in duration and milder than the initial infection [8].

Herpes gladiatorum is most commonly caused by HSV 1, with HSV 2 being the secondary culprit [8]. HSV shedding occurs before vesicle formation, increasing the risk for transmission between athletes. [9].

Diagnosis is typically made clinically but can be confirmed by polymerase chain reaction (PCR), viral culture, or direct fluorescent antibody testing [9]. Treatment is aimed at reducing symptoms and preventing disease spread [7]. Patients must be closely monitored for the development of ocular involvement due to the risks of keratitis [8]. Oral antivirals are the mainstay of treatment, and should be started within 24 hours of symptom development [8].

Current National Collegiate Athletic Association (NCAA) guidelines recommend that an experienced physician examine the skin of all wrestlers before each practice and competition. In cases of a known HSV skin infection, the athlete must be treated with appropriate antivirals for 120 hours prior to participation. The infected wrestler must also be free of systemic symptoms, have had no new vesicles within the last 72 hours, and all existing lesions be non-moist and covered by a firm and adherent crust (NCAA) [10].

3.2.1.2 Eczema Herpeticum

Eczema herpeticum is a severe form of cutaneous HSV infection which occurs in individuals with an underlying skin insult, such as atopic dermatitis, pemphigus,

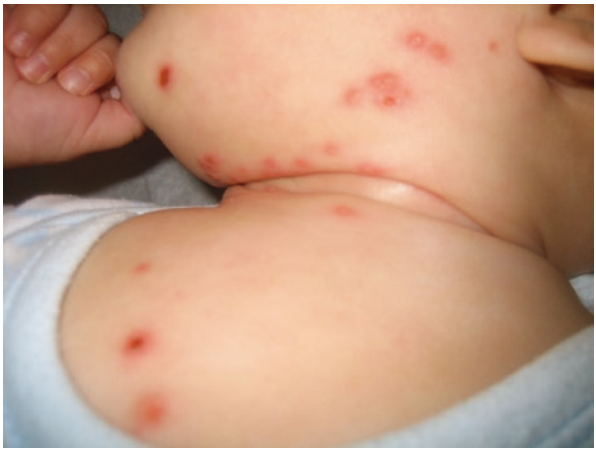

Fig. 3.3 Eczema herpeticum

Darier disease or trauma. Initial infection occurs via direct contact of virus-containing secretions with compromised skin. The exanthem presents as widespread painful, umbilicated vesicopustules which progress to punched-out erosions that can be confluent in some areas (Fig. 3.3). Hemorrhagic crusts can form as lesions heal. Reactivation of latent virus can also occur, but symptoms are typically less severe than at initial presentation [11].

Severity of disease can range from a localized lesion, to disseminated disease, and rarely to encephalitis. Periorbital infection is of particular concern as patients can consequently develop keratoconjunctivitis [11]. HSV superinfection has been shown to be associated with an increased rate of hospitalization for patients with Darier's disease [12].

Eczema herpeticum can be difficult to distinguish from secondary bacterial infection of compromised skin. Skin cultures can be positive for staphylococcal or streptococcal species in either condition [13]. A clue to diagnosis is that in eczema herpeticum lesions are usually of similar size and appearance, whereas impetigo and other secondary infections often appear polymorphous [11]. Diagnosis is made clinically but can be aided with a Tzanck smear, a fluorescent antibody smear, PCR, or viral culture from a lesion.

Treatment is with systemic acyclovir, and delay of acyclovir initiation has been associated with longer hospital stays in children with eczema herpeticum [14]. Acyclovir should be given intravenously if the child appears systemically ill [11]. Before the advent of antivirals, mortality was up to 75% [15].

3.2.1.3 Erythema Multiforme

Erythema multiforme (EM) is the abrupt onset of multiple targetoid lesions on the skin which classically occurs 1–10 days after an episode of herpes labialis or genitalis. Often, the oral, genital, and ocular mucosae are involved. The exanthem is self-limited and usually persists for 2–3 weeks. [16].

The classic targetoid lesion of EM has a central dusky zone which may be vesicular, surrounded by a pale ring of edema, with a peripheral ring of erythema. While

lesions on a given patient at a given time typically appear uniform, the appearance can vary significantly between patients or evolve on a single patient through the disease course. The targetoid lesions typically have a symmetric distribution, often initially appearing on the hands and feet and spreading centrally. Involved mucosal surfaces express painful erosions or bullae. The oral mucosa has been shown to be affected in up to 65% of patients [17].

EM is an immune mediated reaction [17]. In children, most cases are related to HSV infection. However, other pathogens have also been implicated such as varicella [18], EBV, group A streptococcus, and *Mycoplasma pneumoniae* [19]. Drug reactions have also been implicated [20]. The exanthem is most common in young adults, with a slight female predominance.

While most patients recover without serious sequelae, itching and burning skin, pain, and poor oral intake due to mucosal erosions are important causes of morbidity. Post-inflammatory hyper or hypo-pigmentation can persist for several months. In patients with ocular mucosal involvement, keratitis, conjunctival scarring, or uveitis can occur, at times leading to permanent visual impairment. Rare but serious complications include esophagitis with resultant strictures or upper airway erosions leading to pneumonia [16].

The differential diagnosis includes Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and bullous pemphigoid (BP). Diagnosis is clinical, as there are no unique lab findings in the disease [16]. Biopsy can assist in diagnosis [16, 21].

Treatment of EM involves addressing all possible inciting factors. Symptom management is the most significant part of treatment. For most cases oral antihistamines and topical corticosteroids are sufficient, but systemic steroids may be necessary in more severe disease [21].

3.2.2 VZV (HHV 3)

Like HSV, Varicella-zoster virus (VZV) is a member of the *Alphaherpesvirinae* subfamily characterized by rapid reproduction, efficient spread, and latency in sensory neurons [2]. The virus establishes latent infection in the dorsal root ganglia. Unlike HSV, VZV is most commonly transmitted through aerosolized droplets [3]. It is highly contagious, and infection between household contacts is close to 90% [3].

3.2.2.1 Varicella

After infection, viral replication occurs in the oropharynx and regional lymph nodes. Ten to twenty days after exposure, 50% of patients develop prodromal symptoms including fever, malaise, pharyngitis, and myalgia [3]. Soon after the onset of these symptoms, patients develop a generalized erythematous macular exanthem. The exanthem usually originates at the hairline and spreads downward, with the scalp and mucus membranes commonly involved.

Lesions progress over the following days into pruritic fluid-filled vesicles on an erythematous base, commonly described as “dewdrops on a rose petal” (Fig. 3.4). Approximately 4–5 days after presentation, vesicles become cloudy, then

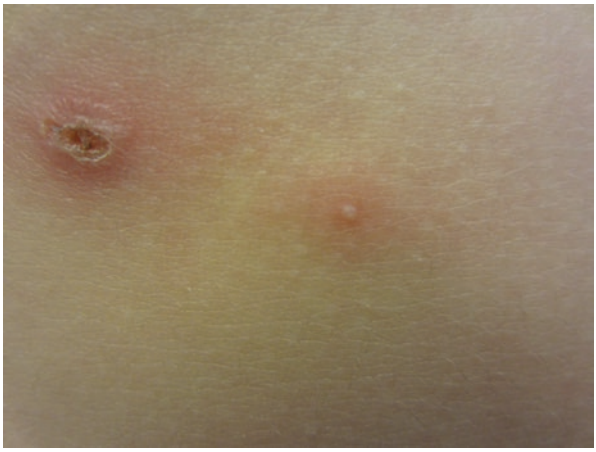

Fig. 3.4 Varicella

umbilicated, and then crust over [3]. New lesions continue to appear even as older lesions begin to crust, so the overall exanthem does not maintain a uniform appearance. The average number of lesions per patient is 300 but can be up to 2000 [3]. Healing lesions may lead to temporary skin hypopigmentation.

The most common complication of VZV infection in children is secondary bacterial infection, usually due to *Staphylococcus aureus* or *Streptococcus pyogenes*. It is more common in children who exhibit significant scratching [3]. Serious neurologic complications can occur, including meningoencephalitis, cerebellar ataxia, and Guillain-Barre Syndrome. Immunocompromised patients are at risk for severe and protracted varicella and systemic involvement. Severe lesions can cause permanent skin discoloration or scarring.

The differential diagnosis includes HSV, pityriasis lichenoides et varioliformis acuta, arthropod bites, and impetigo. Diagnosis is usually made by clinical history and exam. The most rapid and sensitive test to confirm diagnosis is PCR of vesicle fluid, CSF, or tissue [3].

In healthy patients with a typical disease course, treatment is supportive. Immunocompromised patients or patients who have developed severe or disseminated disease should be treated with intravenous acyclovir for 7 days or until no new vesicles have appeared for 48 hours [3]. Varicella immunoglobulin administration is recommended for post-exposure prophylaxis as soon as possible within 10 days of exposure in patients without immunity and who are at greater risks for complications from infection than the general population, including the immunocompromised, premature infants, and pregnant women [22]. Fever should be controlled with acetaminophen, as aspirin may contribute to the development of Reye's syndrome in children infected with VZV. Patients are infective from 2 days prior to the onset of the exanthem until all vesicles have crusted over [3].

The incidence of varicella has been decreasing since the advent of a vaccination against the virus in 1995. The current regimen is 94% effective in preventing disease [23]. Vaccination has led to an 88% decrease in varicella associated mortality, with a 97% reduction in mortality in patients under 20 years of age. In the post-vaccination

era, the vast majority of varicella related deaths occur in unvaccinated patients [24]. Vaccinated individuals may still develop the disease, but it is generally much shorter and milder than infection in an unvaccinated individual [3].

3.2.2.2 Herpes Zoster

After an initial VZV infection, the virus becomes latent in the dorsal root ganglia. If the virus later becomes reactivated, it travels along the nerve to the skin, where it causes a painful and pruritic eruption along the dermatome innervated by the infected nerve.

For days to weeks prior to exanthem eruption, most patients experience pain or burning along the infected dermatome. The rash initially presents as erythematous papules which evolve rapidly into grouped vesicles. The rashes eventually become pustular and then crust over within 10 days (Fig. 3.5). This reactivation occurs most commonly in the immunosuppressed and in the elderly, but can happen at any time throughout a patient's life. Reactivation is typically milder in children than in adults.

Contracting VZV within the first 2 years of life increases the likelihood of later development of herpes zoster [25]. There are reports of immunocompetent children developing herpes zoster due the Oka strain, the vaccine-type of VZV, after receiving the varicella vaccine [26, 27]. There is conflicting evidence as to whether or not VZV vaccination lowers the risk for later development of herpes zoster [25, 28].

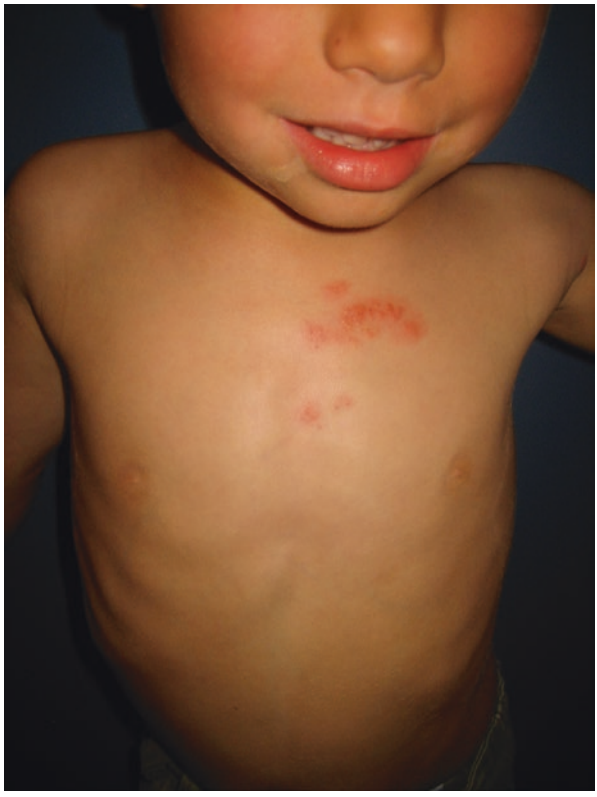

Fig. 3.5 Zoster

3.2.3 EBV (HHV 4)

Epstein Barr Virus (EBV) is a member of the *Gammaherpesvirinae* subfamily. These viruses replicate in lymphoblastoid cells and establish latency in lymphoid tissue [2]. Primary infection with EBV is often silent in children but usually presents as symptomatic infectious mononucleosis in adolescents and adults. Patients develop fever, fatigue, and pharyngitis, and frequently lymphadenopathy. The acute phase of the disease usually lasts 1–2 weeks [3] A non-specific viral exanthem is present in 34% of children infected with EBV, but much less common in older patients [3].

3.2.3.1 Reaction with Aminopenicillins

The majority of adolescents and adults infected with EBV and inappropriately treated with amoxicillin or ampicillin manifest a bright red nonspecific morbiliform eruption. The eruption begins on the trunk and then spreads over the body and becomes confluent. The eruption typically occurs 5–9 days after medication exposure and is likely caused by antibody-ampicillin complex deposition. The rash resolves after cessation of antibiotic administration [3]. It should be made clear to patients that this reaction does not represent a drug allergy.

3.2.3.2 Papular Acrodermatitis of Childhood

Papular acrodermatitis of childhood (PAC), also known as Gianotti-Crosti Syndrome, is a relatively common dermatosis seen primary in children aged 2–6 years. Primary EBV infection or secondary reactivation has been found to be most commonly present in children with the rash, though many viruses have been associated with the disease [29]. PAC is characterized by the abrupt expression of monomorphous papular or papulovesicular exanthem. Papules are erythematous and edematous [29] (Fig. 3.6a, b). Occasionally papules coalesce into large plaques and can become hemorrhagic or scaly. Lesions are typically distributed symmetrically on the extensor aspects of the extremities, the buttocks, and the face with truncal sparing. Lesions may be pruritic [30].

Eruption of the exanthem may be preceded by a viral prodrome of upper respiratory or gastrointestinal symptoms. Once the rash has presented, patients may experience fever, hepatosplenomegaly, or lymphadenopathy [30].

PAC is a clinical diagnosis. The differential includes erythema multiforme, papular urticaria, and atopic dermatitis. The disease is self-limiting and the exanthem usually fades without intervention but complete resolution can take more than 2 months. Oral antihistamines can be helpful in relieving pruritus [30].

3.2.4 HHV 6 and 7

HHV 6 and 7 are members of the *Betaherpesvirinae* subfamily. These viruses have a long reproduction cycle and are slower to spread between cells in viral culture. They establish latency in a variety of non-ganglionic sites throughout the body [2]. The infections are extremely common, with 77% of children contracting HHV 6 before age 2 and 45% of children contracting HHV 7 before age 4. Seroprevalence

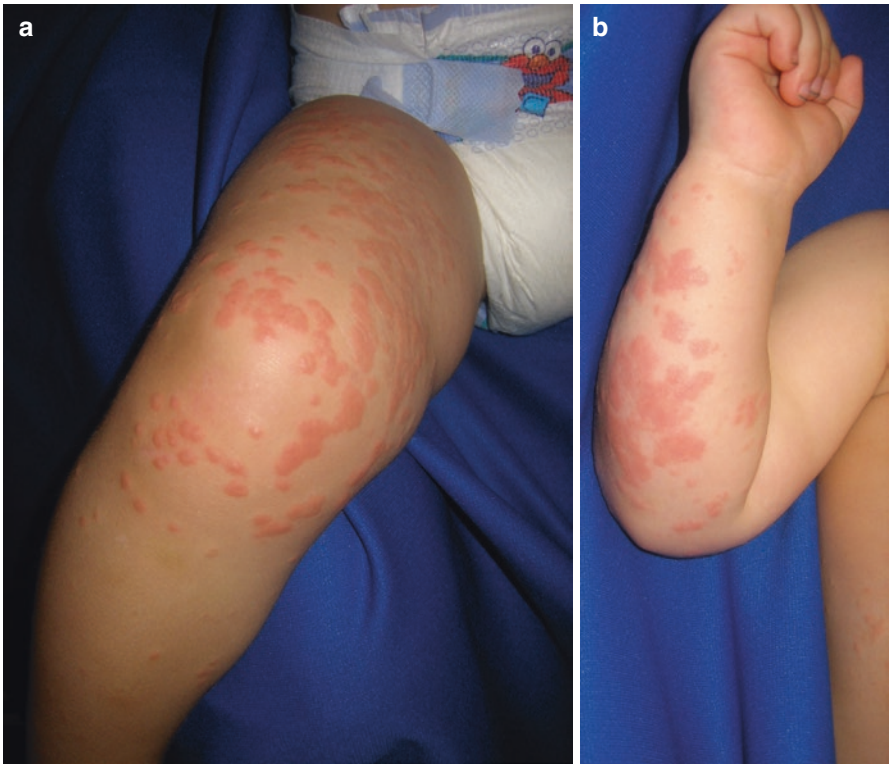

Fig. 3.6 (**a**, **b**) Gianotti-Crosti (PAC)

in the general population exceeds 85% [3]. The principal mode of transmission to children is through the saliva of siblings or adult family members [31].

3.2.4.1 Roseola Infantum

The classic presentation of roseola infantum (RI) is an exanthem which develops in a young child upon resolution of a high fever. Typically, patients develop a fever, often greater than 39.5 °C (103.1 °F), that persists for 3–5 days. The fever can be constant or have an intermittent course [31]. Other prodromal symptoms, such as anorexia, fatigue, and rhinorrhea may be present, although most children are well appearing.

Within 2 days of fever resolution, an exanthem consisting of faint rose colored (hence the name "roseola") maculopapules appears on the neck or trunk and spreads to the extremities (Fig. 3.7). Lesions are discrete, circular or elliptical, 2–3 mm in diameter, and blanch under pressure [31]. The rash persists for between a few hours and 2 days, and is most commonly non-pruritic [3].

RI is typically self-limiting and benign. Febrile seizures are the most common complications, and occur in between 6 and 15% of cases of HHV 6 and 7 infection [3, 31]. Typically, supportive care is sufficient. Acetaminophen can be used to control high fever early in the disease course.

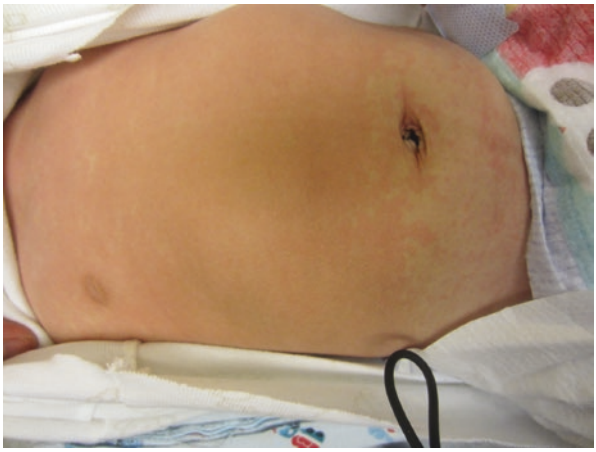

Fig. 3.7 Roseola viral exanthem

3.2.4.2 Pityriasis Rosea

Reactivation of HHV 6 and 7 has been implicated in several conditions, one of which is pityriasis rosea. Classically, pityriasis rosea presents with a "herald patch"- a pink or salmon colored sharply demarcated patch located somewhere on the trunk. These lesions are usually 2–10 cm in diameter, ovoid, and slightly raised. Lesions scale and begin to clear from the center, leaving a ring of scale referred to as a "collarette" at the border (Fig. 3.8). Depending on the location of the patch on the trunk, it might not be noticed by the patient.

Days to weeks after the herald patch presentation, numerous smaller scaly salmon colored plaques appear along the trunk and proximal extremities. The eruption spreads outwards over the course of a few days. In children, an "inverse pityriasis rosea" may present, which presents on the face and extremities and spares the trunk. Vesicular, pustular, uriticarial and hemorrhagic variants of the disease have also been described. Pityriasis rosea is most common in older children and young adults, and has a slight female predominance. The exanthem resolves within 8 weeks in 80% of patients. Lesions may leave residual hypopigmentation.

The diagnosis of pityriasis rosea is almost always made clinically. The differential includes tinea corporis, tinea versicolor, and nummular dermatitis. Skin biopsy can be performed in difficult cases. Treatment is generally supportive.

3.2.4.3 DRESS Syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a rare, potentially life threatening adverse drug reaction frequently associated with HHV 6 reactivation.

The disease generally presents within 6 weeks of exposure to the inciting medication. Patients typically present with a prodrome of fever between 38 and 40 °C (100.4 and 104 °F) accompanied by pruritus. Several days later, a diffuse, pruritic macular

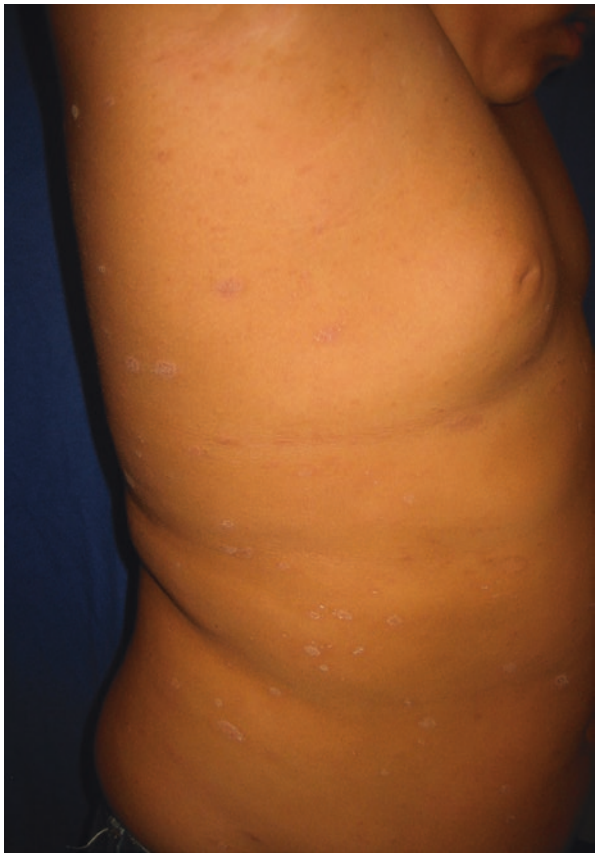

Fig. 3.8 Pityriasis rosea

exanthem presents on the face and upper trunk (Fig. 3.9). The exanthem spreads downwards and rapidly becomes indurated and infiltrative, typically involving at least 50% of the body surface area [32]. Patients may also express vesicles, purpura, and pustules. In severe cases the exanthem may involve almost all skin surface and extensive mucosa, and progress to an exfoliative dermatitis. Approximately half of patients present with erythematous facial edema [32]. Edema can be so severe that it leads to disfigurement. As the rash progresses it may exhibit significant scaling.

Organ systems may be affected, with different inciting medications showing to cause toxicity in different systems. For example, ampicillin is associated with abnormalities, while dapsone is associated with hepatic and renal problems [33, 34]. Many patients experience a marked leukocytosis and eosinophilia.

The disease entity is generally accepted as a severe T cell mediated hypersensitivity reaction to a medication [35]. Anticonvulsants and sulfonamides are most frequently associated [33, 34]. Immunosuppression appears to predispose to DRESS, especially when accompanied by HHV 6 reactivation [33, 34]. The pathogenesis is not yet well understood, but it is hypothesized that genetic mutations in drug metabolizing enzymes may play a role [33, 34]. Symptoms may continue for many weeks after discontinuation of the inciting drug.

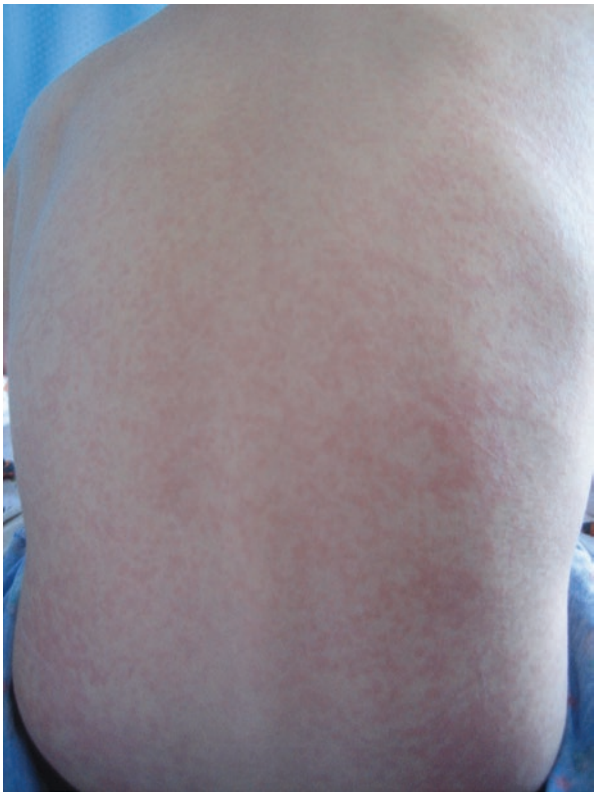

Fig. 3.9 DRESS to lamotrigene

DRESS syndrome must be distinguished from SJS, TEN, acute generalized exanthemous pustulosis, and erythroderma, among others. Further, determining the responsible agent can be difficult if patients were started on many new medications in quick succession. Clinical judgment is often the best method of determination [33, 34]. Suspected medication should have been begun more than 2 weeks and less than 3 months prior to exanthem eruption. Patch testing and lymphocyte transformation testing have been used, with high specificity but low sensitivity [36].

The first step in treatment is immediate cessation of the offending agent. Systemic steroids are the mainstay of treatment. Severe exfoliative dermatitis often mandates management in a burn treatment center and necessitate fluid and electrolyte support.

3.3 Measles Virus

Measles is caused by the measles virus, a highly contagious member of the *Paramyxoviridae* family. Measles spreads through respiratory inoculation, and the virus can remain viable for up to 2 hours outside of a host after inoculation of airspace with coughing or sneezing [37]. After an incubation period of 10–12 days, patients experience a prodromal phase consisting of fever, fatigue, and the "three

C's" of measles; conjunctivitis, coryza, and dry cough. During this time patients also present with Koplik spots, which are gray-white sand grain sized papules on the buccal mucosa highly suggestive of measles [38]. Some patients present with a Stimson line, a characteristic transverse line of inflammation along the lower eyelid margin.

The characteristic exanthematous phase presents 3–4 days after the beginning of the viral prodrome and is often accompanied by high fever of between 40 and 40.5 °C (104 and 104.9 °F). Erythematous macules and papules 3–8 mm in diameter begin behind the ears and at the hairline, and the rash spreads downwards over the remainder of the body during the following day [39]. Areas of rash often become confluent, and the rash can become petechial or hemorrhagic. The exanthem typically clears in the distribution in which it appeared, and frequently desquamates.

Measles can cause a variety of complications. A transient immunosuppression due to a decline in CD4 lymphocytes can last up to 1 month [39]. Infected individuals are consequently at risk for acquiring secondary infections, most commonly otitis media. Pneumonia is the most common cause of measles related death in young children [40]. Other complications include acute post-infectious encephalitis, inclusion-body encephalitis in immunocompromised patients, and subacute sclerosing pan-encephalitis.

In previously vaccinated patients, patients with maternal IgG passive immunity, and patients receiving intravenous immunoglobulin (IVIG) therapy, a form of measles known as modified measles, with a shorter and milder prodrome and exanthem, can occur.

As there is currently no specific antiviral treatment for the measles virus, care is mostly supportive. The WHO recommends the use of high dose Vitamin A in hospitalized children [41]. Since the advent of the measles vaccine, rates of measles in developed country have dropped significantly. One dose of the MMR vaccine is 93% effective at preventing measles, and two doses are 97% effective (CDC 2014).

3.4 Rubella Virus

Rubella, also known as the German measles, is caused by the rubella virus, a member of the Togaviridae family. It spreads through airborne transmission, and infected patients are contagious 1 week prior to the exanthematous eruption until up to 2 weeks after the rash resolves.

Twenty-five to fifty percent of patients who are infected have a subclinical course. After an incubation period of 2–3 weeks, most patients experience a prodromal phase with symptoms including low grade fever, rhinorrhea, headache, sore throat, and myalgias. After 2–5 days a rose colored macular or maculopapular exanthem appears on the head and spreads downwards. The rash usually last for 3 days and is less prominent than in measles. The exanthem is often accompanied by retroauricular, posterior cervical, and posterior occipital lymphadenopathy. Patients can also experience arthralgias, most commonly in the hands.

The most serious complication of rubella is congenital rubella syndrome, which occurs when non-immune pregnant women are infected with the rubella virus. Fetal

effects can include deafness along with hepatic, ophthalmologic, cardiac, and neurologic defects [42]. More than 90% of first-trimester infections result in fetal infection with a generalized vasculitis. Infected infants are often born with "blueberry muffin" skin lesions [43]. Infants with congenital rubella may spread the virus through infected urine and nasopharyngeal secretions past the first 12 months of life. Congenital rubella syndrome can occur even with subclinical maternal infection, but defects are rare after 20 weeks gestation [44].

There is currently no treatment for rubella, and care is supportive. Post-exposure vaccination is recommended for susceptible, non-pregnant individuals exposed to Rubella. In pregnant woman exposed to the virus, immune status should be determined using a serologic test for IgG. Non-immune woman should undergo further evaluation to verify infection and to determine fetal age at the time of infection to assess further fetal risk. Immunoglobulin administration does not prevent viremia and will therefore not protect the fetus from infection, and is consequently not recommended for pregnant woman exposed to the virus [45].

3.5 Parvovirus B19

Parvovirus B19 is a single stranded DNA virus transmitted through respiratory droplets. It causes a variety of disease presentations, from benign to life threatening. 25–50% of infections are clinically silent [46]. Young children often present with erythema infectiosum, which presents with a characteristic facial exanthem followed by a rash over the truncal area. Young adults more commonly present with papular purpuric glove and socks syndrome, a painful acral exanthem accompanied by systemic symptoms. Other presentations include a generalized petechial exanthem associated with fever [47], and skin manifestations in a "bathing trunk" pattern, where patients present with eruptions in the genital and buttocks area. This eruption has been reported in various patients as petechial or associated with pustules [48].

Parvovirus B19 divides inside and causes lysis of actively dividing erythroid cells, which can lead to erythroid aplasia and anemia in patients with low physiologic reserve, such as in sickle cell disease, thalassemias, and spherocytosis. Previously healthy children can also experience transient hematologic abnormalities when infected with parvovirus. In utero infection of fetal erythroid cells can result in fetal heart failure, hydrops fetalis, and fetal death. Treatment is supportive with hematologic abnormalities being addressed as needed.

3.5.1 Erythema Infectiosum

Erythema infectiosum, also known as fifth disease, is the most common clinical manifestation of Parvovirus B19 infection [49]. In healthy children it has a benign course. After an incubation of 1–2 weeks during which patients may or may not experience a viral prodrome, infected children present with fiery-red malar erythema, creating a "slapped cheek" appearance. One to four days after this initial

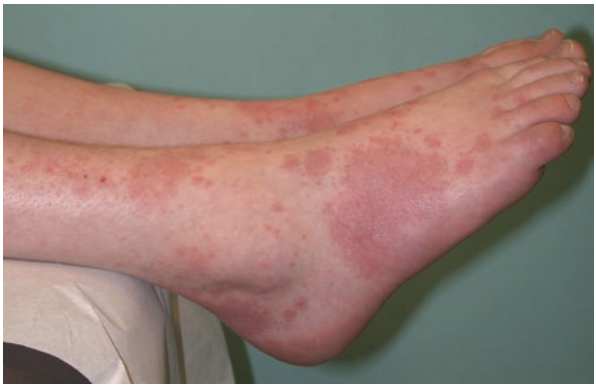

Fig. 3.10 Papular pruritic glove and socks syndrome

eruption, patients develop an erythematous symmetric macular or urticarial exanthem over the trunk and proximal extremities. This exanthem exhibits central clearing to give a distinctive lacy, reticular rash that may be pruritic but does not desquamate. The rash may recur months later in response to environmental or psychological stressors [43]. Ten percent of children will also have an asymmetric arthropathy in the large joints. This symptom is much more common in adults. Erythema infectiosum is usually diagnosed clinically, but PCR can confirm the diagnosis if necessary.

3.5.2 Papular Pruritic Glove and Socks Syndrome

Papular pruritic glove and socks syndrome (PPGSS) is a unique exanthem associated with Parvovirus B19 that most commonly presents in young adults. Clinically, it patients exhibit a symmetric, painful, edematous erythema of the hands and feet, often with a sharp demarcation at the wrists and ankles, with lesions progressing above this point to papular and purpuric form (Fig. 3.10). The inner thighs, extensor surfaces, buccal mucosa, and genital mucosa, may also be involved. Systemic symptoms include fatigue, anorexia, fever, and arthralgias [50, 51]. There are reports of a PPGS like syndrome with additional distribution to the chin and perioral area, referred to as an "acropetechial syndrome" [52].

3.6 Coxsackie Viruses

Coxsackie viruses belong to the genus Enteroviridae, and are non-enveloped viruses with single stranded linear RNA. Coxsackie viruses are divided into coxsackie group A and coxsackie group B based on different molecular and serologic characteristics. Coxsackie A viruses can cause neurologic disease similar to poliomyelitis, another member of the enterovirus genus, and aseptic meningitis. Coxsackie B viruses have been found to cause myocarditis and pericarditis, pleurodynia, and

pancreatitis. The viruses are transmitted through infected bodily secretions, either fecal-oral or through contact with respiratory aerosols [53].

3.6.1 Hand Foot and Mouth Disease

The presentation of hand-foot-mouth disease (HFMD) is well described by the disease name. Patients initially present with a mild prodrome of fever and lymphadenopathy, followed in 1–2 days by the appearance of painful, 2–8 mm diameter oval vesicles on the palmar and plantar surfaces, buccal mucosa, tongue, and often hard palate (Fig. 3.11). Vesicles are gray and may have a surrounding red halo. Lesions can also appear on other parts of the body, and a nonspecific eruption may appear on the buttocks prior to presentation of the vesicular exanthem.

HFMD is most commonly caused by the coxsackie A16 virus, but has also been associated with Enterovirus 71 which on rare occasions has been documented to cause encephalitis [54]. The disease most commonly presents in patients under age 5 [53], and cases are most common in the late summer and fall [43]. Most cases are self-limiting and no treatment other than supportive care is required. Rarely, meningitis or myocarditis may develop.

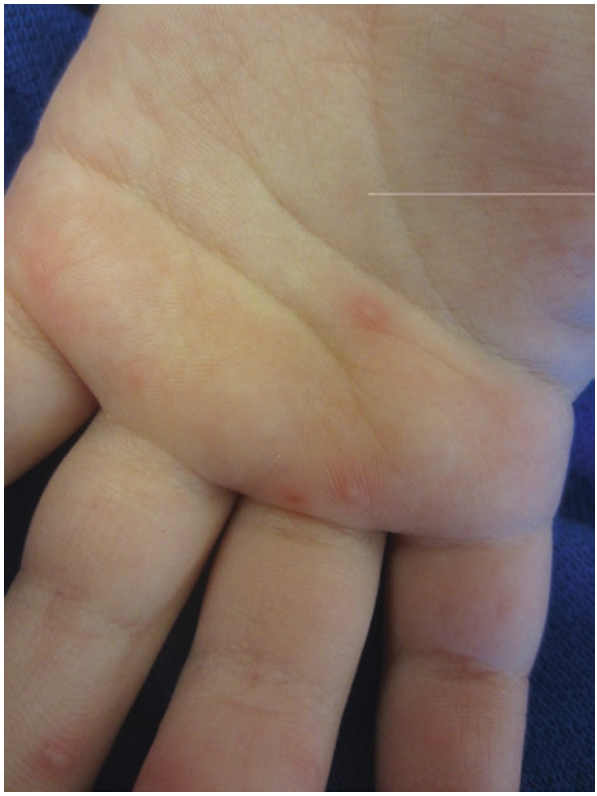

Fig. 3.11 Hand-foot-mouth disease

3.6.2 Eczema Coxsackium

Since 2011, a more severe and extensive form of HFMD associated with coxsackie virus A6 has been reported [55, 56]. The presentation has been termed "eczema coxsackium", a reference to eczema herpeticum, as the vesicles and bullae seen in affected patients appear to preferentially present in areas of skin with pre-existing atopic dermatitis, trauma, or inflammation (Fig. 3.12).

Other notable differences between eczema coxsackium and classic HFMD have been identified. Firstly, lesions extend beyond the palms and soles and present in the perirectal area, on the torso, and on the extremities. The majority of patients have vesicles, bullae, or erosions involving >10% of their body surface area. Intraoral lesions are less commonly present than in classic HFMD. Secondly, approximately one third of patients experience lesions in a distribution similar to Gianotti-Crosti, with lesions on the cheeks, buttocks, and extensor surfaces of extremities with truncal sparing. Finally, some patients experience a petechial or purpuric eruption. Such an eruption was documented in 17% of patients included in the study, most commonly patients over the age of 5.

Additionally, some patients develop impetigo and crusting along the perioral exanthem [55]. Children with underlying atopic dermatitis often have accompanying fever and systemic symptoms [13]. Many patients were reported to have delayed dermatologic manifestations. Nail changes such as oychomadesis and development of Beau's lines have been reported, as well as desquamation of the palms and soles after resolution of the eruption [56].

3.7 Molluscum Contagiosum Virus

Molluscum contagiosum is an infection of the skin and mucus membranes caused by a virus of the same name. The virus is highly contagious and transmitted by physical contact, fomites, and autoinoculation. Patients present with characteristic

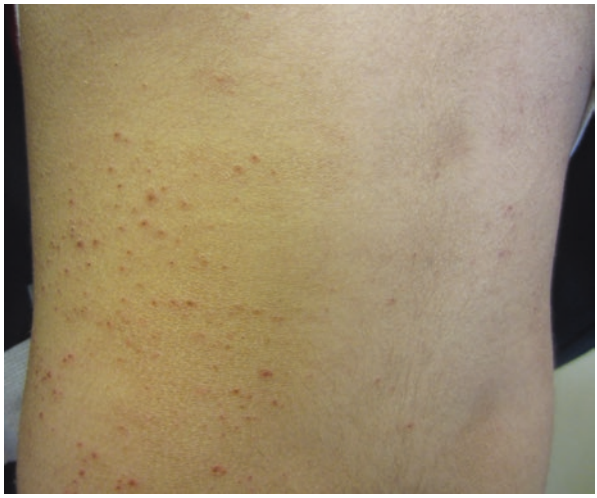

Fig. 3.12 Eczema coxsackium hand foot mouth

flesh colored pearly, umbilicated, dome shaped papules of 2–8 mm in diameter (Fig. 3.13). A creamy, grey-white material can be expressed from these lesions.

Approximately 30% of patients develop an eczematous rash surrounding the lesions, known as a hypersensitivity or id reaction. Id reactions are asymptomatic or minimally pruritic, and can appear on skin distant from mulluscum lesions. This exanthem usually resolves as the lesions resolve and additional intervention is unnecessary [57].

Lesions usually resolve spontaneously, but the disease course can be protracted. The virus does not cross the epidermal basement membrane and thus temporarily avoids immune detection [58]. A single lesion resolves in an average of 2 months, but because of the ease of autoinoculation the overall infection and exanthem can persist for up to a year [58]. Lesional resolution can be preceded by the "BOTE sign", a host inflammatory response in which lesions take on an erythematous and crusted appearance. Lesions become tender and can be mistaken for bacterial infection, but antibiotic treatment is not necessary [59].

In the early stages of the disease lesions can appear flat and can be confused with varicella infection. Diagnosis is usually made clinically by observation of characteristic lesions and can be aided by use of a dermatoscope [58].

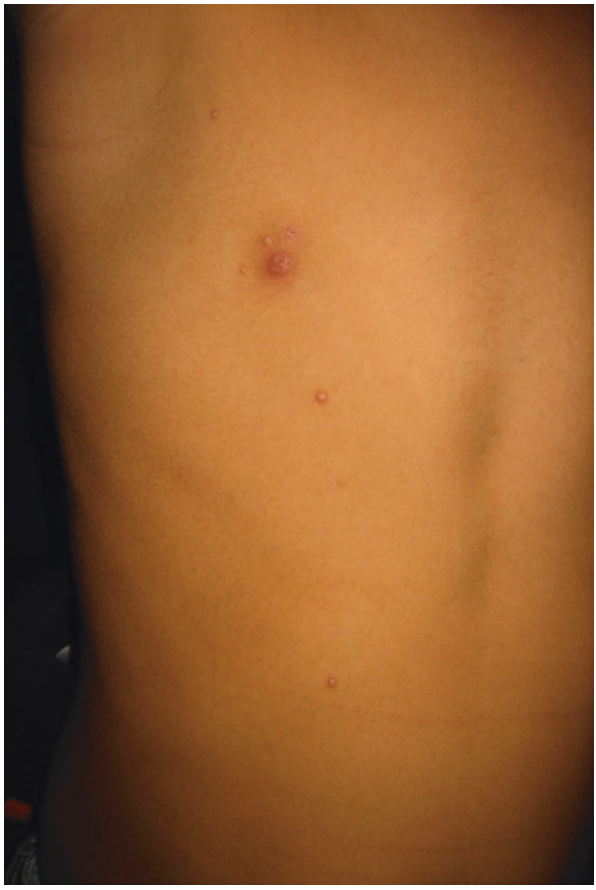

Fig. 3.13 Molluscum contagiosum

Treatment is indicated for patient comfort in order to alleviate itching, to shorten the disease course, to prevent spread to other children, and to limit long-term scarring or superinfection. A common treatment approach is gentle local tissue destruction with cantharidin, a solution derived from *Lytta vesicatoria*, commonly known as blister beetles. Other options include curettage, cryotherapy with liquid nitrogen, and peeling agents such as lactic acid and topical retinoids. Immune enhancing agents seek to boost immune clearance of the Molluscum virus, and include topical imiquimod, oral cimetidine and intralesional *Candida* antigen [60]. Research varies on which treatment modalities are most effective [58]. Antiviral therapy is most commonly reserved for patients with immunodeficiencies.

3.8 Unknown Viral Cause

3.8.1 ULTE (Unilateral Laterothoracic Exanthem)

Usually preceded by a prodrome of upper respiratory or gastrointestinal symptoms, unilateral laterothoracic exanthem (ULTE) is a rash which begins unilaterally in the groin or axillae region and spreads centrifugally onto the torso and arm. The rash occasionally reaches the contralateral side of the body but maintains unilateral predominance [61] (Fig. 3.14). The mucus membranes, face, palms, and soles are usually spared. Early in the disease course the rash may appear mobiliform with some coalescence and may be surrounded by surrounded by a pale halo. As the course progresses lesions tend to become scaly and may develop a central dusky color. The rash is typically mildly pruritic [43] with regional lymphadenopathy being present in approximately 50% of cases [61]. The rash usually resolves with desquamation within 4–6 weeks of appearance, but some cases can last up to 8 weeks. Patients are usually between the ages of 1 and 5 years, and the disease is most commonly diagnosed in Caucasian females [43].

The cause of ULTE is unknown. It is believed to have an underlying viral cause due to a variety of factors; young age of onset, seasonal distribution of cases (more common in winter and spring), associated prodrome, reports of familial cases, and lack of response to antibiotics.

ULTE is commonly misdiagnosed as contact dermatitis. Other differential diagnoses include nonspecific viral exanthem, drug-related eruption, and superficial fungal infection [62]. As the cause is unknown, the diagnosis is based on clinical judgment and treatment is supportive. Antihistamines can be used for any pruritus that occurs [43].

3.8.2 AGEP (Acute Generalized Exanthemous Pustulosis)

Acute generalized exanthemous pustulosis (AGEP) presents as the acute onset of fever and multiple non-follicular pinpoint sterile papulopustules overlying a generalized erythroderma, most commonly resulting from viral infection in children (Fig. 3.15). Distribution of the exanthem is typically on the trunk and intertriginous

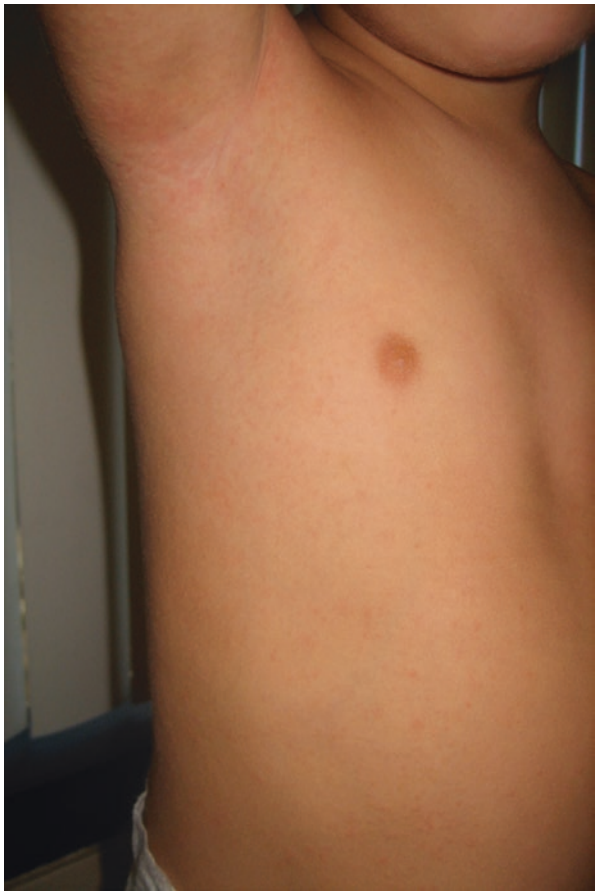

Fig. 3.14 Unilateral laterothoracic exanthem

regions, and there is minimal to no mucus membrane involvement. Desquamation occurs upon resolution of the exanthem. Patients also present with a leukocytosis with neutrophilia [63]. A small number of patients develop systemic disease, with the hepatic and renal systems being most frequently involved [64].

AGEP is attributed to adverse drug reactions in most adult cases, most commonly antibiotics [63]. However, a study of pediatric patients suggested a viral association in 80% [65]. AGEP associated with Parvovirus B19 reactivation has been reported [66]. Various investigations suggest that AGEP is a T-cell mediated reaction. In response to activation, T-cells migrate into the epidermis and induce apoptosis of keratinocytes, leading to vesicle formation. Later, T cells induce chemotaxis of neutrophils, leading to the formation of sterile pustules [63].

AGEP can be difficult to distinguish from pustular psoriasis, DRESS, and SJS/TEN. To aid in diagnosis, an AGEP validation score has been developed based on results of a multi-national study of sever cutaneous reactions. It factors in exanthem morphology, erythema, and distribution, disease course, and lesional histology [67].

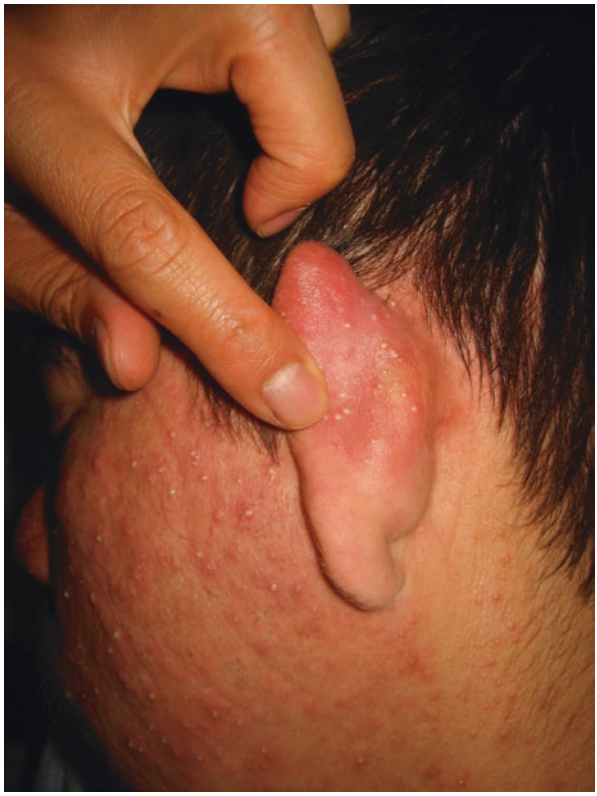

Fig. 3.15 Acute generalised exanthemous pustulosis

In severe cases of AGEP, hospitalization may be indicated. Treatment is mainly symptomatic. In drug-associated cases, cessation of the offending agent is indicated. Moist dressings and antiseptic solutions can help to prevent skin infection during the pustular phase. Treatment with potent topical steroids has been shown to been associated with a reduced hospital stay [68]. Clinical data regarding use of oral steroids for treatment of AGEP in North America is currently lacking.

3.9 Nonspecific Viral Exanthems

A variety of viruses can cause exanthems in association with an upper respiratory tract infection or gastroenteritis. Such exanthems are usually erythematous macules and papules, but may be urticarial (Fig. 3.16). Commonly associated viruses include nonpolio enteroviruses in the summer months and rhinovirus, adenovirus, parainfluenza virus, respiratory syncytial virus and influenza virus in the winter months. Parvoviruses causes have also been demonstrated [46]. Such rashes are self-limited and don't usually warrant additional investigation.

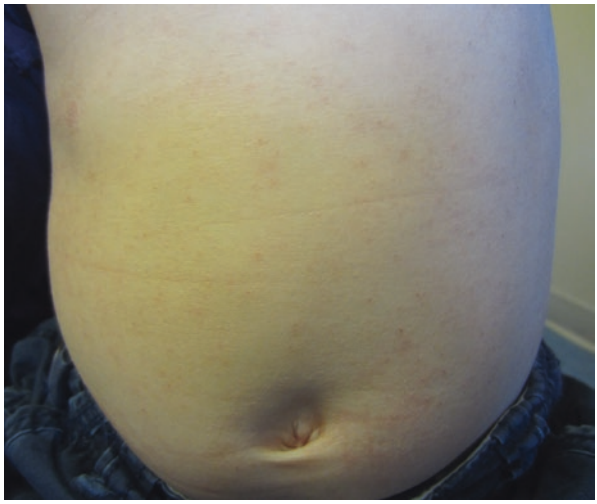

Fig. 3.16 Non-specific viral exanthem

3.10 Antiviral Vaccines

Based on the WHO recommendation for routine immunization [69], measles and rubella vaccines are advocated in all parts of the world, as part of the "Expanded Program of Immunization".

Two doses of measles vaccine are recommended. In countries with ongoing measles transmission and high risk of disease-associated morbidity and mortality, the first dose should be given a 9 months and subsequent dose between 15–18 months.

In countries with low measles rates, the first dose should be administered at 12 months and the second dose programmatically. Countries with high HIV rates may elect early measles vaccine administration.

Measles vaccine is a live-attenuated vaccine derived from Edmonston or other strains, through attenuation in primary chick embryo or cell culture. The vaccine is administered subcutaneously.

Rubella vaccine is administered in two approaches; exclusive focus on reducing congenital transmission – vaccination of adolescent girls and women of childbearing age; or focus on interrupting transmission of rubella by vaccination as part of the childhood immunization schedule. Because rubella is not as contagious as measles one dose is advocated.

Varicella vaccine is advocated in countries where varicella is an important public health concern. 1–2 doses are given with the first dose at 12–18 months of age.

3.11 Conclusions

Viral exanthems in children range from benign symptoms of minor illnesses to part of the presentation of potentially life threatening disease. Our knowledge of the underlying etiology, varying presentation, and best approaches to treatment and prevention of these illnesses continues to expand. While many once common, potentially devastating diseases are now preventable by vaccination, new infections and presentations continue to be discovered. It is the role of the pediatric physician to detect and interpret the dermatologic clues that help to guide treatment of the patient.

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Viral Infections of the Central Nervous System

4

Izelle Smuts and Gregory V. Lamb

Abstract

Viral-mediated central nervous system (CNS) disease is a complex spectrum of clinical syndromes that result from viral tropism and individual immune responses and genetic susceptibility of patients. The epidemiology of the pathogens is constantly influenced by the availability, or non-availability, of health care services; preventative strategies; and the process of globalization, with rapid movement of people, animals and products. It is further complicated by natural disasters, wars and changes in lifestyle.

The effects of the neurotropic viruses are discussed against the background of the epidemiology. The pathogenesis is a chain of events with the point of departure when the virus enters the body to spread and reach the different sites of the CNS. The blood-brain barrier and blood-cerebrospinal fluid barrier are then overcome by captivating mechanisms. Once the different viruses have settled at the preferred site or sites, and have sidestepped the initial immune surveillance, the phases of injury commence. The cytopathic effect of the viruses elicits a para- and post-infectious inflammatory response and a vicious circle of continued damage, viral entry and inflammation results in a process not merely of inflammation, but of intense inflammation.

The different clinical syndromes are then identifiable and should be interpreted against their own specific and appropriate epidemiological backgrounds. Clinicians face the challenge of problematic management decisions while awaiting results on gravely ill patients and differential diagnostic considerations have to be taken into account. Establishing a diagnosis is a two-tier process: first it

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requires the integration of cerebrospinal fluid findings, imaging results, electrophysiological studies, serology and ancillary blood tests, for example full blood count, liver function tests and other appropriate microbiological investigations, and then these should be correlated with the clinical condition of the patient. Treatment should be initiated as soon as possible.

General treatment principles for stabilizing and maintaining vital functions are crucial and empiric treatment should be initiated as soon as possible. This usually includes a broad-spectrum antibiotic, such as third-generation cephalosporin and acyclovir. As soon as specific etiologies have been excluded antibiotics can be stopped. The use of acyclovir is discussed. In the last section of the chapter specific characteristics of the neurotropic viral families are summarized.

4.1 Introduction

Children are often admitted with a differential diagnosis of a possible viral-associated central nervous system (CNS) infection. Viruses affect the CNS in many different ways and clinical manifestations may overlap, resulting in a spectrum of syndromes. Sejvar (2014) eloquently summarizes the different alternatives of the viral-mediated disease in the CNS responsible for these syndromes [1]. In the more acute phase patients may present with meningitis, encephalitis, myelitis or combinations if multiple regions are affected e.g. meningoencpehalitis or encephalomyelitis [1–3]. If vasculitis is a prominent component in a specific disease process, patients may present with more focal signs due to areas of infarcts [1]. In the long term, reactivation of a dormant infection with episodic recurrence will be observed, or a relentless chronic neurodegenerative process may occur and cause subacute sclerosing panencephalitis (SSPE) or "slow viruses" [1]. Congenital infections, such as cytomegalovirus (CMV) or rubella, may result in neurodevelopmental disorders with a more chronic nature [1]. The CNS may also be affected secondarily by a viral-induced immune-mediated attack on the CNS, or indirectly, as seen in liver failure-associated encephalopathy due to viral hepatitis or Reye's syndrome, which is precipitated by salicylate treatment in children with influenza or varicella-zoster virus (VZV) infection [1].

However, to confirm a specific diagnosis is challenging, because the clinical presentation as well as the special investigations are often non-specific. The aim of this chapter is to outline the facts which are known and the many conundrums still faced, and to aid clinicians in making informed decisions on the management of their patients. General principles applicable to virus-associated CNS infections are discussed in the first part of the chapter, and specific viruses of interest at the end.

4.2 Case Definitions and Descriptions of Common Syndromes Associated with Viral Infections of the CNS

Although it is often difficult to apply specific case definitions for the various viral-related CNS syndromes pedantically in a clinical setting, such definitions are ultimately important in patient management and research. The definitions are based on the anatomic site or sites affected. Sejvar et al. (2007) publish case definitions for encephalitis, myelitis and acute disseminated encephalomyelitis (ADEM) on behalf of the Brighton Collaboration Encephalitis Working Group [4]. Britton et al. (2015) compare the different definitions for encephalitis, including the Brighton definition, used in five large epidemiological studies [5]. For the purpose of this chapter different definitions have been collated; in essence the key features overlap and represent the main clinical syndromes related to the anatomic site affected. The broader clinical terminology used in the definitions is explained in the section on clinical manifestations.

4.2.1 Encephalitis

Encephalitis is inflammation of the brain tissue with infiltration of inflammatory cell and perivascular cuffing, therefore in essence a histopathological diagnosis [4, 6], but brain biopsies are impractical and not readily available. A clinical approach has thus been followed, and case definitions have been formulated in a number of excellent epidemiological studies, but these definitions vary slightly, for example in the age of the patients and inclusion criteria [4, 7–9].

In practice the definition of encephalitis depends on the presence of clinical signs due to the involvement of the brain tissue itself manifesting as encephalopathy for a period of at least 24 hours and/or specific neurological features with evidence of inflammation [4, 5, 7–9]. The indicators of inflammation are fever, cerebrospinal fluid (CSF) pleocytosis, and electroencephalogram (EEG) and neuroimaging findings consistent with encephalitis [4]. One of the most useful ways to think of infection is “fever for infection”. The clinical signs of encephalitis are usually non specific but not subtle. However, in immune suppressed patients they may be subtle and often also chronic. The encephalopathy is not due to other metabolic causes, toxins, other neurological disorders or systemic infections [5]. It can be caused by a wide variety of etiological factors including viruses, bacteria, parasites, atypical bacteria or immune-mediated processes [5], but the specific etiology is only confirmed in 60% of cases [8]. The disease course can be acute, sub-acute or chronic, and it is determined by the immune status of the patient [10]. Viruses responsible for sub-acute or chronic presentations in immunocompromised patients are measles virus causing inclusion body encephalitis, VZV causing multifocal leukoencephalopathy, CMV, herpes simplex virus (HSV) type 2, human herpes virus (HHV) type 6, enteroviruses, John Cunningham virus and BK virus causing progressive multifocal leukoencephalopathy and human immunodeficiency virus (HIV). In immune

competent patients John Cunningham virus and BK virus can also cause progressive multifocal leukoencephalopathy, whereas measles virus causes SSPE [10].

4.2.2 Meningitis

In contrast to viral encephalitis, the brain tissue is not involved in viral meningitis and the patients do not have an associated encephalopathy or myelitis, but they present with the triad of fever, headache and signs of meningeal irritation [6, 11]. Viral meningitis is also referred to as aseptic meningitis if the bacterial cultures are negative where meningitis has been suspected and no antibiotics were administered before the lumbar puncture (LP) was done [4, 6, 11]. It is often a mild disease, which has a favorable outcome with complete recovery within 7–10 days [4, 6, 11]. Enteroviruses are identified in up to 95% of aseptic meningitis cases [11].

4.2.3 Meningoencephalitis

If both the brain parenchyma and the meninges are affected it is referred to as meningoencephalitis. It is often difficult to assess signs of meningeal irritation in an encephalopathic patient and confirm meningeal involvement [4].

4.2.4 Myelitis

Myelitis implies that inflammation of the spinal cord parenchyma is present, usually in the anterior horn cell [4]. The viruses implicated are enteroviruses, arboviruses, HSV-1, VZV, poliovirus and coxsackie virus-A and B. If both the brain parenchyma and the spinal cord are affected it is called encephalomyelitis [4]. Patients present with acute flaccid paralysis. Transverse myelitis is a post-infectious demyelination, with 20–40% of patients showing evidence of a viral infection [12].

4.2.5 Myelopathy

Myelopathy is the more diffuse and non-specific involvement of the spinal cord caused by human T-cell lymphotropic virus (HTLV) I and II, HIV and in rare occasions by HSV, CMV or enteroviruses [1, 12]. HTLV-I causes tropical spastic paraparesis and HTLV-I-associated myelopathy, and although these usually present later in life, around the fourth and fifth decades, they have been observed in younger patients [1]. The onset of disease is slow but progressive, and associated with backache and typical sparing of the arms [1]. The legs are affected and the clinical signs are stiffness, spasticity, hyperreflexia, dysesthesia and a positive Babinski sign [1]. The posterior columns are often involved with a loss of position and vibration sense [1]. A similar presentation has been observed by a number of South African clinicians (unpublished data), who have seen children with HIV-1 infection present with

spastic diplegia and no bowel or bladder involvement. The magnetic resonance imaging (MRI) findings for the brain and spinal cord are normal. It is unclear whether this may perhaps overlap with HIV-associated vacuolar myelopathy, as these patients also present with spastic paraparesis and weakness exceeding the degree of spasticity, with hyperreflexia, positive Babinski signs, ataxic gait and dysmetria, and both bowel and bladder incontinence are present [12]. The position and vibration senses are also affected [12]. The macroscopic examination of the spinal cord and dura mater is normal but there is loss of myelin in the lateral and posterior columns, with spongy degeneration or microvacuolization of the white matter [12].

4.2.6 Acute Disseminated Encephalomyelitis

Although ADEM is one of the immune-mediated encephalitides, it is referred to regularly in pediatrics and therefore merits being singled out and set into the context of encephalitis. It is a monophasic syndrome with focal or disseminated demyelination and inflammation of the brain parenchyma. It is also regarded as one of the CNS demyelinating conditions, which include transverse myelitis, optic neuritis, acute hemorrhagic leukoencephalitis and multiple sclerosis. It has an immunological basis and is usually preceded by an infection or vaccination [13]. The Encephalitis/ADEM Working Group emphasizes the fact that encephalomyelitis or ADEM that occurs after the administration of an inactivated component or live vaccine is not inevitably the result of the vaccine, but may be just temporarily associated with it [4].

The clinical features overlap significantly with encephalitis, but in essence encephalitis is predominantly a grey matter problem as a result of the cytopathic effect on the cell bodies in the cortex, basal ganglia and thalami, presenting with a change in the sensorium and with seizures, as opposed to ADEM, which is primarily a white matter disease. Features of white matter disease or demyelination are spasticity, optic neuritis and/or atrophy, ataxia, neuropathy, myelopathy and occasionally seizures; the sensorium is affected to a lesser extent [4, 14].

A mild pleocytosis may be present, but oligoclonal bands are less common (less than 7%). MRI is helpful to identify the demyelination of ADEM. In the absence of specific biomarkers of ADEM, diagnostic criteria have been formulated. A diagnosis of ADEM can be confirmed if all five of the following criteria are met [15]:

- It is the first episode of a presumed inflammatory demyelinating disorder resulting in multifocal CNS manifestations
- There is encephalopathy without fever
- An MRI is abnormal, with lesions predominantly in the cerebral white matter. The lesions are large, diffuse and poorly demarcated. In rare cases T1-hypointense lesions may be present in the white matter. The thalami or basal ganglia may also be affected
- The MRI shows no new lesions after 3 months
- There are no other reasonably possible etiologies.

It is extremely important to be diagnosed promptly as aggressive treatment with corticosteroids and other immune modulatory drugs have shown promising results [16]. The first line of treatment includes steroids, intravenous immunoglobulins and/or plasma exchange. Second line therapy is azathioprine, cyclophosphamide, rituximab or other treatments. In some centers, rituximab is used as a first-line treatment [14].

4.2.7 Brain Stem Encephalitis

Brain stem encephalitis, or rhombencephalitis, is the result of para-neoplastic syndromes or bacterial and viral infections. The viruses implicated are enteroviruses (specifically enterovirus-71), flaviviruses, alphaviruses and rabies. Patients present with typical brain stem symptoms including lower cranial nerve palsies, myoclonus, respiratory drive disturbances, autonomic dysfunction and locked-in syndrome [13]. There are MRI changes in the brain stem and basal enhancement with gadolinium contrast [10].

Bickerstaff's encephalitis has a classic triad of symptoms of abnormal mental status, bilateral external ophthalmoplegia and ataxia, and relates to Miller-Fisher syndrome. Collectively, this has been referred to by some clinicians as GQ1b antibody syndrome, because the IgG anti-GQ1b is highly specific for these conditions [14].

4.2.8 Autoimmune Encephalitis

Immune-mediated encephalitides form a broad group of disorders including ADEM, but the recently described group of encephalitides associated with antibodies against the proteins in the synapses and cell surfaces of neurons or with antibodies against intracellular antigens, is specifically referred to as autoimmune encephalitis and is potentially treatable [13, 14, 16]. Demyelinating disorders can present as autoimmune encephalitis, but the two entities can co-occur and must rather be investigated separately than seen as an expansion of the spectrum of a single disease [14].

The constant discoveries of new antibodies over the past decade have revealed novel mechanisms in the pathogenesis of altered memory, cognition, behavior, psychosis, seizures and movement disorders. A detailed discussion of the different antibodies falls beyond the scope of this chapter because many are more frequently associated with disease manifestations in adults. Leypoldt et al. (2015) have reviewed them in great detail [17].

In a multicenter study in England in which the etiology of encephalitis was studied, an immune-mediated etiology was identified in 21% of patients [8]. In the California Encephalitis Project, the frequency of anti-*N*-methyl-*D*-aspartate receptor (anti-NMDAR) encephalitis was four times higher than that of viral-mediated encephalitis and 65% of the patients were younger than 18 years [18]. Although anti-NMDAR encephalitis has been associated with tumors, mostly ovarian teratomas, it is seldom present in children younger than 12 years [16]. To complicate

matters even further, it has also been found that herpes simplex encephalitis (HSE) is able to trigger autoimmune encephalitis through synaptic autoimmunity or choreo-athetosis post-HSE [16, 19].

Autoimmune encephalitis, rather than a primary viral encephalitis, should be considered in a patient presenting with a movement disorder and psychiatric disturbances (psychosis, catatonia and abnormal behavior) [13]. Other associated clinical features may be diverse but may include seizures, language disturbances, a change in the level of consciousness, and autonomic disturbances [16]. Fever may be present during the course of the disease in 50% of cases and there may be a history of prodromal flu-like symptoms with headache [16]. In the reactivation of VZV, skin lesions may or may not be present [16]. In anti-NMDAR encephalitis, rabies might be considered in the differential diagnosis, because the patient may also have severe agitation, hypersalivation and dyskinesia [16].

Standard diagnostic tests are used in correlation with the clinical facts to make a preliminary diagnosis in order to initiate treatment while awaiting more specific confirmatory test results [14]. The CSF reveals a mild pleocytosis, normal glucose and mildly elevated protein [16]. MRI is useful, and specific findings have been related to various antibodies [17]. The MRI in anti-NMDAR encephalitis can be normal in 60% of cases, and the rest may have non-specific findings, best seen on T2/fluid-attenuated inversion recovery (FLAIR) MRI images demonstrating cortical and subcortical changes in the brain and posterior fossa. Transient meningeal enhancement or demyelination have also been observed [16]. The MRI in rabies, by contrast, may show changes in the basal ganglia, thalamus, gray matter of the dorsal brain stem and central regions of the spinal cord [16]. In limbic encephalitis (usually in elderly patients rather than children), uni- or bilateral involvement in the medial aspects of the temporal lobes has been demonstrated on T2/FLAIR images but the diffusion weighted images are normal and there is no meningeal enhancement [16]. The frontal, occipital and parietal lobes of children, when affected, may have more extensive MRI abnormalities [16].

The gold standard for the confirmation of a diagnosis is to prove the presence of the specific antibodies, but the absence of autoantibodies does not exclude the diagnosis [14]. It is important to test for antibodies in the serum as well as in the CSF, because some of the antibodies may be detected only in the CSF. Furthermore, the CSF and serum antibodies can differ, but the clinical presentation usually correlates with the CSF antibodies. In addition, the concentrations of the antibodies in CSF and serum may vary. There are fewer false positive or negative results with the determination of antibodies in CSF, than in serum [14].

4.3 Epidemiology

The epidemiology of CNS viral infections is a constantly changing scene as new viruses emerge and old ones re-emerge. It is complex, and influenced by the interplay between the three constituents of the “epidemiologic triad”, namely the host, the agent and the environment [1]. With modernization and constant population

growth and increase in population density, not only is the transmission of infectious agents between humans easier, but zoonotic transmission is also favored [1]. Within dense urban communities, with social behaviour that involves increased promiscuity, with easier methods of travel, and with exposure to exotic pets, viruses can spread with great ease. With advances in health care such as the use of chemotherapy and immunosuppressive drugs in transplant patients, opportunistic infections emerge. The food industry has become mass-production orientated, and this favors more food-borne outbreaks. The natural evolution of viruses may increase the virulence of the organisms. Natural disasters and war responsible for the breakdown of infrastructure, as well as deliberate biological warfare, all contribute to the emergence, re-emergence and spread of viruses [1].

It is difficult to compare incidences and prevalences, because the case definitions used in different studies vary, and most studies reflect the endemic disease in industrialized countries [1]. Another contributing factor complicating agreement on incidence and prevalence is that encephalitis is, in most countries, not a notifiable disease [20]. Britton et al. (2016) mention incidence ranges of between 2.8 and 10.5 per 100,000 that have been reported in England, Sweden and the USA [21]. The highest rates have been documented in infants less than 1 year of age. Hospital admissions of children due to encephalitis decreased over a period of 11 years in Australia, but the average hospitalization rate was 5/100,000 [21]. There has been a significant decrease in varicella encephalitis, explained by good varicella vaccine coverage [21]. By contrast, an increase in ADEM-related encephalitis has been documented, and ADEM-related encephalitis now accounts for 15–17% of encephalitis-related admissions [21].

4.4 Viral Etiology

There are many viruses associated with CNS infection. Table 4.1 summarizes the global distribution of viruses associated with CNS manifestations [1]. At least eight virus families have been associated with CNS infection, and these include different species from the deoxyribonucleic acid (DNA) virus families *Herpesviridae* and *Polyomaviridae*, as well as from the ribonucleic acid (RNA) virus families *Flaviviridae*, *Paramyxoviridae*, *Picornaviridae*, *Retroviridae*, *Rhabdoviridae* and *Togaviridae* [3]. Table 4.2 summarizes the classification of these most common viruses. In general it is accepted that HSV, VZV and enteroviruses, as a group, are responsible for most of the CNS infections in children [5].

4.5 Pathogenesis

For neurotropic viruses to be able to cause disease in the brain, a chain of events must happen. Swanson and McGavern outline the current understanding of this process clearly [2]. First of all the virus has to enter the host. This can happen through inhalation or ingestion, or through the skin. Viruses such as mumps and

Table 4.1 Global distribution of viruses causing CNS infections and clinical manifestations [1, 10]

Distribution	Virus	Clinical manifestations				
		Encephalitis	Meningitis	Anterior myelitis	Associated with immunosuppression	Other comments
Worldwide	Adenovirus	+	+	+	+	Reye's syndrome
	Cytomegalovirus	+	+		+	Congenital neurodevelopmental disorder, polyradiculitis
	Enteroviruses (many serotypes)	++	+++	++		Large epidemics Enterovirus-70 hemorrhagic conjunctivitis, Enterovirus-71 hand foot and mouth disease, brain stem encephalitis
	Epstein-Barr virus	++	++		+	Brachial plexopathy, Guillain-Barré syndrome, CNS lymphoma
	Herpes simplex virus 1 and 2	+++	+	+		Radiculomyelitis
	Human herpesvirus-6	++			+++	Febrile convulsion
	Human herpes virus-7	++			+++	Febrile convulsion
	Human immunodeficiency virus	Subacute	+		Causes immunosuppression	Dementia, peripheral neuropathy, myelopathy
	Human T-cell lymphotropic virus (HTLV)				Chronic HTLV-1 myelitis	Tropical spastic paraparesis, HTLV-1 associated myelopathy
	Influenza (A, B)					Uncommon associated encephalopathy, Reye's syndrome
	John Cunningham virus				+++	Progressive multifocal leukoencephalopathy
	Lymphocytic choriomeningitis virus	+	+		++	

(continued)

Table 4.1 (continued)

Distribution	Virus	Clinical manifestations				
		Encephalitis	Meningitis	Anterior myelitis	Associated with immunosuppression	Other comments
	Measles virus	+	+			Subacute sclerosing panencephalitis
	Mumps virus	+	++			Parotitis, orchitis, pancreatitis
	Rabies virus	Fatal				Rare in first world, paralytic illness possible
	Rotavirus	+	+			
	Rubella virus	+	+			Congenital rubella syndrome, progressive rubella panencephalitis
	Varicella-zoster virus	+	+	+		Cerebellitis, granulomatous, arteritis. Shingles, postherpetic neuralgia, vasculopathy
Africa	Chikungunya virus	++ Epidemics				Arthritis associated with febrile illness
	Poliovirus	+	+	+++		Eradicated in western world
Americas	Eastern equine encephalitis virus	Epidemics				Encephalitis in horses
	Western equine encephalitis virus	+				Encephalitis in horses
	Venezuelan equine encephalitis virus	Epidemics				Encephalitis in horses
	St. Louis encephalitis virus	++ Epidemics				
North America	La Crosse encephalitis virus	Sporadic seasonal				
	Other California encephalitis viruses	Sporadic seasonal				

	Tick-borne encephalitis virus	+	+			Travel in Eastern Europe, tick bites, upper limb flaccid paralysis
	West Nile virus	+++	+	+		Flaccid paralysis, parkinsonian movement disorder
South America	"New world" (Junin, Machupo, Guanarito, Sabia viruses)	++				Hemorrhagic fever
Asia and Pacific	Chikungunya virus	++ Epidemics				Arthritis associated with febrile illness
	Japanese encephalitis virus	+++	++	++		Flaccid paralysis, parkinsonian movement disorder
	Nipah virus	Epidemics	Unknown			Relapsing neurological disease, transmitted in feces of fruit bats in Malaysia and Bangladesh
	Poliovirus	+	+	+++		Eradicated in western world
	Tick-borne encephalitis virus	+	+			Travel in Eastern Europe Tick bites, Upper limb flaccid paralysis
	West Nile virus (excluding Asia)	+	+	+		
Australia	Hendra virus	+				Severe encephalitis
	Murray Valley encephalitis	+++ Epidemics				
Europe	Tick-borne encephalitis virus	++	++			Eastern Europe, upper limb flaccid paralysis

Adapted from Sejvar (2014) [1] and Kneen et al. (2012) [10]
+ uncommon, ++ occasional, +++ most common

Table 4.2 Classification of most common viruses affecting the central nervous system and their points of entry

Virus family	Species name	BBB	BCSFB
Herpesviridae	Cytomegalovirus	+	+
Double-stranded DNA	Herpes simplex virus-1	+	
	Herpes simplex virus-2	+	
	Human herpes virus-6	+	
	Varicella-zoster virus	+	
Polyomaviridae	John Cunningham virus	+	
Double-stranded DNA			
Flaviviridae	Japanese encephalitis virus	+	
(+) Single-stranded RNA	Tick-borne encephalitis virus	+	
	West Nile virus	+	
Paramyxoviridae	Measles virus	+	
(−) Single-stranded RNA	Mumps virus	+	+
Picornaviridae	Human parechovirus	+	+
(+) Single-stranded RNA	Nonpolio enterovirus	+	+
	Poliovirus	+	
Retroviridae	Human immunodeficiency virus	+	
(+) Single-stranded RNA	Human T-lymphotropic virus-1		
Rhabdoviridae	Rabies virus	+	
(−) Single-stranded RNA			
Togaviridae	Chikungunya virus	+	+
(+) Single-stranded RNA	Eastern equine encephalitis virus	+	

Adapted from Dahm et al. (2016) [3]; *BBB* blood-brain-burrier; *BCSFB* blood cerebrospinal fluid barrier

measles are spread via droplets, and are inhaled to reach the mucous membranes of the upper respiratory tract. The fecal-oral route of ingestion is a way for other viruses, such as enteroviruses, to enter through the alimentary tract. Once at the mucosal membrane, the viruses pass the epithelial barrier and cause infection in the lymphoid tissue of the oropharynx and gut. Insect bites, abrasions and wounds all create a back door through which viruses can enter the body via the skin. Langerhans cells carry arboviruses delivered by insect bites to the adjacent lymph nodes [2].

The second step, for viruses on their way to reach the CNS, is to spread via one of two main routes, blood or peripheral nerves [2, 6]. Viruses either just float to the brain in the bloodstream, or are transported in white blood cells. The "Trojan horses" for Epstein Barr virus are monocytes. HSV-1 and VZV migrate from the keratinocytes to the peripheral sensory neurons to reach the trigeminal ganglion, where they can be latent for years before being reactivated [2]. The dendrites of the olfactory nerve are in direct contact with mucosa in the nose and offer a unique port of entry for HSV-1, Nipah virus, influenza virus and rabies virus [2]. In the case of a dog bite, rabies virus first infects the myocytes, and migration via the peripheral somatic nerves follows [2].

The third step, once in closer proximity to the brain parenchyma, is for the virus to overcome the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) protecting the brain [2, 3] by creating physical, metabolic and transport barriers [3]. The BBB is between the lumen of the blood vessels and the brain parenchyma while the BCSFB is between the CSF and apical choroid plexus blood vessels [3]. The permeability of these barriers is regulated by tight junctions and adherence junctions [3]. The tight junctions are complexes of different proteins and adhesion molecules, whereas adherence junctions are transmembrane cadherins (named for calcium dependent adhesion) linked to the cytoskeleton [3]. Most viruses enter through the BBB, whilst coxsackie virus-B3, chikungunya virus, mumps virus and echovirus-30 may also use the BCSFB as their port of entry [3].

There are six different possible mechanisms for viruses to cross the barriers:

- Virus-carrying white blood cells squeeze through between the endothelial cells and deposit the viruses in the brain parenchyma [2]
- Some viruses enter the vascular endothelial cells directly and then cross over into the CSF [2]
- The open pores in the choroid plexus provide for direct entry of viruses into the CNS [2]
- The BBB is not intact in the circumventricular organs, for example the area postrema and lamina terminalis. This forms an ideal site for viruses to enter the CNS [2]
- The CNS lymphatic system as newly described by Louveau et al., in which the meningeal lymphatic vessels act as a reservoir for leukocytes, is a groundbreaking discovery [22] that may play an important role in future explanation of the pathogenesis of CNS infections [22, 23]
- The barriers are disrupted as a direct cytotoxic effect of the pathogen and secondary inflammatory mediators [3].

By step 4, when the viruses have entered the brain, it is very difficult to detect them as a result of their "hiding" in the cells and being almost invulnerable to immune control [6]. The BBB acts as a strong immunological barrier and hampers the migration of leukocytes into the parenchyma, while the BCSF is regarded as a selective gate primarily responsible for immune surveillance in the CNS [3].

Step five is the phase of injury, hallmarked by a cascade of events. It starts with the direct cytopathic effect, and para- and post-infectious inflammatory responses follow [13]. These responses are unique for specific viruses [3], and are influenced by viral tropism [2]. Viral tropism is the specificity that a virus has for a specific cell type of the host. Neurotropic viral tropism is summarized in Table 4.3 [2]. As an example, John Cunningham virus affects the oligodendrocytes [2], and therefore myelin production is compromised and

Table 4.3 Viral tropism in the central nervous system

Region or component of the central nervous system affected	Viruses
Meninges	Human enteroviruses
	Human immunodeficiency virus-1
	Japanese encephalitis virus
	Lymphocytic choriomeningitis virus
	Measles virus
	Mumps virus
	Nipah virus
Cortex	Alphaviruses
	Bunyaviruses
	Herpes simplex virus
	Japanese encephalitis virus
	Measles virus
	St. Louis encephalitis virus
	Tick-borne encephalitis virus
	West Nile virus
Cerebellum	Epstein-Barr virus
	Human enteroviruses
	West Nile virus
	Varicella-zoster virus
Brain stem	Human enteroviruses
	Poliovirus
	Rabies virus
	West Nile virus
Thalamus	Human enteroviruses
	Rabies virus
	West Nile virus
Hippocampus	Human enteroviruses
	Rabies virus
	West Nile virus
Choroid plexus/Ependyma	Cytomegalovirus
	Human enteroviruses
	Lymphocytic choriomeningitis virus
	Mumps virus
Oligodendrocytes	John Cunningham virus
Microglia	Human immunodeficiency virus
Anterior horn of the spinal cord	Human enteroviruses
	Japanese encephalitis virus
	Poliovirus
	Rabies virus
	Tick-borne encephalitis virus
	West Nile virus

Adapted from Swanson and McGavern [2] and Glaser et al. [7]
The viruses are listed in alphabetical order within each region or component

white matter is affected. Viruses that affect the temporal lobe are HSV, VZV, Epstein-Barr virus and HHV-6 [7].

The cytopathic effect of viruses elicits not merely brain inflammation, but intense brain inflammation with breakdown of the BBB, allowing further entrance of viruses; in addition, the repair mechanisms are restricted [2]. Due to the limited blood supply the brain depends more on cell than on humoral-mediated immunity. The interstitium is constantly patrolled by microglia and antigen presentation is weakly developed [2]. Apoptosis follows and the inflammation intensifies [2]. The cascade may further be complicated by autoimmune mediated mechanisms [13].

4.6 Clinical Manifestations

Viral infections of the CNS result in a spectrum of complex neurological syndromes and therefore clinical manifestations must always be interpreted in the context that relates to the specific patient, considering demographics, epidemiology and individual immune status.

4.6.1 Meningeal Irritation

Signs of meningeal irritation include neck stiffness, photophobia and a positive Kernig or Brudzinski sign [6, 11].

4.6.2 Encephalopathy

Encephalopathy is a change in the mental state of a patient characterized by an altered level of consciousness, and may refer to anything on the continuum from lethargy to coma, with alterations in the behavior or personality [4, 5, 9]. It is the result of diffuse cortical involvement [4]. A new-onset psychosis is more likely associated with an autoimmune encephalitis than with a viral infection [7].

4.6.3 Focal Neurological Signs

Focal neurological signs depend on the specific areas of the CNS that may be affected. Focal cortical signs may include, for example, aphasia, alexia or cortical blindness. If the motor area is affected motor weakness may be present, and abnormal sensation is experienced in the case of an affected sensory cortex. Cranial nerve fallout and visual defects are common. Deep tendon reflexes may be either absent or brisk, and primitive reflexes may appear. Cerebellar involvement will manifest as nystagmus, dysmetria, ataxia and dysdiadochokinesia [4].

4.6.4 Raised Intracranial Pressure

It is of utmost importance to diagnose raised intracranial pressure (ICP) clinically. The pressure may be normal in viral meningitis [24], but elevated in encephalitis [25]. Infants may have a bulging fontanel, splayed sutures, sunsetting eyes, vomiting, severe irritability or lethargy that may progress into coma [24]. Older children may have headache, vomiting, cranial nerve IV or VI palsies, a Cushing triad (elevated blood pressure with a slow pulse and respiratory slowing, coma and papilledema) [24]. Papilledema can take days to develop and may be absent in the initial stages. For less experienced clinicians it may be difficult to identify papilledema as a sign of raised ICP. When this is the case it may be helpful to assess the posturing (decorticate or decerebrate), respiratory patterns and pupillary responses [13, 25].

4.6.5 Seizures

Seizures are common in viral encephalitis and are often subtle, but intractable [7]. Such cases may evolve into status epilepticus and even non-convulsive status epilepticus [10]. If a patient presents with a new-onset status epilepticus a viral cause should be considered [7]. Patients with viral encephalitis may have electroclinical dissociation, so that motor activity during the seizure is not visible, and can be detected only with an EEG [10]. Other subtle clinical signs of seizures are a bitten tongue, injuries, and twitching of an eyelid or corner of the mouth [10]. Failure to control the seizures inevitably increases the metabolic activity, resulting in acidosis with vasodilation and increased ICP [13].

4.6.6 Acute Flaccid Paralysis

Flaccid paralysis occurs if the anterior horn cells are affected, and is associated with polio, enterovirus-71 and flaviviruses [10, 12]. Rabies also presents with a rapid ascending weakness [26].

4.6.7 Systemic Involvement

Many viruses cause multi-system involvement, so a careful examination should always be made for possible associated manifestations. This may assist the clinician in the selection of appropriate special investigations.

4.6.7.1 Skin Manifestations

A variety of skin manifestations are associated with neurotropic viruses. A vesicular rash is found with HSV and VZV [27]. Enteroviruses and coxsackie virus may also have an accompanying rash on the palms of the hands, soles of the feet and inside of the mouth [27]. Inflamed oral mucosa, referred to as herpangina, is often associated with coxsackie virus, HSV and adenovirus [27]. A slapped cheek appearance

in association with fever and headache is due to fifth disease, also called erythema infectiosum, caused by human parvovirus B19 [28]. Roseola infantum (sixth disease) has a morbiliform rash and is caused by HHV-6 [29]. An eschar from a tick bite may be hidden in the hairline or groin, between the fingers or toes, or even in the ear canal. Measles has a typical maculopapular rash [10].

4.6.7.2 Cardiac Manifestations

Cardiac manifestations in patient with CNS viral infections can be either primary or secondary phenomena. Primary cardiac involvement is caused by viruses with both neurotropic and cardiotropic features causing myocarditis. These cardiotropic viruses are EV, coxsackie virus, adenovirus, HIV, human parvovirus B19, HHV-6 and Epstein-Barr virus [30]. Hypotension and arrhythmias may be the result of brain stem encephalitis or be a subtle manifestation of seizures.

4.6.7.3 Respiratory Symptoms

Paramyxoviridae and influenza viruses may cause encephalitis preceded by respiratory symptoms [10] This was initially believed only to occur on rare occasions [7], but it has become evident that respiratory viruses are increasingly becoming relevant in the context of CNS-associated infections. Coronavirus, responsible for 20% of common colds, has been linked to fatal encephalitis in a child who was immunocompromised [31].

4.6.7.4 Gastrointestinal Symptoms

Enteroviruses, human parechovirus and rotavirus cause gastrointestinal symptoms and may also affect the CNS. Mumps is often associated with parotitis and abdominal pain due to pancreatitis and orchitis [13]. Patients with CMV and Epstein-Barr virus-associated hepatitis may have elevated liver enzymes [13].

4.6.7.5 Myositis

Myositis is a common symptom in influenza infections [10].

4.7 Differential Diagnostic Considerations

The diagnosis of CNS viral infections and confirmation of a specific etiology is a tedious process often veiled in both clinical and diagnostic uncertainties. Alongside the bed of a gravely ill patient with suspected CNS infections where the clinician is awaiting confirmatory results, it is inevitable that other differential diagnoses should be considered and excluded. The background information, history and clinical examination are crucial. The key questions necessary to draft a list of possible etiologies are [10]:

- What is the age of the patient?
- Where does the patient live?
- Is the child vaccinated?
- Is the child immunocompromised?
- Are other children affected?

- Is there a travel history or any possible exposure to ticks and mosquitoes?
- Which sites of the CNS are involved? [10]

Table 4.1 summarizes the viruses present in different geographical areas and the clinical manifestations associated with them [1, 10], and may guide clinicians towards possible etiologies.

In a child with an encephalopathy four groups of conditions should be excluded, namely infections outside the CNS, toxins, autoimmune and metabolic disorders [10]. Persistent metabolic acidosis may be a clue to an underlying metabolic disorder, because respiratory acidosis is the consequence of hypoventilation associated with a decrease in the level of consciousness [13]. Encephalopathy associated with a movement disorder is uncommon in uncomplicated viral encephalitis. Where it is present, autoimmune encephalitis, ADEM, streptococcal infection or mycoplasma infections should be considered.

The differential diagnoses for a lymphocytic pleocytosis in the CSF or aseptic meningitis are partially treated meningitis, tuberculous meningitis, HIV encephalopathy or – often overlooked – neighborhood syndrome frequently associated with mastoiditis. A lymphocytosis in the blood supports a viral etiology [13].

When there is cranial nerve involvement in a patient with encephalopathy, HSE, tuberculous meningitis, raised ICP, Bickerstaff (brain stem) encephalitis or Miller Fischer syndrome should be considered.

Hydrocephalus is not associated with encephalitis, but rather a complication with meningitis caused by other bacteria, tuberculous, fungi or cryptococcus [7].

4.8 Diagnostic Procedures and Special Investigations

Brain biopsies have been the gold standard for confirming viral encephalitis, but they are invasive and unfeasible in most centers. Various other investigations have thus been developed for use in the first tier of investigations. A stereotactic brain biopsy has a place only if a diagnosis remains unable to be confirmed after a week and other alternatives have been considered, and then only provided it is performed by an experienced neurosurgeon [10].

To make an accurate diagnosis, the interpretation and integration of different test results should be done with caution, as there is no single solution that addresses all possibilities, and every modality has its limitations. Furthermore, interpretation of test results should always be correlated with the patient's clinical condition, and CSF analyses, done in the acute phase, should be paired with those done in the convalescent phase [20].

4.8.1 Lumbar Puncture

It is relatively easy to collect CSF, but always exclude any contraindications before it is performed. These contraindications are summarized by Kneen et al. and Boyles

et al. [10, 32]. The first group of contraindications, which necessitates imaging before an LP, includes the following:

- A change in the level of consciousness, or coma. There is no consensus on the depth of the coma, but the British Guidelines recommend that prior imaging is indicated if the Glasgow coma scale is less than 13 or fluctuates more than 2 [10]
- The presence of papilledema. Clinicians should bear in mind that papilledema may take time to develop, and will not be observed in the initial clinical assessment [32]
- Relative bradycardia in the presence of hypertension or abnormal doll's eye movements [10]
- New-onset focal neurological deficits including unequal, dilated or poorly responsive pupils [10, 32]. If the level of consciousness is normal, isolated cranial nerve palsies are, however, not regarded as a contraindication to performing an LP [32]
- Inexplicable seizures. These should first be stabilized [32] and stabilization should be followed by imaging
- Patients with ventriculoperitoneal shunts in situ [32]
- Immunocompromised patients [10].

If a computed tomography (CT) scan reveals midline shifts or narrow basal cisterns associated with space-occupying lesions or brain edema it is dangerous to perform an LP as it may precipitate brain stem and/or tonsillar herniation [10]. It is very important to remember that CT scanning cannot be used to rule out raised ICP; this remains a clinical diagnosis [10].

Other contraindications to LP include:

- Underlying coagulation disorders with unexplained bleeding from mucous membranes, a petechial rash, expanding purpura or other features associated with disseminated intravascular coagulopathy [32]. Although a platelet count $<100 \times 10^9$/L is used as a cut-off point, an LP may still be possible after careful consideration if the platelet count is 50×10^9/L [10]
- Sepsis in the area of the LP site
- Hemodynamic instability with shock and respiratory insufficiency [10, 32].

If an LP cannot be performed, the patient must be reviewed every 24 hours and then the LP must be performed as soon as the contraindications are cleared [10]. If the analyses of the CSF obtained with the first LP are non-diagnostic, the LP should be repeated 24–28 hours later [10].

4.8.2 Cerebrospinal Fluid

The analyses of CSF include assessment of the opening pressures, the biochemistry, the different cell types and the microbiology [10]. The normal opening pressure is 10–20 cm H_2O, but this can be normal or mildly elevated in viral encephalitis [10].

4.8.2.1 Biochemistry

The brain is protected by the BBB and therefore the CSF is merely an ultrafiltrate of plasma filtrates across the BBB, containing water, electrolytes, glucose and protein – mostly albumin because of its low molecular weight. The protein concentration of the CSF is very low in comparison to that of the serum. Under normal conditions albumin is 50% of the total protein in the serum, but the major protein in CSF. Immunoglobulins may be present in the CSF of normal individuals with an intact BBB, in which case the immunoglobulin G (IgG):total CSF protein is in the order of two thirds of the serum IgG:total protein. The CSF protein concentration increases either when the BBB is damaged or when intrathecal IgG production occurs. Various indices help in determining whether the BBB is intact and in ascertaining the contribution of intrathecal IgG synthesis. It is important that serum and CSF are sent to be analyzed simultaneously [33].

High resolution electrophoresis and isoelectric focusing are techniques to determine protein bands in specimens. Normal individuals will have no bands in the CSF that do not correspond to bands present in the serum. If there is intrathecal IgG production then additional bands will be detected in the CSF, and if two or more different bands are present these are known as oligoclonal bands. If the BBB is damaged it may help create additional bands. To distinguish between intrathecal IgG production and the contribution from IgG in serum that might have leaked across the BBB, four indices are helpful provided that the tap is not traumatic: the albumin index (Q_{Alb}), IgG index, IgG synthesis rate and local IgG synthesis [33].

Albumin is not produced intrathecally and therefore the ratio of CSF to serum albumin concentration, or Q_{Alb}, is constant in healthy individuals, and less than 9.0. When the BBB is damaged albumin leaks into the CSF and the albumin concentration increases. The Q_{Alb} reflects the degree of damage: if it is more than 100 then there is almost total breakdown of the BBB [33].

The IgG index or quotient (Q_{IgG}) is the CSF:serum IgG ratio, and can be elevated with either intrathecal IgG production or BBB damage; the Q_{Alb} is normal in the case of the former and elevated in the case of the latter.

The IgG synthesis rate is a formula for calculating the amount of intrathecally produced IgG by correcting for differences in molecular weights, daily CSF production and possible serum IgG in the event of the BBB being damaged. The reference range is −9.9–3.3 mg/day, but false elevated levels may occur if the BBB is damaged [33].

Local IgG synthesis calculation is valuable because the diagnostic sensitivity is high and the false positive rate is low. It is used to determine the minimum amount of local synthesis in the CNS. Any value above the upper limit of normal (0.0 mg/dL) in conjunction with an elevated Q_{IgG} is strongly suggestive of increased intrathecal IgG synthesis [33].

The biochemical analyses of the CSF also include lactate and glucose in addition to the determination of protein. The glucose has to be compared to a plasma glucose which should be taken before the LP [10]. For viral-related CNS infections the protein is normal or mildly elevated (<0.95 g/L), the glucose ratio normal or decreased

(normal = >0.4–0.5), and the lactate normal. Albuminocytologic dissociation (elevated protein and normal CSF cell count) is a strong marker for acute and chronic demyelinating polyneuropathies, but may be detected only after at least 1 week of illness [34].

4.8.2.2 Cell Types

There are immune cells in the CSF of healthy persons, but in limited numbers [3]. The majority of the cells are $CD3^+$ memory T cells, $CD4^+$ and $CD8^+$ cells. The group of B-cells, natural killer cells, dendritic cells, mast cells, monocytes and polymorphonuclear granulocytes is in the minority and makes up not more than 20–30% of the immune cells [3]. CSF leukocytosis is an indicator of an inflammatory process [4, 7, 9], but the composition of cells changes constantly during the disease progress and is also influenced by the primary site of infection [3]. An increased number of leukocytes is more likely in viral meningitis than in encephalitis [3]. If the primary site is the meninges the number of leukocytes in the CSF is increased, with polymorphonuclear granulocytes the dominant cell type early in the disease, followed later on by monocytes and lymphocytes [4, 10]. In encephalitis the CSF may be normal in up to two thirds of cases [3]. Sejvar et al. define CSF pleocytosis as >15 cells/mm^3 in babies less than 2 months of age and >5 cells/mm^3 in older infants and children [4]. However the CSF may also be completely acellular, and this has been associated with VZV, Epstein-Barr virus and CMV infections. It is also often observed in immunocompromised patients [10].

Red blood cells (RBC) are elevated in approximately 50% of HSE cases [10]. The differential diagnoses for an elevated RBC include a traumatic tap or subarachnoidal hemorrhage. In the case of a traumatic tap, corrections should be made for the protein and cell counts [10]. Although more complicated formulae adjusting for anemia and peripheral leukocytosis are available online at http://reference.medscape.com/calculator/csf-protein-concentration-correction, a simplified way to correct for the influence of a traumatic tap is to subtract one white blood cell for every 700 RBC/mm^3 and 1.1 mg/dL protein for every 1000 RBC/mm^3 [35, 36].

4.8.2.3 Microbiology

Microscopy, culture and sensitivity for bacteria should be performed on all CSF samples. Antigen detection may also be helpful [10]. Testing for *Mycobacterium tuberculosis* should always be considered in endemic areas and in immunocompromised patients [10]. Specific virological studies on CSF depend mainly on epidemiology. It is advisable to keep and store an extra CSF sample if further specific investigations are indicated [10, 20]. Viral cultures nowadays play an inferior role in the identification of the viruses, because they are costly and have a low yield [20]. They are still used to serotype enteroviruses [20].

Polymerase chain reaction (PCR) has changed diagnostic virology because it can detect low copy numbers and has a high sensitivity in the detection of viruses, but the diagnostic window has not been clearly described for viruses other than HSV [37]. Despite this a CSF specimen for HSV-1, HSV-2, VZV and enteroviruses should be sent for PCR for patients with suspected viral CNS infection, as it will

identify 90% of known viral causes. A HSV PCR is often negative for the first 3 days after the onset of the disease [32], and then remains positive for the next 7–10 days even if acyclovir treatment has been started [10]. The probability of getting a positive PCR is thus reduced if the sample is taken early (that is, within 3 days) or late (after 14 days) in the course of the disease [37]. It may be worthwhile to defer the initial LP for two reasons: if there is a contraindication for the LP due to severe cerebral edema, and to give time for the edema to subside and the PCR to have a better diagnostic yield. There is a correlation between viral replication, degree of clinical severity and the possibility of a positive PCR.

Furthermore, a positive PCR result should be interpreted with caution, because three different scenarios should be considered: firstly a primary infection, secondly the reactivation of a latent infection, and thirdly concomitant infection that may stimulate reactivation of a latent virus [20]. The fact that more than one type of virus can be in the brain simultaneously, and that there can be an interplay between them, complicates matters further [20]. False positive and negative results are always an issue of concern, and therefore it is important to standardize the molecular diagnostic tests. This is illustrated clearly in a study that examined nine different European reference laboratories and found concordant results in only 28–32% of specimens tested for HSV by PCR, whereas real-time PCR has 94% specificity and almost 100% sensitivity [38].

The selection of additional microbiological investigations is directed by the clinical features, travel history and local epidemiology [10]. Virus cultures or PCR on samples from other sites are useful in specific cases. Rectal and throat swabs should be investigated for enteroviruses in all cases of encephalitis [10]. For respiratory viruses, a PCR on throat swabs or sputum is indicated if a patient has had a recent respiratory infection [10].

4.8.2.4 Cytokines, Chemokines and Associated Mediators

There is a constant drive to explore novel ways to assist in the diagnosis of encephalitis and to differentiate between infectious, immune-mediated and unknown etiologies. Although a detailed discussion of the diagnostic value and role of mediators in CNS infections falls beyond the scope of this chapter, it has been shown that the cytokine and associated mediator profiles particularly, differ in the CSF of patients with an underlying infection and of those with an immune-mediated pathology [39].

Cytokines are polypeptide messengers and important regulators in a variety of biological processes, but particularly of importance in proinflammatory and anti-inflammatory processes [3]. Four groups of cytokines have been identified. The first group (interleukin (IL)-1, IL-5, IL-6 and IL-8) is involved in innate immunity, the second group (IL-1, IL-4 and transforming growth factor (TGF)-ß) orchestrates inflammatory processes, the third group (IL-2 and IL-4) is responsible for the activation and proliferation of lymphocytes and the fourth group (IL-1, IL-3, IL-5, IL-6) is involved in leukocyte growth [3]. Chemokines are specific cytokines involved in the attraction or trafficking of other cells. There are four subgroups, CXC, CC, XC and CX3C [3].

4.8.3 Serology

Although serology, in practice, refers to the antibodies in the blood, in the context of CNS viral infections the CSF antibodies are also measured and interlinked with the serological diagnosis of viral infections. Serology in general is of limited value unless serial samples are analyzed and serum and CSF results are compared. Antibody production is a dynamic process. It takes 10–14 days for antibodies to become positive initially, and then antibodies steadily rise to peak production and remain positive for years in latent infections [10, 20].

There are certain specific scenarios where serology is beneficial. The presence of Immunoglobulin M (IgM) in CSF is an indication of an intrathecal antiviral immune response and is more useful in RNA viruses, such as flaviviruses, which are usually primary infections and not merely reactivations of DNA virus-associated disease [10]. The serological investigations for Epstein-Barr virus or arboviruses are useful if any of these are suspected as the cause of CNS infection [10]. In the case of Eastern equine encephalitis, serum antibody testing is most helpful, as the disease can be detected within 6 days of onset, and increases fourfold in just 4 days [40]. As seroconversion is a dynamic process, serial specimens should be analyzed and the results should be paired with the CSF results [20]. The interpretation of CSF serology is discussed in Sect. 4.8.2.1.

4.8.4 Imaging

Acutely ill patients with the possibility of a CNS infection are usually imaged to exclude other possible causes or complications, but the limitations of imaging should always be kept in mind. A recent study by Granerod et al. shows that there is a “subjective component to scan interpretation”. The matter is further complicated by the fact that imaging data are also influenced by the timing of the scan and the specific imaging techniques. These factors directly influence the value of imaging among diagnostic criteria for encephalitis, other than HSE, based on radiological abnormalities. Further research in this area is required [41].

4.8.4.1 Computed Tomography of the Brain

It is common practice to perform a CT brain scan before an LP is performed if there is any doubt about relative contraindications. An LP should not be performed if there is overwhelming brain edema with swelling, or any midline shifts or space-occupying lesions [32]. A normal CT brain scan is, however, not a guarantee that the ICP is normal [32]. In the case of HSE, a first CT scan may also be normal, with abnormalities detected only in a follow-up scan [10].

4.8.4.2 Magnetic Resonance Imaging

Under ideal circumstances an MRI scan should be performed on all patients with suspected encephalitis within 24–48 hours after admission to hospital [10]. For specific details, refer to the different sections on clinical syndromes of viruses.

4.8.5 Electroencephalogram

An EEG is not routinely done on all patients with suspected encephalitis, but is useful to confirm encephalopathy and to exclude possible psychiatric conditions as an alternative reason for associated behavioral changes [10]. It is also important to detect seizure activity in subtle or non-convulsive seizures [10], because seizure activity has a significant effect on the development of brain edema and worsens coma. A recent study by Mohammad et al. shows that an early EEG is a non-specific marker for encephalitis and has a high sensitivity, as 86% of patients in the study had abnormalities on their first EEG [42].

The general characteristic EEG features of encephalopathy are slowing and focal or generalized epileptiform features [25]. More specific patterns have also been described. Periodic lateralized epileptiform discharges have been regarded as pathognomonic for HSE, but it may also occur in patients with SSPE [10]. An early reactive EEG background and extreme spindles have been associated with anti-NDMAR encephalitis [42].

EEG has some prognostic value in encephalitis. A normal EEG in patients with suspected encephalitis is associated with a low relative risk for death [43], but a non-reactive background in an EEG performed early in the disease predicts abnormal outcome [42].

4.8.6 Additional Investigations

It is advised that HIV must be excluded in every patient with encephalitis for a number of reasons. Patients may present with acute meningoencephalitis during the primary HIV-1 infection or longstanding encephalopathy. HIV predisposes the patient to other rarer CNS infections, such as CMV, and the incidence of common CNS infections is higher in HIV-infected patients [10]. Other additional investigations are selectively requested on the basis of specific systemic involvement.

4.9 Treatment

4.9.1 General Measures

Ensure that the patient is hemodynamically stable and treat hypoglycemia, which is often present in viral encephalitis, instantly [13]. Treat seizures and raised ICP according to standard protocols [13], but because the pathogenesis of raised ICP, associated with viral encephalitis, is different to that of other contexts, further studies are essential to investigate the efficacy of specifically edema-lowering modalities [44]. Observe for autonomic instability. While results are pending treatment should be administered without delay and should include broad-spectrum antibiotics, often a third-generation cephalosporin and acyclovir [13].

The role of steroids as adjuvant therapy for HSE is still controversial, and steroids should thus not be administered routinely [10]. Results are currently awaited from a multicenter, multinational, double-blind placebo-controlled European study known as the German Trial of Acyclovir and Corticosteroids in HSE [45].

4.9.2 Antiviral Treatment

Empirical treatment with intravenous acyclovir should be started sooner rather than later, and within 6 hours of hospital admission, if viral encephalitis is strongly suspected [10]. This is usually combined with a third-generation cephalosporin for possible bacterial meningitis. There are two treatment categories. In neonates a higher dosage of acyclovir, 20 mg/kg per dose 8 hourly, is administered and if HSE is confirmed it is continued for a period of 21 days [46, 47]. In children of 28 days to 16 years, acyclovir should be started at 10 mg/kg 8 hourly IVI and continued for 14–21 days if HSE is confirmed, and then the LP should be repeated to confirm that the CSF PCR is negative for HSV [10, 46]. If the PCR is positive in the repeat LP, acyclovir should be continued and PCR should be performed weekly until it becomes negative [10]. The dose should be reduced for patients with renal impairment [10].

The next question to be answered is when the acyclovir can be stopped if the patient with the suspected encephalitis has a negative HSV PCR. If the patient is immunocompetent it can be stopped as soon as another diagnosis has been confirmed, or when the HSV PCR has been negative on two LPs, performed 24–48 hours apart and there are no HSV-associated characteristics on the MRI at least 72 hours after the onset of the disease [10]. In a case where the LP has been deferred for some reason, acyclovir has been started empirically and the patient has subsequently improved, the acyclovir can be stopped if the level of consciousness is normal, both the HSV PCR and the MRI performed 72 hours after symptom onset are normal, and the CSF white blood cell count is less than 5×10^6/L [10].

An alternative, simplified regime for HSE involves administering acyclovir intravenously at 10–15 mg/kg per dose 8 hourly for 21 days [6]. It has also been suggested that all patients should have a CSF HSV PCR negative to confirm that treatment can be stopped [47]. Some patients have benefitted from a second course of acyclovir, which supports the hypothesis that the virus has not been completely inactivated and it may be related if a shorter course of acyclovir has been given [48]. Suppressive acyclovir treatment for a period of 6 months has been associated with less damage and fewer episodes of recurrence [6]. It is most likely that patients with post-infectious encephalopathy will benefit from steroid therapy rather than acyclovir [49].

Oral acyclovir cannot be used for HSE, because it does not reach adequate levels in the CSF. Valacyclovir has been used orally in children after 10–14 days of intravenous acyclovir when venous access became problematic, but it is not registered for use in children and further research is required [10].

In the case of VZV encephalitis the dose is higher, namely 15 mg/kg 8 hourly for 14 days in all age groups. Treatment should be continued if the patient is immunocompromised [10]. VZV cerebellitis does not require treatment, because it is a self-limiting disease resolving within 3 weeks [10], but if vasculopathy is present corticosteroids are indicated [10].

Enterovirus encephalitis is not routinely treated, but intravenous immunoglobulin has been used in patients with chronic enterovirus meningitis or severe enterovirus-71 infection [10]. Treatment protocols for CMV encephalitis have not been well established, but ganciclovir, foscarnet and cidofovir have been studied in open-label studies [10].

4.9.3 Treatment of Autoimmune Encephalitis

Evidence for specific protocols is still lacking, but aggressive treatment in the acute phase includes intravenous steroids, plasma exchange or immunoglobulins. Such treatments are then followed up with oral steroid and corticosteroid sparing drugs, for example azathioprine and cyclophosphamide [10, 13].

4.9.4 Novel Therapies

There is a constant search for novel drugs in the treatment of viral-related CNS infections and a detailed discussion falls beyond the scope of this chapter, but there are a few interesting ideas that deserve mention. Nucleotidyltransferase superfamily enzyme inhibitors have been identified as a potential novel treatment for HSV infections and suppress the replication of the virus [50]. Significant advances in gene editing have been made and include three possible strategies in antiviral drug development: zinc-finger nucleases, transcription activator-like effector nucleases and clustered regulatory interspaced short palindromic repeat-associated nine systems [51].

4.10 Complications and Prognosis

The complications and prognosis vary in the different clinical syndromes of CNS infections due to viruses [52]. The mortality rates for encephalitis vary between five and 15% [52]. The morbidity for encephalitis in adults has been reported as 20% [52].

In the acute phase status epilepticus, coma, thrombocytopenia, hyponatremia as a result of inappropriate secretion of antidiuretic hormone, and cerebral edema are serious complications. Cerebral edema is the result of direct viral infection, for which enteroviruses are known, or for seizure activity. Both the seizure activity and accompanying hypoxia in untreated convulsive status epilepticus may contribute to the maintenance of a vicious cycle of continued cell damage.

A number of studies identify prognostic factors in the acute phase. Cerebral edema, status epilepticus and thrombocytopenia were associated with in-hospital mortality [52]. Additional poor prognostic factors are a lower level of consciousness on admission, hypothermia and elevated CSF protein [52]. The presence of glial and neuroaxonal protein in CSF are indicative of inflammation and neuronal damage and are potential biomarkers to determine prognosis [52]. Lower quality-of-life scores have been found in patients who had abnormal MRI findings or were admitted with seizures that resulted in epilepsy [53]. A normal EEG has been associated with survival [52].

Long-term outcomes are not always very well described or quantified, but an Israeli study found attention deficit hyperactivity disorder and behavioral disorders each to be present in 50% of individuals, with 10% of patients showing residual motor deficits. It has also been documented that cognition was affected [52]. Other long-term sequelae are spasticity, epilepsy, movement disorders and feeding difficulties [13]. A systematic review and meta-analysis by Khandaker et al. concluded that almost 50% of children show incomplete recovery, and the sequelae are developmental delay, behavioral disturbances and other neurological complications, including seizures [54]. Patients treated for anti-NDMAR encephalitis in the acute phase generally have good outcomes, but 50% may experience complications from chronic use of immunotherapy [55]. It has been shown that there is a relationship between patients readmitted after the acute illness and the development of neurological sequelae, as well as between the later onset of epilepsy in patients with neurological sequelae [56].

4.11 Prevention

The first and foremost preventative strategy is to avoid exposure. Hygiene is important in such avoidance. Protection against vectors includes the wearing of protective clothing, control of breeding sites and use of insect repellents [57, 58], although insect repellants are not always effective anymore. Insects become insensitive to insecticides, and climate variability and change in vegetation influence the survival of arthropods [58].

The second important strategy in the prevention of CNS viral infections is vaccination. There are vaccines available for mumps, measles, rubella, influenza, Japanese encephalitis virus, rabies and tick-born encephalitis virus [5]. A group of researchers has however found that the current vaccine against Japanese encephalitis virus may not protect against a the new emerging G5 strain of the virus [59]. A new vaccine against enterovirus 70 and 71 has been proven successful [6]. The biggest threat to successful prevention through vaccination is low vaccination coverage due to religious beliefs, mistrust and inadequate vaccination programs as a result of many different reasons [58].

The majority of vaccines are against communicable diseases and very few exist for use against arboviruses [58]. In response to this problem scientists are investigating different innovative strategies. Most of these are aimed at preventing the

virus from completing its life-cycle in the vector, ultimately preventing transmission to humans. These vaccines are called transmission blocking vaccines [58]. One example is dengue virus vaccine. The proteins required in the mosquito for the attachment of the virion to target cells in its midgut, are used in the vaccine as antigens. When a mosquito feeds on a vaccinated human, the antibodies are ingested and subsequently impair the virion attachment in the mosquito, interrupting the completion of its life cycle. This blocks any further transmission by preventing infection of the vector. This type of vaccine is referred to as an "altruistic" vaccine because, while it may not protect the person who has been vaccinated from infection, it prevents the disease from spreading to other members of the community [58]. Significant advances have been made in development of transmission blocking vaccines to control viral vector-borne disease, but further research is still required [58].

4.12 Specific Viruses

Specific characteristics and manifestations of the different viral families and relevant species are highlighted in this section.

4.12.1 Herpesviridae

The family *Herpesviridae* is a large family of double-stranded DNA viruses. The species commonly associated with CNS viral-related diseases are CMV, Epstein-Barr virus, HSV-1, HSV-2, HHV-6 and HHV-7 and VZV [3]. It must be noted that the test specificity for differentiating between the lymphotropic herpes viruses (Epstein-Barr virus, CMV, HHV-6) and neurotropic viruses (HSV, VZV), varies and is much better for the latter [60].

4.12.1.1 Herpes Simplex Virus

Herpes simplex viruses, including type 1 and 2 are the most common causes of sporadic encephalitis in children and one of the few treatable causes [8, 61, 62]. Schleede et al. report in their multicenter study that HSV-1 accounts for 97% of the HSE cases they studied and HSV-2 caused only 3% [62]. The morbidity and mortality are severe and the mortality rates vary from 11 to 19% [8]. Neonates are more affected by HSV-2, but HSV-1 is the predominate type in non-neonates [46, 62]. Males are more readily affected than females [63].

The virus migrates along the trigeminal or olfactory nerve to the brain and causes HSE predominantly affecting the temporal and frontal lobes of the brain. It results in focal neurological signs. HSV may remain latent in the dorsal roots of the sensory ganglia throughout life [3]. Two thirds of HSE case are not during the primary infection, but due to reactivation or reinfection [64].

The central chemokine receptors (CCR2, CCR5 and CXCR3) and related ligands (CCL2 and CCL5) are the main role players in the pathogenesis of HSV-1 infection

in humans [3]. The ligand CCL5 is presented by T-cells and macrophages which are important in leukocyte migration. In an experimental model for HSV-1 and autoimmune encephalitis, the interaction between CCL5 and CCR5 has played an important role in the recruitment of T-cells into the CNS [3, 65]. The chemokines CCL2, CCL5, CCL9 and CCL10 were elevated in the trigeminal ganglia and brain stems of $CCR5^{-/-}$ mice infected with HSV-1. The consequence was an increased viral load, followed by an increased $CD4^{+}$and $CD8^{+}$ infiltration in the respected areas [3, 66]. Interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are elevated in the CSF of patients with HSE and may contribute to demyelination [67].

The clinical presentation of children with HSE varies; de Tiège et al. summarize eloquently the spectrum of disease [63]. It can present with acute onset of fever, encephalopathy, seizures and focal signs, but sub-acute and milder forms have also been described [63]. The fever may be absent initially [63]. Opercular syndrome, hallmarked by dysarthria, dysphagia and oro-facial palsy, may also manifest [63]. In the California Encephalitis Project, two age groups in which HSE peaks were identified [68]. The first group includes younger children, from 6 months to 4 years, and the second peaked in the age group 10–18 years [68]. Lethargy, fever, confusion and seizures are the most common manifestations, but seizures are observed more commonly in the younger age group, and the difference is statistically significant [68]. In contrast to adults, children who develop encephalitis with primary HSV infection may be affected by herpes labialis [10]. Deaths observed in this project were all in children older than 13 years, but this point was not statistically significant [68].

Patients who have had HSE may find it recurs [69]. Such relapses may happen early, within weeks after the disease, or later, after months or years [70]. Relapse rates of up to 24% have been reported [62]. The reactivation of the virus is triggered by the release of corticosteroids under stressful conditions responsible for activating the c-Jun N-terminal kinases pathway. The methylation/phosphorylation switch is then switched on and viral gene expression can proceed [71]. Patients present with a variety of neurological symptoms, of which abnormal movement is the most common, present in 56% of patients studied by Schleede et al. Other important clinical manifestations are lethargy, seizures, hemiparesis and cranial nerve palsies [62]. Patients may have a negative HSV PCR during these episodes [69].

The CSF may be normal in up to 5% of patients, but protein may be elevated and continue to rise even after treatment has been started [46]. It may even stay elevated after the treatment is stopped [46]. In the California Encephalitis Project, only 47% of children with HSE had elevated protein in the CSF, while 95% of them had pleocytosis with a median of 47 cells/mm^3, and the median RBC count was only three cells/mm^3 [68]. De Tiège et al. note also that polymorphonuclear cells may predominate early in the disease process, and the disease may then be mistaken for bacterial infection [63]. The RBC may be elevated, reflecting underlying necrosis [63]. Glucose in the CSF may be normal or slightly decreased; 13% of patients in the Schleede et al. study had values <2.8 mmol/L [62].

The gold standard for diagnosis remains an HSV PCR [46, 72]. The PCR may be negative initially, but become positive if the LP is repeated 2–4 days later, with a median of 6 days after the onset of symptoms [68]. Multiple hypotheses have been

suggested to explain the false negative PCR. One of the reasons may be a very low viral load in the CSF at the onset of the disease [69]. A link between a negative PCR and low CSF protein and white cell count has also been described [69].

Fluid from vesicles may be sent for PCR if it is present in a primary HSV infection, but most cases of HSE and VZV encephalitis do not have skin lesions [20]. It is also true that a peri-oral vesicle does not mean the patient has associated encephalitis as well.

Serology is often not helpful to confirm a diagnosis in the initial stage, because it can take up to 2 weeks for HSV IgM to be produced intrathecally [73]. HSV IgG can be detected in the CSF 10–14 days after the onset of illness, then rises to peak at around 30 days and may be detectable for years after the disease [10].

Imaging, including CT and MRI scans, is helpful in the diagnosis. MRI is more sensitive, and 95% of patients in the California Encephalitis Project had abnormal MRI findings [68], but MRI findings may nevertheless be normal [62, 68]. Although temporal lobe involvement was present in 86% of patients, 59% had extra temporal lobe abnormalities either in association with temporal lobe abnormalities or in isolation [68]. T2-weighted images may demonstrate signal changes right at the onset, followed by diffusion-weighted changes visible 3 days after the onset of symptoms [62, 68]. Contrast enhancement in MRI becomes positive over a period of 4–90 days after the onset of symptoms. T1-weighted changes develop during the course of the illness and can be normal, high or low. Necrotic lesions develop later, at 2 weeks, after the onset of symptoms [62]. Neonatal MRI images differ from those of older children. The parietal lobes, occipital lobes and insula may be affected more frequently than the temporal lobes [62]. Diffuse white matter lesions occur in patients with relapse HSE [62].

The diagnosis is also supported by EEG. The most common finding in the California Encephalitis Project was the presence of multifocal or diffuse slowing in 53% of patients. Periodic lateralized epileptiform discharges were present in 13% of the cases, and focal epileptiform discharges were identified in 13% of patients [68].

Prompt treatment limits morbidity and mortality, but if HSE is left untreated the mortality rate is 70%, and only 2.5% of patients may recover completely [6, 61]. For a more detailed discussion of treatment refer to Sect. 4.9.2. It is documented that immunotherapy is 100% beneficial in the treatment of autoimmune post-HSE [74].

4.12.1.2 Varicella-Zoster Virus

A highly contagious virus, VZV presents with fever and a vesicular exanthema [1]. Two different disease patterns are recognized, namely chickenpox during the primary infection and shingles or herpes zoster during reactivation [75]. The rash may precede the CNS infection, but it may be completely absent or even appear later [10]. The CNS is involved in one to three in 10,000 clinical cases, and it manifests as encephalitis, vasculopathy or post-infectious immune-mediated cerebellar ataxia [1, 10]. The latter is often benign and self-limiting, but hydrocephalus may develop if the cerebellum is extensively swollen [10]. Around one third of arterial strokes in children can be associated with VZV; from 1 week up to 48 months after the rash,

patients present with acute-onset, but permanent, hemiparesis [10]. Other clinical features include transient facial weakness, chorea, seizures, and visual and speech disturbances [10]. The VZV PCR may be positive in only 30% of cases, but VZV IgG antibodies are positive in as many as 90% of cases. It is recommended that both assays are done [9]. The CSF IgG levels must be compared to serum VZV IgG to confirm intrathecal synthesis [10].

4.12.1.3 Cytomegalovirus

CMV is the HHV with the largest genome and affects mainly immunocompromised patients, with an expanded range of clinical manifestations including encephalitis, meningitis, extensive transverse myelitis and polyradiculomyelitis. The outcome is highly variable. The major sites of the brain that are affected are the basal ganglia, brain stem and diencephalon. Although astrocytes are commonly infected, almost all the other cell types in the CNS can be involved. Congenital CMV infection causes severe cerebral palsy, cognitive impairment and sensorineural deafness [75]. CMV can be treated with acyclovir, but the effectiveness in CNS complications is unclear.

4.12.1.4 Human Herpes Virus-6

There are two species of HHV-6, A and B, and these are important pathogens in both immunocompetent and immunocompromised patients [76], and are common in the general population, with 90% of the population already seroconverted at the age of 1 year [77]. These viruses have, in addition to lymphotropic and neurotropic features, the ability to be integrated into the telomeric regions of the chromosomes of the host and subsequently to be transmitted vertically with a Mendelian pattern of inheritance, via infected organs in organ transplantations, and transplacentally [76]. Babies with congenitally-acquired HHV-6 may exhibit an inability to control exogenous HHV-6 and may suffer from neurological symptoms [76].

There are three stages of disease manifestation. The primary infection is a febrile illness in infants, with fussiness and rhinorrhea and the possibility of encephalitis. The second stage is in children and adults, with roseola infantum (sixth disease), a common disease in childhood. The virus replicates in the salivary glands, is spread via saliva, and becomes latent in the monocytes and lymphocytes. In addition to meningitis and encephalitis, other diseases associated with HHV-6 are multiple sclerosis, temporal lobe epilepsy and status epilepsy. The third stage is due to re-infection or reactivation of the virus in immunocompromised patients [77].

The role of HHV-6 in the pathogenesis of seizure is currently being actively researched. Mohammadpour Touserkani et al. have conducted a meta-analyses and systematic review on this topic, and although there are interesting findings on potential mechanisms involving HHV-6, microglial cells, oligodendrocytes and the immune regulatory effect of astrocytes, further studies to validate the relationship are required [77]. It is however clear that HHV-6 may be present in 19% of children with febrile seizures and that some children with febrile-associated status epilepsy are infected with HHV-6 [77].

HHV-6 poses some difficulties to diagnose, because the viral DNA integrates into the host DNA and consequently high levels of HHV-6 DNA are detected in CSF, blood and plasma [78]. Treatment during the primary infection is not indicated, but ganciclovir and foscarnet may be used firstly, and cidofovir secondly, in reactivation of HHV-6 CNS infections [76, 79]. Another consideration to bear in mind is the fact that the unnecessary use of antibiotics and cortisone in a small child with fever and a skin rash may aggravate viral replication. *In-vitro* experiments have shown that amoxicillin, carbamazepine and valproate activate HHV-6 and cortisone my increase the viral load in CSF [76].

4.12.1.5 Epstein-Barr Virus

CNS infection due to Epstein-Barr virus accounts for less than 5% of primary Epstein-Barr virus infections [75]. Epstein-Barr virus causes encephalitis and encephalomyelitis in teenagers in the absence of the typical infective mononucleosis features, but it may also occur shortly before, or after, infective mononucleosis [75]. Infections in the CNS may also be due to reactivation or post-infectious immune-mediated responses [75]. Visual hallucinations may be a specific characteristic in association with other signs of encephalitis [10]. The outcome varies, and patients with isolated gray or white matter lesions recover well, but almost half of patients in whom the thalami are affected will have residual effects, and the highest mortality is among patients with brain stem involvement [75].

4.12.2 Polyomaviridae

John Cunningham virus is a double-stranded DNA virus from the family Polyomaviridae [3]. Infection during childhood is very common and usually asymptomatic [1]. It is postulated that the virus may persist as a latent infection in the kidneys or mononuclear cells, and then reactivate if the patient becomes immune suppressed [1]. The cerebral white matter is seriously affected, with patchy and confluent demyelination [1]. Other clinical manifestations include rapid neurocognitive deterioration, focal neurological signs, visual field defects and ataxia [1]. Patients may die within 6 months after the onset of the disease [1]. The diagnosis can be confirmed with CSF PCR or a brain biopsy [1].

4.12.3 Flaviviridae

Flaviviridae are single-stranded RNA viruses of which tick-borne encephalitis virus, Japanese encephalitis virus, Zika virus and West Nile virus (WNV) are responsible for severe CNS infections [3]. These viruses are transmitted through tick or mosquito bites and are therefore also referred to as arboviruses. The term "arbovirus" is an acronym for "**AR**thropod-**BO**rne" virus, including not only flaviviruses, but also other viruses, like chikungunya virus, from the family Togaviridae [58].

Outbreaks of WNV are increasing in Europe and North America, and a range of animal models have been studied to explain the pathogenesis. Although a range of cytokines and chemokines that are involved have been identified many questions remain unanswered, but the specific role played by IL-1ß in the attraction of immune cells and regulation of WNV-induced inflammation is unique, and deserves mention [3]. Only a small portion of patients infected with WNV are symptomatic; 20% develop a self-limiting flu-like disease and less than 1% develop neuroinvasive disease [80]. The clinical manifestations are meningitis, myelitis, encephalitis or an overlap syndrome, and they are worse in immunocompromised patients [80]. The use of WNV PCR for diagnostic purposes is limited, because the viremia is short and precedes the clinical features; therefore serology is the preferred diagnostic modality [80].

Although dengue viruses types one to four cause mainly arthralgia, hemorrhagic disease and a skin rash, they can occasionally cause CNS infection [10]. In most arboviruses serological testing is preferred, because the clinical symptoms follow only later, after the viremic peak [9].

CNS infection due to tick-borne encephalitis virus is common in Asia and Europe. Tick-borne encephalitis virus can be contracted not only through tick bites, but also through the ingestion of unpasteurized cow's or goat's milk from infected livestock [75]. The incubation period is only 3–5 days when ingested via the gut, but is 7–14 days after a tick bite. The majority of infections are asymptomatic or, at most, associated with flu-like symptoms, and the disease course can be mono- or biphasic. Meningitis, meningoencephalitis or meningoencephalomyelitis, as well as cardiac arrhythmia and autonomic instability, may occur. The Siberian subtype is associated with chronic manifestations that affect cognitive function, hearing, vision and balance, and that may also cause psychiatric disturbances or flaccid paralysis [75].

4.12.4 Paramyxoviridae

Mumps virus and measles virus are well known single-stranded RNA viruses from the Paramyxoviridae family that are encountered in children [3]. Other members of this group that may potentially affect the CNS are hendra virus and Nipah virus [75].

4.12.4.1 Measles Virus

Despite the availability of a very effective vaccine against measles, it still accounts for significant morbidity and mortality. The highest mortality is among girls, but boys are more readily affected by SSPE [81].

The infection presents with a skin rash and simultaneously the $CD8^+$ T cell-mediated clearance and adaptive immune response appear. Measles RNA persists after the virus has been cleared, and can be detected in blood, saliva, urine and lymphoid tissue for months [81]. The virus can spread across the synapses once in the neurons and accumulate mutations, and the infection then becomes chronic [81]. CXCL10 and CCL5 were identified as important role players in a mouse model, but the pathogenesis may further be influenced by the different CNS cell types, such as

astrocytes or microglia, involved [3]. Severe immunosuppression is present in the later stages of the disease [75].

Measles can affect the CNS in four different ways, namely primary measles encephalitis, postmeasles encephalitis, measles inclusion body encephalitis (MIBE) and SSPE [3]. MIBE is a late manifestation, 3–6 months after the acute episode of measles, in immunocompromised patients [75].

The disease mechanism for MIBE and SSPE is similar, affecting both the neurons and the oligodendrocytes in the frontal, occipital and parietal cortices and the thalami, pons and medulla [75]. It results in severe perivascular infiltrates, neuronal degeneration and gliosis [75].

It is unclear why the measles virus persists in patients developing SSPE years after an initial uneventful measles rash. Children who develop SSPE are usually between 5 and 15 years old, with males more affected than females [1]. Measles before the age of 18 months poses the greatest risk for developing SSPE [1]. The onset is unannounced, and hallmarked by behavioral changes, neurocognitive decline and movement disorders [1]. It is often associated with myoclonus, and the EEG pattern is fairly typical. The disease rapidly progresses to a vegetative state, and affected patients may die within months, and up to 3 years after the onset of the disease [1].

Apart from SSPE, measles virus RNA has been linked to range of other conditions namely multiple sclerosis, Paget's disease, otosclerosis, chronic active hepatitis, achalasia and Chron's disease [81].

4.12.4.2 Mumps Virus

It is astonishing, but little is known about the pathogenesis of mumps [75]. The classical picture is that of bilateral parotitis after 7–21 days' incubation, but in 30% of these cases CNS infection may occur [75]. Mumps encephalitis is characterized by perivascular demyelination in the cerebrum, cerebellum, brain stem and spinal cord. The basal ganglia may also be affected [75]. In children with mumps meningitis, in contrast to other causes of meningitis, there is an increase of IL-8, IL-10, IL-12, IL-13 and IFN-ɣ [3]. Mumps encephalitis is confirmed with a PCR on the CSF, and serum or saliva antibodies can provide supportive evidence [10].

4.12.5 Picornaviridae

The Picornaviridae are a family of RNA viruses that include human enteroviruses and human parechovirus, responsible for CNS infections and sepsis-like illness in children [82].

4.12.5.1 Enteroviruses

The nomenclature may appear confusing to non-virologists. There are four species of enterovirus, enterovirus-A to enterovirus-D [82]. Polio virus is an enterovirus-C species with three different serotypes, but a number of coxsackie-A viruses also belong to enterovirus-C. The nonpolio enteroviruses are enterovirus-A (including enterovirus-71 and several coxsackie-A viruses), enterovirus-B (including coxsackie virus-B

and all echoviruses) and enterovirus-D [75]. The recently described enterovirus-D68 has been associated with significant mortality and morbidity [82]. Enterovirus-A71, coxsackie virus-A9 and coxsackie virus-B are responsible for most of the CNS infections worldwide, and are associated with high morbidity and mortality [3, 82].

The clinical manifestations vary, including meningitis, encephalitis and meningoencephalitis [3]. Most of the experimental work done to determine the pathogenesis of nonpolio enterovirus CNS infection is done with coxsackie virus-B3. A key element in the cell migration across the BCSFB into the CSF is CCL12, a monocyte attractant. B-cells are also involved in the "Trojan horse" mechanism. In addition, the coxsackie virus-B3 infects neural stem cells and thus a viral presence persists [3]. There is a very low yield of positive enterovirus PCR in the CSF, but there is often a higher yield in throat swabs and stool specimens. The virus can often persist in the stools for weeks after a gastro-intestinal infection, therefore it is recommended that not only CSF but also peripheral sites are tested [9].

Before vaccination the poliovirus was the most common cause of anterior myelitis, responsible for the syndrome of poliomyelitis. It was regarded as epidemic in the developed world and endemic in the developing world, mostly affecting children between 6 months and 2 years [1]. Since 1974, enormous emphasis, initiated by the World Health Organization, has been placed on the eradication of vaccine-preventable diseases, including poliomyelitis. Although poliovirus has been controlled to a great extent worldwide, there have been outbreaks reported in Tajikistan, the Republic of the Congo and elsewhere [1]. Two poliovirus vaccines are available, oral (OPV) and intramuscular (IPV). In polio-endemic countries the WHO recommends a birth OPV dose, followed by a primary series of 3 OPV doses and at least one IPV dose. The primary series is administered from the age of 6 week, at 4 week intervals. The clinical presentation is fairly easy to identify, as patients present with typical lower motor neuron symptoms comprising asymmetrical flaccid paralysis, areflexia, fasciculations and wasting, while sensation remains intact and sphincter functions are not usually affected [12]. It is interesting that the weakness seldom progresses after the febrile illness has subsided [12].

4.12.5.2 Human Parechovirus

The usual presentations of human parechovirus are upper respiratory and gastrointestinal tract infections. In children younger than 3 months old, feeding problems and irritability are clinical signs of CNS involvement and which is usually associated with fever. Extensive subcortical white matter involvement has been observed in neonatal encephalitis, with meningothelial and vascular smooth muscles affected as proposed underlying mechanism for the fatal leukoencephalopathy. The exact pathogenesis of human parechovirus has not yet been explained [75].

4.12.6 Retroviridae

Both HTLV-1 and HIV are able to affect the CNS in numerous ways [3]. The CNS manifestations associated with HIV are often collectively referred to as

HIV-associated neurocognitive disorders [3]. During the primary infection a dual attack takes place; both the BBB is disrupted and the CNS is invaded via the "Trojan horse" mechanism for the viruses to migrate within the leukocytes to areas out of the reach of antiretroviral drugs. The virus can persist and replicate, causing long-term chronic disease [3] with a continuous process of monocyte migration, enhanced CCR2 expression on the HIV monocytes, increased levels of CCL2 in CSF, and subsequent migration of $CD14^+$ and $CD16^+$ monocytes into the CNS [3]. It is mandatory to test every patient presenting with suspected viral encephalitis for HIV [10]. A detailed discussion of HIV falls beyond the scope of this chapter.

4.12.7 Rhabdoviridae

Rabies is transmitted not only by infected dog or bat bites, but also through inhalation of droplets, infected donor organs [80] and open wounds if they are licked by a dog infected with rabies [2]. Rabies should always be considered in any child with a rapid progressive encephalitis [80]. As the incubation period can vary from weeks up to 1 year, with an average of 2 months, it may be difficult to link the disease to a specific contact with either bats or infected animals [75]. The prodromal stage is non-specific, with fever, malaise, headache, nausea with vomiting and the more characteristic feature of paresthesia or pain at the point of entry [80]. The disease course is rapid: more specific symptoms, including hypersalivation, agitation, hydrophobia and significant neck stiffness, develop to be followed by coma and subsequently death within 1–2 weeks [80]. The diagnosis relies on serum and CSF serology, but immunohistochemistry on skin may be helpful [80]. Post-exposure management is important and includes wound treatment, vaccination and immunoglobulin [21] as well as prophylaxis of contacts to minimize the risk of secondary transmission [80]. Death is almost 100% preventable if adequate post-exposure prophylaxis is applied [26].

4.12.8 Togaviridae

The chikungunya virus is a single-stranded RNA virus from the genus *Alphavirus,* with three different genotypes. The genotypes are associated with the region of origin: West Africa, East/Central/South Africa and Asia [3]. Several epidemics of this virus have been reported [3]. The CNS is not always affected, and its involvement has been documented in only 16.3% of patients, of which 55.1% presented with encephalitis. The chikungunya virus gains access to the CNS through the olfactory nerve. Although data form a mouse model indicated the upregulation of CCL2, IL-6 and TNF-α, the anti-inflammatory response of IL-4 and the immunosuppressive effect of IL-10, the understanding of the neuropathogenesis in chikungunya virus is still unclear [3].

4.12.9 Other

Both rotavirus, from the family Reoviridae and respiratory syncytial virus from the family Pneumoviridae, have been associated with encephalitis, but there is a controversy about their effect on the CNS [21]. Other rarer causes are adenovirus, erythrovirus B19, lymphocytic choriomeningitis virus, rubella virus and influenza viruses.

Influenza viruses are from the family Orthomyxoviridae, and have a wide range of clinical presentations that vary from very mild encephalitis to ADEM, posterior reversible encephalopathy syndrome, malignant brain edema syndrome and acute necrotizing encephalopathy [10]. Acute necrotizing encephalopathy is associated with influenza A and occurs in young Japanese children. There is a genetic predisposition and an autosomal dominant mutation has been identified. Patients have severe encephalopathy, with involvement of the thalami, brain stem and white matter [10]. The H1N1 influenza virus may cause encephalopathy, focal neurological signs, aphasia and EEG abnormalities [10].

4.13 Conclusion

A variety of viruses from different families, together with viral tropism, successively manifest in an extended spectrum of complex clinical syndromes influenced by the individual immune response of the host and the constantly changing environment, which is affected by globalization, natural disasters, war, availability and influence of health care services and increased population density. Although the outcome of viral encephalitis varies, the morbidity and mortality are significant. Prompt treatment with antiviral treatment may alter the outcome and is usually started empirically when viral encephalitis is suspected, but it is effective for HSV and, to a lesser extent, VZV. Aggressive treatment with immune modulating drugs has been successful in autoimmune-mediated encephalitides. The value of routine use of steroids in viral encephalitis is not clear. Prevention is an important aspect of virus management and the drive to develop new vaccines is ongoing and important. A viral etiology should always be considered in a severely ill child with CNS manifestations.

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Viral Cardiac Infections

5

Brian F. Birnbaum and Charles E. Canter

Abstract

Viral infections can affect the pediatric heart in a multitude of ways. The two most common viral cardiac processes are myocarditis and pericarditis. Numerous viruses have been implicated in these disease states. In addition to direct viral effects on the myocardium and pericardium, inflammatory mediators also play a role in these conditions. A high index of suspicion, thorough history and physical examination, along with directed laboratory testing, electrocardiography and echocardiography are necessary for the diagnosis and management of myocarditis and pericarditis. Occasionally, more advanced studies such as magnetic resonance imaging (MRI) and endomyocardial biopsy may be useful. Finally, human immunodeficiency virus (HIV) can have a number of cardiac related effects. Children with HIV, require routine cardiac monitoring and counseling.

5.1 Introduction

Myocarditis and pericarditis are the two most common viral infections which affect the heart. Myocarditis is defined by the World Health Organization/International Society and Federation of Cardiology as "an inflammatory myocardial disease diagnosed by a combination of histological, immunological and immunohistochemical criteria" [1]. Pericarditis is defined as an inflammatory process of the pericardial sac [2]. The diagnosis of myocarditis and pericarditis can be challenging at times and can be complicated by possible need for invasive studies to support these diagnoses. In addition, the

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presentation of these diseases is both diverse and non-specific, meaning the clinician must have a high index of suspicion to correctly identify these processes.

5.2 Myocarditis

5.2.1 Epidemiology

Myocarditis is a not uncommon clinical manifestation of viral infections. It is estimated to occur in 0.6–1.8% of children and young adults [3–6]. There appear to be age and gender related differences, with prominent peaks in infancy and during adolescence and an increased incidence in males [7, 8]. The increased male susceptibility and age related differences are likely related to gene expression, cellular activation and signaling, as well as virus dependent factors [9, 10].

5.2.2 Etiology, Pathology and Pathophysiology

Nearly any virus can be implicated in myocarditis, including adenovirus, enteroviruses, echoviruses, Epstein–Barr Virus (EBV), hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and influenza. Other common viruses are listed in Table 5.1 [11–19]. As recently as the 1990s, coxsackie viruses were believed to be the most common viral cause of myocarditis. More recently, parvovirus B19 and human herpes virus serotype 6 (HHV-6) have become more frequent causes [11–13]. Reasons for this apparent change in etiology are not known, although it should be pointed out that older studies established viral causes through serologies [20], whereas more recently the use of polymerase chain reaction (PCR) has been used to determine the presence of a virus that can be associated with myocarditis from nearly any body site, including blood [13, 21, 22]. In the study by Simpson et al., 43% of patients were positive for a cardiotropic virus by blood PCR testing. Four

Table 5.1 Myocarditis viruses

Adenovirus
Coxsackie A and B virus
Cytomegalovirus
Echoviruses
Enteroviruses
Epstein–Barr virus
Hepatitis B virus
Hepatitis C virus
Hepatitis E virus
Herpes simplex virus
Human herpes virus 6
Human immunodeficiency virus
Influenza A and B
Parvovirus B19
Respiratory syncytial virus
Varicella

viruses were evaluated for, with enterovirus being the most commonly detected, followed by HHV-6, parvovirus B19 and adenovirus [22].

5.2.2.1 Pathology

Explanted hearts will have increased weight with muscle that grossly appears abnormal, frequently appearing pale. The ventricular walls are frequently dilated and thinned out [23]. A bloody pericardial effusion may be present. Endocardial fibroelastosis (EFE) may be present if the myocarditis has been chronic in nature, and particularly in newborn cases [24]. Thrombus may be present in the left ventricle due blood stagnation from poor systolic function. Occasionally microthombotic disease is identified in the coronary or cerebral vessels [25].

On microscopic examination, lymphocytes, plasma cells and eosinophils are commonly seen early in the course of viral myocarditis. Neutrophil infiltration may be present very early in the disease, but will subside within the first several days. Edema is frequently present, as is extensive necrosis [26].

5.2.2.2 Pathophysiology

Both the infectious agent and the host's immune response have been implicated in the clinical presentation in myocarditis. Initially, there is viral infection and dissemination [27]. The virus first gains entry to the body and then reaches the heart through hematogenous or lymphatic spread. Once the virus reaches the heart, it gains entry to the myocytes via a specific receptor such as coxsackie-adenoviral receptor (CAR) [28, 29]. The virus itself not only causes direct damage to cardiac myocytes, but also activates the host's immune response [30–32]. Murine studies using group B coxsackie virus have shown maximal viral growth at 24–72 hours following inoculation, with near complete resolution by 7–10 days. As the viral titers decline, host antibody concentrations increase, followed by macrophage infiltration of the myocardium [26]. In addition, viral activation of various cell receptors triggers the release of inflammatory cytokines including interleukin 1 and 2 (IL-1 and IL-2), tumor necrosis factor alpha (TNF-α) and interferon gamma [33]. Murine models have shown severe disease when inoculated with group B coxsackie in addition to lipopolysaccharide, TNF-α or IL-1. Anti-TNF-α can significantly reduce disease severity [34]. In the setting of viremia, IL-2 enhances natural killer (NK) cell activity limiting myocardial damage. However, in the non-viremic stage, IL-2 worsens disease severity by increasing the number of infiltrating T-lymphocytes [35, 36]. T-lymphocytes promote accumulation of macrophages, production of antibodies from B-lymphocytes, myolysis by antibody and complement mechanisms and direct T-cell cytotoxicity. NK cell depletion results in a more severe myocarditis in animal models using coxsackie virus. NK cells appear to kill the infected myocytes thus limiting further infection. Efficient NK cell destruction of infected cells will not only limit further direct viral damage, but will also presumably reduce the increased immune mediated response [37]. A persistent immune response can lead to ongoing tissue damage, remodeling and eventually a form of dilated cardiomyopathy (DCM).

Autoimmunity may also play an important role in myocarditis. Myocyte destruction during acute myocarditis results in the release of various cardiac proteins. Auto antibodies can develop if molecular mimicry is present [38, 39]. This results in further inflammation, cellular damage and inflammatory cytokine release [39].

Murine models of myocarditis have shown antibodies to myosin as well as cardiac myocyte beta-adrenergic receptors [38, 40]. Beta-1 adrenergic receptor activation leads to protein kinase A activation and accelerates cellular apoptosis, which can be present due to direct viral effects [41–43]. Other autoantibodies implicated in myocarditis include antibodies to muscarinic-2 receptors, adenosine nucleotide translocator, dihydrolipoamide dehydrogenase and sarcomere specific creatinine kinase (CK) [44–46].

5.2.3 Presentation

Myocarditis may present in either an acute form or a chronic form. Acute myocarditis is often fulminant and may quickly show signs of cardiovascular collapse. Chronic myocarditis is a form of dilated cardiomyopathy with associated chronic congestive heart failure symptoms. A viral prodrome is commonly, but not always, present [47]. Most commonly this consists of respiratory or gastrointestinal symptoms [11, 48–50], or a viral exanthem [51].

5.2.3.1 Acute Myocarditis

Acute myocarditis has been further classified into fulminant and active myocarditis [52]. Acute fulminant myocarditis presents with a very short viral prodrome and sudden onset of heart failure with severe hemodynamic compromise [53–55]. While both fulminant and active myocarditis have a similar degree of systolic ventricular dysfunction at baseline, left ventricular diastolic dimensions in fulminant myocarditis are normal or only slightly enlarged, while significant chamber enlargement exists in the acute non-fulminant form [56, 57]. Cardiogenic shock, multiple organ failure and conduction disturbances are not uncommon in both [58].

Sudden death may also occur in any subgroup of myocarditis, likely due to arrhythmia. Sudden infant death syndrome autopsy studies have shown that 9–43% of infants in this group have evidence of myocarditis [59, 60] and 5–8% of sudden cardiac deaths in athletes may be associated with myocarditis [61–63]. Cardiac dysrhythmias, particularly ventricular tachycardia and complete heart block, are also frequently associated with cardiogenic shock and can be an indication for extracorporeal membrane oxygenation (ECMO) cannulation [47, 58].

5.2.3.2 Chronic Myocarditis

Chronic myocarditis commonly presents as a form of dilated cardiomyopathy. Lieberman et al. further characterized chronic myocarditis into chronic active myocarditis and chronic persistent myocarditis [52]. Chronic active myocarditis is described as a non-distinct onset of illness, frequent clinical/histologic relapses, and ventricular systolic dysfunction associated with chronic inflammatory changes and mild to moderate fibrosis on biopsy. Chronic persistent myocarditis also has a non-distinct onset, but will have a persistent histologic infiltrate with myocyte necrosis and normal ventricular function. Children in either category can present with symptoms of heart failure such as decreased oral intake, weight loss, dyspnea, orthopnea and increased fatigue. Complicating the diagnosis is that viral infections by

themselves can cause a patient with a poorly functioning heart to become symptomatic. This can occur in children who are very tenuous at baseline in which the added stressor of a viral infection becomes too much for the poorly functioning heart to handle. This presents a diagnostic dilemma, as patients will have a viral prodrome, evidence of a current or recent viral infection, and a poorly functioning heart similar to chronic myocarditis.

5.2.4 Physical Examination (Table 5.2) [11, 48–50, 64, 65]

5.2.4.1 Vital Signs

Most commonly, children presenting with viral myocarditis will have abnormal vital signs. Fevers, tachycardia and tachypnea are not uncommon. If patients are presenting in acute decompensated heart failure, hypotension may be present due to poor cardiac output. Pulse oximetry is usually normal, but may be slightly lowered due to cardiogenic pulmonary edema.

5.2.4.2 General Appearance

Children will often be toxic appearing, particularly if they have acute decompensated heart failure as can be seen with fulminant myocarditis. Other patients may be tired or generally ill appearing.

Table 5.2 Physical exam findings in myocarditis

Vital signs	Fevers
	Tachycardia
	Tachypnea
	Hypotension
General appearance	Toxic or generally ill appearing
Pulmonary	Respiratory distress
	Increased work of breathing
	Productive cough
	Decreased aeration
	Rales
Cardiac	Poor perfusion
	Diminished pulses
	Abnormally active or laterally displaced cardiac impulse
	Gallop
	Friction rub (if associated with pericarditis)
	Murmur
	Increased jugular venous distention
Abdomen	Hepatomegaly
	Ascites
Skin	Rashes
	Mottling/poor skin perfusion
Extremities	Edema

5.2.4.3 Pulmonary

Many children will show evidence of respiratory distress, increased work of breathing and using accessory muscles to breathe. A productive cough may be present. On auscultation, symmetrically decreased aeration and rales may be present.

5.2.4.4 Cardiac

Children should be evaluated for signs of shock, including poor perfusion and diminished pulses. The cardiac impulse itself may be hyperactive, hypoactive or laterally displaced. Heart sounds may be diminished. An S3 or S4 gallop is not uncommon due to poor ventricular compliance. A pericardial friction rub may be present if there is associated pericarditis. Murmurs are frequent in this population. An S1 coincident murmur consistent with mitral regurgitation may be present due to a poorly functioning LV with dilation of both the ventricular chamber and the mitral valve annulus.

5.2.4.5 Abdomen

The abdomen should be examined for hepatomegaly due to venous congestion. Ascites is also not uncommon.

5.2.4.6 Skin

The integument should be evaluated for rashes, as this can be a clue to a specific viral diagnosis. Patients who present with shock from acute heart failure may show signs of poor skin perfusion including mottling.

5.2.4.7 Extremities

Including evaluation of the peripheral pulses and perfusion, the extremities should also be evaluated for evidence of edema indicating elevated central venous pressures from decreased biventricular function. Edema in the setting of heart failure from myocarditis is generally pitting in nature. Although most frequently described as lower extremity edema, sacral edema is not uncommon.

5.2.5 Laboratory Evaluation

Laboratory evaluation in myocarditis can be divided evidence of myocardial injury and strain, evidence of viral infection and the need to evaluate end organ function. Myocardial injury is assessed with cardiac troponin levels (troponin I or troponin T), creatinine kinase (CK) and creatinine kinase myocardial band (CKMB). Notably, elevation of these proteins indicates myocardial injury, but is not specific for injury from myocarditis. Elevation of B-type naturetic peptide (BNP) or n-terminal B-type naturetic peptide (NT-proBNP) can occur and is a predictor of poor outcomes in both the short and long term [66].

Assessment for viral infections can be completed using PCR, viral serologies, or by viral culture [18]. Viral testing is neither sensitive nor specific for the diagnosis

of myocarditis. Many viruses elude detection, and the presence of a virus does not establish that it has caused myocardial dysfunction and inflammation. Isolation of a known causative virus may occur from respiratory secretions, stool, urine or blood [22, 67, 68]. The sensitivity of blood PCR testing appears to be dependent on age. In particular, children ≤12 months of age diagnosed with myocarditis appear to be more likely to test positive for a known cardiotropic virus by blood PCR testing than children who are older with myocarditis [22].

Laboratory assessment with a complete blood count, inflammatory markers, electrolytes and liver enzymes is important in the initial assessment [65]. Leukocytosis is frequently present, and thrombocytosis may occur. However, viral bone marrow suppression with pancytopenia (or suppression of any cell line) may also be present. Fulminant myocarditis can lead to severely reduced cardiac output and multiple organ failure. Ongoing evidence of hypoperfusion is an indication for escalation of therapy which may include mechanical circulatory support, such as ECMO.

5.2.6 Electrocardiography (EKG) (Fig. 5.1)

The EKG in patients with viral myocarditis is frequently abnormal [47, 64]. The most common findings include sinus tachycardia, low voltage QRS complexes and non-specific ST-T wave changes [48], but more significant changes including ST-T wave changes in a specific coronary distribution [69], ventricular tachycardia and complete AV block can occur [49, 50, 64].

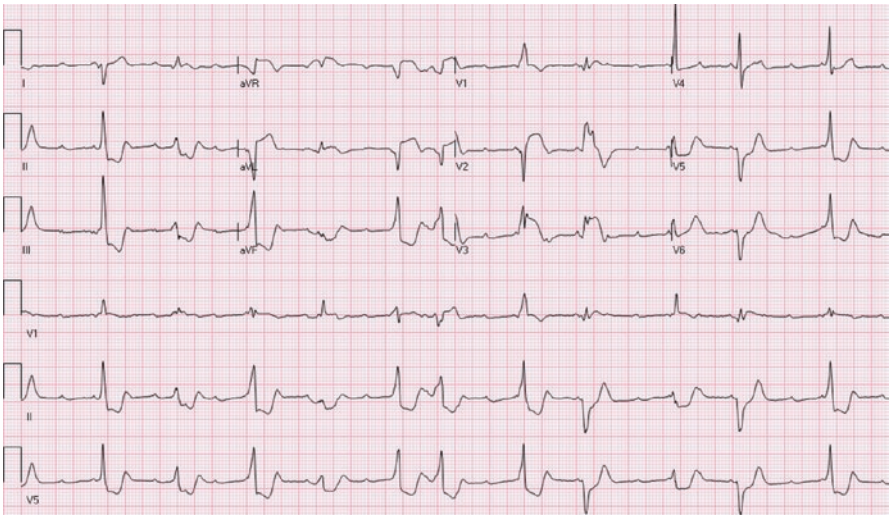

Fig. 5.1 Markedly abnormal EKG findings may be present in myocarditis. In this patient, there is complete heart block with ventricular escape beats

5.2.7 Echocardiography

Echocardiography is valuable in the evaluation of myocarditis. Myocarditis accounts for 22–46% of new onset LV dysfunction in children [68, 70–72]. Chamber size, ventricular wall thickness, valvular function, systolic and diastolic function can be readily assessed with standard echocardiography [56]. Pericardial effusions can also be ruled out. In the infant, echocardiography is also very important in ensuring that there is not a structural cause for the decreased cardiac function, such as an anomalous left coronary artery from the pulmonary artery. In poorly functioning hearts, intracavitary thrombi must be excluded [73].

The echocardiogram is useful in differentiating the various forms of myocarditis from each other, as well as from dilated cardiomyopathy [56]. In acute, fulminant myocarditis, there is increased wall thickness but normal cavity size with markedly reduced systolic function. Acute myocarditis that is not fulminant may have normal wall thickness with left ventricular dilation. In contrast, dilated cardiomyopathy will have markedly dilated chambers, myocardial wall thinning and systolic dysfunction.

The degree of ventricular dysfunction, both of the LV and the RV, is predictive of a worse outcome. In a review of children with myocarditis, an initial LV ejection fraction (EF) less than 15% was associated with more severe cardiac failure [50]. In addition, RV dysfunction measured both qualitatively and quantitatively by right ventricular base descent, also known as tricuspid valve annular plane excursion or TAPSE, is an independent predictor of adverse outcomes [74]. Diastolic dysfunction can be present initially or can develop later on, even in the setting of normal or improved LV EF [75, 76]. While myocarditis most commonly presents with global LV systolic dysfunction, segmental wall motion abnormalities, similar to what is seen in acute coronary syndromes in adults, can be present. Coronary angiography during cardiac catheterization can distinguish these etiologies [77–79].

5.2.8 Radiologic Studies

5.2.8.1 Chest X-Ray (CXR) (Fig. 5.2)

CXR is usually performed upon presentation, as most patients have tachypnea or other signs of respiratory distress. The most common finding is cardiomegaly [64]. Pulmonary edema, pleural effusions, and pulmonary infiltrates may also be seen [49].

5.2.8.2 Cardiac Magnetic Resonance Imaging (CMR)

CMR is used in adults in the assessment of coronary artery disease and myocardial infarction size [80, 81]. In addition to highly reproducible volumetric and functional measurements [82], CMR provides detailed and accurate information regarding areas of myocardial edema, hyperemia, necrosis and fibrosis [83]. Although CMR is non-invasive, due to the need for patients to remain still during the study, anesthesia and its associated risks must be considered in children. Indications for myocarditis assessment with CMR in adults include (1) new-onset or persistent symptoms consistent with myocarditis, (2) evidence of recent or ongoing myocardial injury or dysfunction and (3) a suspected viral or non-ischemic etiology [83].

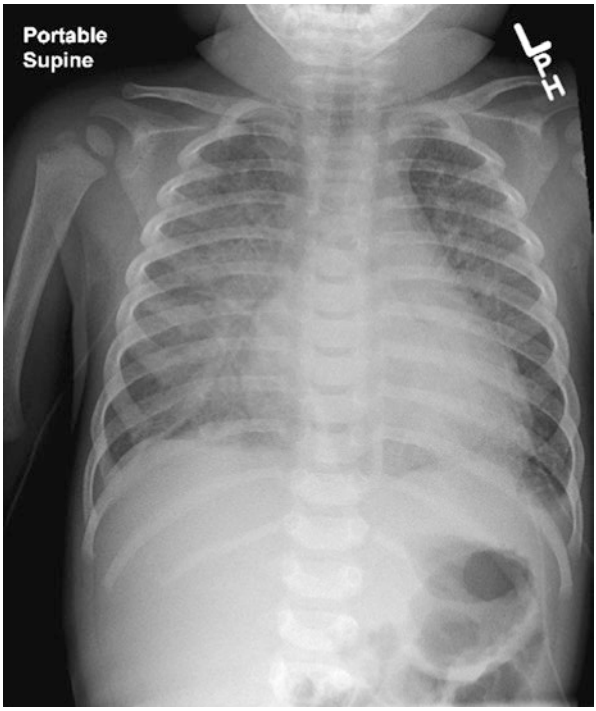

Fig. 5.2 CXR in myocarditis showing cardiomegaly and pulmonary edema

Multiple MRI sequences are typically used in the evaluation of myocarditis, including T2 weighted and T1 weighted with and without gadolinium-diethylenetriaminepentaacetate (Gd-DTPA). T2 weighted imaging is useful in the assessment of myocardial edema [84, 85]. The inflammation in myocarditis results in changes in membrane permeability, tissue edema and tissue fibrosis which result in changes in the water content of the myocardium, of which T2 relaxation parameters are dependent on [86]. ECG-gated T1 weighted imaging obtained shortly after Gd-DPTA administration that shows early myocardial enhancement is consistent with myocardial inflammation or hyperemia [83, 84]. Late gadolinium enhancement (LGE) can be seen with T1-weighted segmented inversion-recovery gradient-echo sequences [86, 87]. This delayed contrast enhancement is often associated with recent cardiac necrosis, but does not differentiate between acute or chronic inflammation [86]. In adults, CMR has also been used to guide myocardial biopsies [88].

Each of these MRI sequences has specific advantages and disadvantages. A combination of these techniques, known as the "Lake Louise" criteria, provides a higher sensitivity and specificity than any of these alone (Table 5.3). Compared to only using LGE, applying two of the three Lake Louise criteria increases the accuracy of CMR from 70 to 78% and the positive predictive value increases from 68 to 91% [83].

CMR is also useful in differentiating myocarditis from other conditions. For example, LGE enhancement is typically subepicardial, although is sometimes transmural in myocarditis and is typically patchy in distribution. In acute coronary

Table 5.3 Lake Louise criteria for cardiac MRI diagnosis of myocarditis [83]

A.	In the case of clinically suspected myocarditis, CMR findings are consistent with a diagnosis of myocardial inflammation (myocarditis) if two or more of the of the following are present
	1. Regional or global myocardial signal intensity is increased in T2-weighted images (indicating myocardial edema)
	2. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images (indicating hyperemia/capillary leak)
	3. At least one focal lesion of late gadolinium-enhanced enhancement is seen in a non-ischemic distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (indicating myocyte injury and/or fibrosis)
B.	CMR study is consistent with myocyte injury and/or scar by myocardial inflammation if criterion 3 is present on CMR evaluation
C.	CMR should be repeated between 1 and 2 weeks after initial CMR if:
	1. None of the above criteria are present at time of initial CMR, but onset of symptoms are very recent and there is strong clinical evidence for myocarditis
	2. Only 1 of the above criteria are present
D.	The presence of left ventricular dysfunction or pericardial effusion on CMR provides additional, supportive evidence for a diagnosis of myocarditis

syndromes, LGE will be subendocardial or transmural in nature, and will be in the distribution of a specific coronary artery. CMR may also be beneficial in differentiating DCM from myocarditis; however, when DCM is present in the setting of myocarditis it may not be possible to determine which condition was present first. Although it appears reasonable to apply the Lake Louise criteria to help differentiate, caution is advised as classifications of myocarditis are based on clinical course and not on imaging findings alone [83].

5.2.9 Endomyocardial Biopsy (EMB)

The gold standard for the diagnosis of myocarditis is EMB with findings consistent with the Dallas Criteria. The Dallas Criteria define myocarditis as a "process characterized by an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of ischemic disease" [89]. Histology may show (1) acute myocarditis with inflammation and myocyte damage, (2) borderline myocarditis with inflammation but absence of associated cellular damage or (3) no acute myocarditis. However, evidence of chronic myocarditis with ongoing inflammation and scar tissue formation may also be seen [27].

While EMB is considered the gold standard, its use in the pediatric population is declining [7]. This is due to the limited specificity and sensitivity of EMB in myocarditis, the relative risk of performing the procedure, and the improved diagnostic capabilities of CMR. The sensitivity of EMB is estimated to be 35–60%, with a specificity of around 80% [90, 91]. This is likely in part due to the focal and transient nature of the inflammation seen in myocarditis. In one autopsy series of 38

patients, right ventricular biopsy was positive in 63%, left ventricular biopsy was positive in 55%, but only 17–20% of all biopsy specimen were positive [90]. In addition, CMR has shown the most common site of involvement is the epicardial surface of the left ventricular free wall, a site which is not typically or easily biopsied [88]. In addition, biopsies themselves are subject to significant inter-observer variability [92]. Because of the limitations of EMB, the American Heart Association, American College of Cardiology and European Society of Cardiology do not recommend routine EMB for suspected myocarditis. EMB may be used for (1) new onset heart failure of <2 weeks duration associated with a normal sized or dilated LV with hemodynamic compromise and (2) new onset heart failure >2 weeks duration with a dilated left ventricle and ventricular arrhythmias or heart block, or failure to respond to usual medical care after 1–2 weeks [93].

Given the shortcomings of the histologic diagnosis of myocarditis, other modalities have found increasing usefulness. Evidence of viral infection by demonstration of viral genome in EMB has been found [92]. In addition, many patients are found to have up regulation of human leukocyte antigen (HLA), formerly referred to as Major Histocompatibility Complex (MHC). Herskowitz [94] first showed this association by analyzing the biopsies of patients with clinically suspected myocarditis, MHC was detected in 11 of 13 patients with histologic evidence of myocarditis, while only 1 of 8 patients with a clearly defined other cause was positive for MHC expression. This MHC expression and recognition likely contributes to ongoing immune system activation and damage to cardiac myocytes. Another study found that 84/202 patients with chronic dilated cardiomyopathy had elevated HLA class I and/or class II expression. However, 61 of these patients with elevated HLA expression (73%) had no histologic evidence of myocarditis [95]. Cardiac autoantibodies may also be indicative of myocarditis, and may be useful in predicting response to therapy (see below) [96].

5.2.10 Differential Diagnosis

The differential diagnosis for a patient presenting with myocarditis will depend on the specific presenting symptoms as well as the age of the patient (Table 5.4). In the newborn and infant presenting with acute heart failure, considerations include sepsis, structural heart disease, and inborn errors of metabolism, DCM, and large arteriovenous malformations. In children and adolescents, DCM and chronic tachyarrhythmias are the most common considerations.

5.2.11 Treatment

5.2.11.1 Acute Treatment

The initial treatment of myocarditis is primarily supportive. In patients who present with acute, fulminant myocarditis, aggressive heart failure support in necessary. Diuresis can improve cardiac function by reducing the stretch on the heart and thus

Table 5.4 Differential diagnosis in myocarditis

Neonate/infant
Sepsis
Hypoxic injury
Hypoglycemia
Structural heart disease
Arteriovenous malformation
Metabolic disease
Dilated cardiomyopathy
Chronic tachyarrhythmia
Child/adolescent
Dilated cardiomyopathy
Chronic tachyarrhythmia
Sepsis related cardiac dysfunction

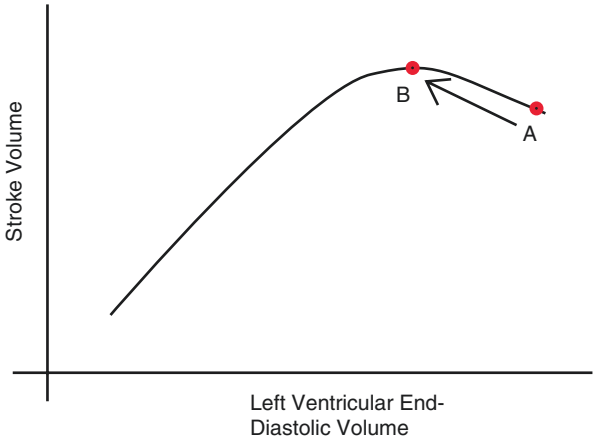

Fig. 5.3 The Frank–Starling Curve. In patients with acute heart failure, the heart may be over distended and lose contractility (point A). With dieresis, contractility and increased stroke volume can occur (point B)

putting the heart into a better position on the Frank–Starling curve (Fig. 5.3). Inotropic therapy also improves cardiac output and can help alleviate symptoms of congestive heart failure. Although milrinone is the most frequently used inotrope in children with myocarditis, trials supporting its use in this setting are limited [97]. Other forms of cardiorespiratory support used, include epinephrine and other inotropic medications, mechanical pressure ventilation, and ECMO [97]. In patients who require long term mechanical support, ventricular assist devices (VAD) afford an opportunity for the child to be extubated and receive supportive therapies such as physical therapy while awaiting recovery or heart transplantation.

Directed therapy for the acute cause is limited. In cases where a specific virus is suspected and antiviral therapy is available, that therapy should be utilized [98]. However, such cases are uncommon. In addition, the delay in patient presentation may prevent antiviral therapy from being effective in reducing inflammation and cardiac damage. However, evidence of ongoing viral load in the myocardium, as

demonstrated with EMB, is associated with worsening LV systolic function compared to patients with viral elimination, indicating the window for anti-viral therapy may extend beyond the initial presentation [99].

Long term medical management of myocarditis primarily involves treatment for congestive heart failure. Diuretic therapy may be necessary for management of edema and volume overload. Angiotensin converting enzyme inhibitor (ACE-I), Angiotensin II receptor blocker (ARB) and beta-blocker therapy are frequently employed, although adequately powered trials confirming their benefits in children do not exist. Arrhythmias must be adequately controlled as well, as cardiac conduction system disease can persist long after the acute myocarditis episode [100]. Occasionally, children may require pacemaker therapy if myocarditis results in high grade atrioventricular block, or an implantable cardioverter defibrillator if the cardiac function is depressed significantly enough to predispose to ventricular arrhythmias.

Because of the inflammatory nature of myocarditis, immunomodulation has been considered a possible therapy. Other forms of inflammatory myocarditis, such as eosinophilic, granulomatous, giant cell myocarditis and inflammation related to rejection of a transplanted graft benefit greatly from immunosuppression [101]. Trials in adults with viral myocarditis have been inconclusive. Mason et al. performed a randomized, controlled trial of patients with a histopathological diagnosis of myocarditis and reduced systolic function to conventional therapy or conventional therapy and immunosuppression. At 28 weeks there was no significant difference ejection fraction or survival [102].

Attempts to determine subgroups of patients with myocarditis or an inflammatory DCM who may benefit from immunosuppression have found two potential prognostic factors. The first is in patients with increased HLA expression on EMB. This group of patients may show improvement in LVEF, LV size, and New York Heart Association (NYHA) class, both during and after therapy with prednisone and azathioprine [95].

The second group of patients that may benefit from immunosuppressive therapy is those who are negative for cardiotropic viruses by PCR on biopsy. This group of patients may also show an increase in LVEF with a reduction in LV size, with the majority of patients in this category responding to a combination of prednisone and azathioprine [96].

Intravenous immunoglobulin (IVIg) is also frequently used in the treatment of myocarditis. In one case series, 21 consecutive children who received IVIg were compared to a historical cohort. The IVIg group showed reduced LV diastolic size, improved systolic function as well as a trend towards improved survival [103]. However, a more recent pediatric study [97], as well as a randomized, controlled trial in adults have not confirmed this benefit, in large part due to the improvement that occurs regardless of the additional of immunotherapy [104]. Non-steroidal anti-inflammatory agents (NSAIDS) are also not recommended during the acute or subacute phases as there is increased inflammation, necrosis and mortality compared to placebo in murine models [105].

In some patients, cardiac function does not return sufficiently to allow weaning of mechanical or intravenous medical support. In such cases, cardiac transplantation

can be considered. Indications for cardiac transplantation are the same in myocarditis as in other disease states [106]. Contraindications are also similar, although in cases of myocarditis many providers will require evidence that the virus has cleared prior to transplantation. Reasons for this include concern for recurrence in the transplanted heart as well as the potential for worsening viremia and its associated complications in the immediate post-operative period when induction immunosuppression is administered. Shirali and colleagues have shown that transplanted patients have a worse outcome if there is evidence of viral re-infection in routine post-transplant biopsies [107]. Pietra et al. have shown that patients transplanted with a diagnosis of viral myocarditis have worse outcomes than those transplanted for other reasons [108]. However, a more recent analysis from the Organ Procurement and Transplant Network database did not show that myocarditis was associated with wait-list mortality or post-transplant graft loss [109]. Thus, it remains unclear whether myocarditis is a risk factor for poor outcome following heart transplantation.

Activity restriction is also necessary in acute myocarditis. Per the most recent AHA guidelines [110], prior to returning to competitive sports, patients should undergo echocardiography, 24 hour Holter monitoring and an exercise ECG no less than 3–6 months after the initial illness. If ventricular systolic function, myocardial injury markers and inflammatory markers have normalized, and there is no evidence of clinically relevant arrhythmias on Holter and exercise ECG, then it is reasonable for the patient to return to training and competition.

Although there are no specific prevention tactics for myocarditis, vaccination is useful in preventing acquisition of many of the viruses that can cause myocarditis. Evidence of this success comes from studies in children with DCM and EFE. Prior to the availability of the mumps vaccine, 1 in 5000 live births in the United States were diagnosed with this form of DCM. Ninety percent of biopsy samples in children with DCM and EFE contained evidence of mumps RNA. Following near universal vaccination, this entity has essentially been eliminated in the United States [24].

5.3 Pericarditis

5.3.1 Epidemiology

The pericardium consists of the visceral pericardium and parietal pericardium. In a healthy adult, there is 15–50 mL of fluid in the intrapericardial space between these two layers. This space is well innervated, which may account for physiologic reflexes and also allows transmission of pain when pericarditis is present. The pericardium and pericardial sac also influence diastolic filling [111].

Acute pericarditis is defined as symptoms or signs resulting from inflammation of the pericardium of no more than 1–2 weeks in duration [112, 113]. The overall incidence of acute pericarditis is quite difficult to estimate, but may be as high as 5% in children presenting to the emergency department with acute chest pain [114], and 80% of patients are male [115].

5.3.2 Etiology, Pathology and Pathophysiology

5.3.2.1 Etiology

Most cases of pericarditis are idiopathic but presumed to be viral in origin [111, 112]. Investigation of particular viral causes in pericarditis has been very limited. In adults, a prospective series of 231 patients with primary, acute pericardial disease found a specific cause in only 14%, and only 2 were diagnosed with a specific viral cause [116]. Another study which evaluated the etiology of pericardial effusions showed viral causes were frequent, including CMV, parvovirus B19, hepatitis C, influenza, adenovirus and enterovirus [117]. Other viruses that have been associated with pericarditis are shown in Table 5.5. In children, coxsackie virus has been reported to be the most common. Prior to the onset of the chest pain that accompanies acute pericarditis, many patients will have had a viral syndrome in the preceding days to weeks, such as rhinosinusitis, bronchiolitis or gastroenteritis.

Previously, diagnosis was primarily through serologic testing, with a pre-defined cut-off or rise defined as being positive [117, 118]. There is now increased detection by PCR identification of the virus in any sample, not just the pericardium or pericardial fluid [117].

5.3.2.2 Pathology

Pericardial inflammation will often lead to an accumulation of additional fluid within the pericardial space. Pericardiocentesis will reveal serous or serosanguinous fluid with a lymphocyte predominance, although neutrophils may be present initially. The causative virus can be determined with viral culture or PCR of this fluid [119, 120]. Both the visceral and parietal pericardium may be injected and inflamed [113].

5.3.2.3 Pathophysiology

Inflammation of the pericardial tissue leads to increased permeability and fluid collection in the pericardial space. This fluid collection is thought to account for the symptoms that are seen with acute pericarditis. Myocardial function is rarely

Table 5.5 Viral causes of pericarditis

Enterovirus (including coxsackie B virus)
Adenovirus
Influenza virus A and B
Rubella
Epstein–Barr virus
Measles
Mumps
Cytomegalovirus
Respiratory syncytial virus
Herpes simplex virus
Hepatitis B
Human immunodeficiency virus

reduced if only pericarditis is present. However, myocarditis complicates episodes of pericarditis in many cases [111–113] and may cause a decrease in systolic function. In addition, an effusion that develops rapidly can result in tamponade physiology with reduced cardiac output, potentially leading to signs and symptoms consistent with congestive heart failure.

5.3.3 Presentation

As discussed above, most patients with acute, uncomplicated pericarditis will present with an acute or subacute episode of chest pain [115]. The pain is typically described as sharp or stabbing in nature. The quality and severity of the chest pain may change when patients change position. Most patients will have pain that is worse with deep inspiration. The pain will also decrease in severity when sitting up or leaning forward. Shortness of breath is frequently present [111, 115, 121]. Patients will not uncommonly have a gastrointestinal or respiratory infection in the weeks prior to presenting with chest pain.

The presentation can be varied if the pericardial effusion that is present is significant enough to cause tamponade, or if inflammation has been ongoing resulting in constrictive physiology. Cardiac tamponade occurs when the atria and ventricles have restricted filling due to an effusion, leading to a decrease in cardiac output [122]. In this case, the effusion is large enough and has developed rapidly enough that the pericardial space is unable to expand further to provide for intracardiac filling. Such patients are typically in cardiorespiratory distress.

Constrictive pericarditis also results in reduced ventricular filling, typically due to a thickened and fibrotic pericardium. Although the most common cause of constrictive pericarditis worldwide is tuberculosis [123], prolonged viral etiologies of pericarditis can lead to constriction [124]. Patients with constrictive pericarditis will typically present with dyspnea, swelling, fatigue, abdominal discomfort, or exercise intolerance, in addition to chest pain [124].

5.3.4 Physical Examination

As in the presentation of pericarditis discussed above, the physical examination will also be dependent on the presence of an effusion and whether there is constriction present. Effusions and constriction may have significant hemodynamic consequences which will alter the patient's examination.

5.3.4.1 Vital Signs

Because of the viral etiology, fevers are not uncommon, however high fevers (>38 °C/100.4 °F) may indicate purulent pericarditis [111]. In addition, many patients will be tachycardic. A large pericardial effusion resulting in cardiac tamponade may result in a low arterial blood pressure, which is part of the classic triad first described by Beck. In addition to hypotension, Beck's triad also includes an elevated jugular venous

pulsation and muffled heart sounds. Pulsus paradoxus, signified by a greater than 10 mmHg decrease in systolic blood pressure during inspiration, also occurs with tamponade and occasionally in constrictive pericarditis.

5.3.4.2 General Appearance

Most patients will be anxious and uncomfortable appearing due to the pain that is present. This is especially true in children as most children have been healthy outside of their episode.

5.3.4.3 Cardiac

Muffled heart sounds and a pericardial friction rub are frequently present in pericarditis with an effusion. The pericardial friction rub is considered pathognomonic for pericarditis [125]. The rub is often dynamic but will be best heard with the patient leaning forward and auscultating at the left lower sternal border. It consists of three phases—ventricular contraction, early diastolic filling and atrial contraction [111, 126]. As mentioned above, jugular venous distention or Kussmaul's sign may also be present if there is cardiac tamponade [127].

5.3.4.4 Skin

As in myocarditis, a thorough examination of the skin is useful in evaluating for a specific viral cause.

5.3.4.5 Extremities

Evaluation of peripheral pulses and perfusion is important with pericarditis, and in particular with a pericardial effusion, as reduced cardiac output is not uncommon in this setting.

5.3.5 Initial Laboratory Evaluation

There may be a leukocytosis, often with an increase in lymphocytes suggestive of a viral etiology. A marked leukocytosis may be indicative of a purulent etiology [111]. Liver enzymes rarely can be elevated if the viral infection has hepatic involvement. Many patients with pericarditis will have cardiac enzymes measured, and a significant portion of those will be elevated [128]. Most likely this represents myocardial inflammation and injury, as the pericardium itself does not contain these proteins. Inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) are also frequently elevated [111, 129].

5.3.6 Electrocardiography

The classic electrocardiogram in acute pericarditis shows diffuse ST elevation with diffuse PR depression (Fig. 5.4) [130]. This is thought to be due to local inflammatory changes in the epicardium [131]. In pericarditis with a pericardial effusion,

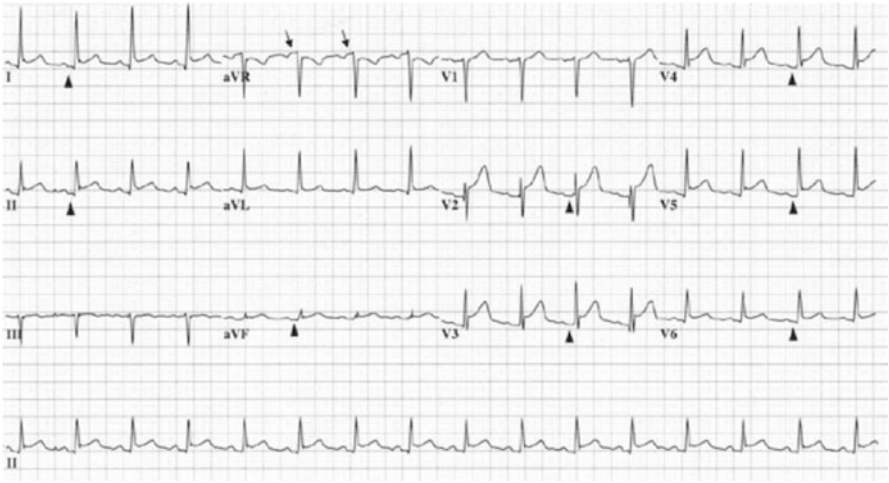

Fig. 5.4 ECG in acute pericarditis. There is diffuse PR depression and ST elevation [130]

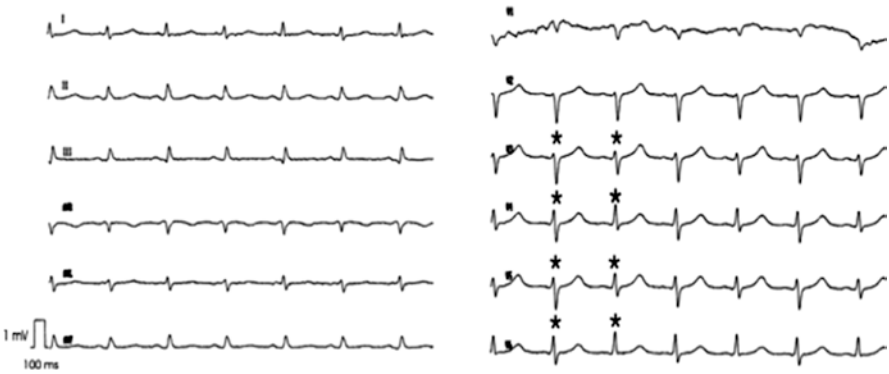

Fig. 5.5 ECG with low voltage QRS complexes and electrical alternans [133]

regardless of whether tamponade is present, the EKG will be non-specific, but can show reduced voltages as well as electrical alternans. The electrical alternans is thought to be secondary to the heart swaying back and forth within the pericardial sac with each beat (Fig. 5.5) [126, 132, 133].

5.3.7 Echocardiography

Children with symptoms consistent with pericarditis should undergo a complete echocardiogram. Echocardiography can be used to assess for pericardial effusion and whether there is evidence of tamponade. Although the echocardiogram can suggest cardiac tamponade, it should be remembered that tamponade is a clinical

diagnosis. Findings on echocardiogram that can suggest tamponade include right atrial systolic collapse, right ventricular diastolic collapse and a significant change in tricuspid and mitral inflow as assessed with Doppler flow. In the absence of an effusion, the echocardiogram in pericarditis is most commonly normal, however, the pericardium can be visualized by ultrasound and may be thickened and echobright [127].

5.3.8 Radiologic Studies

In acute, uncomplicated pericarditis, the chest radiograph is typically normal. Occasionally, calcifications can be seen. If pericarditis is complicated by a pericardial effusion, the cardiac silhouette may appear enlarged, and there may be delineation of fluid between the heart itself and the pericardial sac.

Although CT and MRI are not typically required in the assessment of pericarditis, occasionally patients will undergo one of these imaging modalities for further assessment of their chest pain and an incidental finding of a pericardial effusion will be found, leading to the eventual diagnosis of pericarditis.

5.3.9 Differential Diagnosis

The differential diagnosis for acute pericarditis primarily focuses around the more common causes of chest pain in the child and adolescent. In children and adolescents, the most common causes of chest pain are not cardiac in origin, but rather related to gastroesophageal reflux, musculoskeletal pain or anxiety most commonly. In addition, autoimmune diseases should be considered as they are a not uncommon cause of non-infective pericarditis.

5.3.10 Treatment

The initial treatment for uncomplicated pericarditis is nonsteroidal anti-inflammatory drugs (NSAIDs). In general, most patients with viral pericarditis respond well to this therapy. In patients who do not respond well to NSAID therapy, colchicine is an excellent adjunct. In a randomized adult trial, the addition of colchicine to conventional anti-inflammatory therapy reduced the rate of symptoms persistent at 72 hours, the number of recurrences, the hospitalization rate and the 1 week remission rate [134].

Previously, short courses of corticosteroids were considered the standard of care for the treatment of acute pericarditis. However, several studies have indicated an increased risk of recurrence when corticosteroids are used, [112, 113] and thus they are now less commonly used.

In patients with a pericardial effusion, consideration can be given for pericardiocentesis. The indications for pericardiocentesis include evidence of tamponade or

concern that tamponade will develop, as well as the need for fluid to make a diagnosis. Pericardial fluid can be analyzed for cell count with differential, lactate dehydrogenase, protein and cultures, if clinically indicated.

The long term outcome for acute viral pericarditis is excellent, with an estimated 70–90% resolution without recurrence [111–113, 135]. Pericarditis with or without an effusion can recur in up to 20% of patients [136]. In such cases, a repeat course of medical therapy may be useful. In patients with recurrent pericarditis or pericardial effusions, reinitiation of NSAID therapy with colchicine is recommended [137]. Treatment with NSAIDs and colchicine in these cases is prolonged, typically lasting months [138].

There is little data available to guide the need for activity restrictions. The most recent European Society of Cardiology guidelines indicate that athletes should refrain from exercise until resolution of symptoms and normalization of inflammatory markers, ECG and echocardiogram, with a minimum time of 3 months [138]. If myopericarditis is present, the guidelines for myocarditis should be followed (see above).

5.4 Viral Endocarditis

Experimental models of viral endocarditis exist in mice and monkeys [139, 140]. However, evidence in humans is generally lacking. One case report from Belgium [141] reported on a 4 month old with trisomy 21 with three repeated episodes of prosthetic patch dehiscence. Coxsackie B2 virus was ultimately cultured from the excised patch, in addition to fecal samples and nasopharyngeal samples. The excised patch showed evidence of vegetations, necrosis, and cellular infiltrate. Following the second episode a short course of IVIg was given. A 2 week course of IVIg was given following his third episode of presumed viral endocarditis. The patient ultimately recovered and was free of endocarditis symptoms at 19 months follow up. Critics of this case report point to the lack of evidence of endocardial cell infection by immunohistochemistry and electron microscopy [142].

5.5 Cardiac Involvement in Human Immunodeficiency Virus (HIV)

HIV results in various cardiac manifestations. Pericardial effusions occur in about a quarter of children infected with HIV; however tamponade is rare [143, 144]. In addition, infection with HIV, particularly if untreated, increases the risk of other infections resulting in pericarditis and endocarditis in particular. This can involve both common and exotic organisms (Table 5.6). Typically the LV is hyperdynamic in HIV infection, however, both LV systolic and diastolic dysfunction can occur late in HIV-infected individuals [143, 145, 146]. Increased LV wall thickness can also occur in the setting of HIV, and, along with reduced systolic function, is a mortality

Table 5.6 Organisms causing pericarditis or endocarditis in HIV-infected patients

Staphylococcus aureus
Cryptococcus neoformans
Herpes simples
Mycobacterium tuberculosis
Mycobacterium avium
Streptococcus pneumoniae
Haemophilus influenzae
Candida albicans
Aspergillus fumigatus

risk factor [147]. In patients with untreated HIV infection, myocardial biopsy has revealed myocarditis with known cardiotropic viruses, as well as opportunistic infections and drug induced hypersensitivity [148]. Kaposi's sarcoma within the myocardium, coronary artery adventitia, and epicardium has also been reported in patients with late stage disease [149]. Atrial ectopy, ventricular ectopy and atrioventricular block may occur. HIV treatments, particularly protease inhibitors, also have cardiovascular complications, including lipodystrophy, metabolic abnormalities, insulin resistance, hypertriglyceridemia and increased atherosclerotic risk [150]. As children survive longer, increased surveillance with risk factor modification will help to prolong and improve their quality of life.

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Viral Gastroenteritis

6

Elizabeth Goddard

Abstract

Although acute gastroenteritis (AGE) is preventable and treatable, it is still the second most common cause of death in children under 5 years. In both developing and developed countries, viruses are the most common cause of gastroenteritis in young children. Known enteric viral pathogens include rotavirus, calciviruses (norovirus and sapovirus), adenovirus and astrovirus. Rotavirus is a common cause of diarrhea in this age group. RotaRix and RotaTeq are both oral live attenuated vaccines recommended by the World Health Organisation for routine immunization of all infants in both developing and developed countries. The benefits of these vaccinations outweigh the risk of intussusception although ongoing surveillance for intussusception is recommended. The introduction of successful rotavirus immunisation programmes in some countries has significantly decreased rotavirus associated AGE. In these areas norovirus has now become a significant cause of AGE. Globally the most common norovirus genotype is G11.4. At present there are no commercially available norovirus vaccines. Viral diagnosis is required in determining the etiology of outbreaks of diarrhea and in investigating causes of gastroenteritis in children. In the future, multiplex PCR tests allowing, simultaneous detection of several different diarrhea-causing microorganisms, are expected to become more common. Many new viruses have been identified in the gastrointestinal tract but their role as enteropathogens is not clear. The presence of a virus in a fecal sample does not mean that the virus is replicating in the intestinal cells. Prevention and treatment of childhood diarrhea will involve improvements in hygiene and sanitation, access to oral rehydration therapy and zinc supplementation as well as inclusion of universal rotavirus vaccination in national immunization programs in both resource wealthy and resource poor countries.

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6.1 Introduction

Acute gastroenteritis (AGE) is a very common pediatric illness throughout the world and is a significant cause of morbidity and mortality, particularly in low and middle income countries. It is the second most common cause of mortality worldwide in children <5 years and it is estimated that 600,000–700,000 infants and young children die from diarrhea each year [1]. Most of the deaths occur in sub-Saharan Africa and South Asia and mortality is highest in children <2 years. Mortality is uncommon in developed countries, but diarrhea is often associated with substantial medical and healthcare costs. In the United Kingdom acute gastroenteritis is estimated to cost GBP 115 million per year. Children <5 years are estimated to have three to four episodes of diarrhea per child per year. Although most episodes are self-limiting each lasts 4–5 days, repeated episodes of AGE particularly in resource poor settings lead to undernutrition and stunting.

The causes of AGE vary with the location and time of year. Although more than 25 different bacteria and protozoa can cause AGE, more than 75% of cases are caused by viruses.

In the developing world diarrhea caused by bacterial and parasitic infections has decreased as a result of improved sanitation and safe drinking water but viral gastroenteritis has not declined. In the developed world viruses are the most common pathogens causing diarrhea.

In both developing and developed countries viruses are the major etiological agents of AGE in children <5 years of age. The viral gastrointestinal pathogens infect the intestine and cause gastrointestinal symptoms.

Before 1970, the etiology of more than 80% of AGE episodes was unknown and was attributed to weaning, malnutrition, or idiopathic causes. In 1972 the electron microscope was used to examine stool samples from patients with AGE and within 10 years, several new enteric viruses had been discovered: noroviruses, rotaviruses, astroviruses, enteric adenoviruses and sapovirus. Other viruses, such as aichivirus, human parechovirus, and human bocavirus, have recently been described in patients with diarrhea, but their association with AGE has not yet been established as most data have been reported in symptomatic individuals only and did not include age-matched healthy controls. Diagnostic investigations to determine the etiology of viral gastroenteritis include viral isolation on cell cultures, electron microscopy, antigen detection, nucleic acid detection as well as virus-specific serological responses. Comparison between different assays is difficult as sensitivities of tests vary. Molecular techniques offer a standard screening method and have a high sensitivity and specificity. Molecular assays are now commercially available to detect viral pathogens and are better than other investigations for the routine diagnosis of diarrhea. The detection of several pathogens simultaneously using multiplex tests is now possible. In a recent study using multiplex molecular testing in children with AGE, a pathogen was present in 63.9% of children with AGE as opposed to 11% in previous studies where traditional diagnostic methods were used. Viruses were commonly identified with NoV G11 present in 36.1%, rotavirus 13%, sapovirus 8%, adenovirus 7.8% and astrovirus 6.9% of cases [2]. The identification of viral pathogens is expensive and time consuming but it is important to identify specific

etiologies of AGE in order to target potential preventive interventions, such as vaccinations.

Poverty, under-nutrition, poor sanitation and hygiene, lack of clean water supply, overcrowding and lack of exclusive breast feeding are all risk factors for AGE. The clinical treatment options are rehydration and supportive. The efficacy of oral rehydration solution was shown over 40 years ago. Early use of fluid replacement can prevent progress and reduce the length of the AGE episode. However, access to oral rehydration solution and zinc treatment in AGE is very low (34%) in resource poor settings. The introduction of successful rotavirus immunization programs in some areas has significantly decreased rotavirus associated AGE. In these areas norovirus has now become a significant cause of AGE.

6.2 Rotavirus (RV) Disease

Rotaviruses were discovered in 1973 as a major cause of non-bacterial severe diarrhea in young children. Rotavirus is a common cause of gastroenteritis in young children globally and almost all children under 5 years of age have had RV infection. The incidence of RV infection in resource rich and resource poor countries is similar. In temperate climates the RV infections peak in the late autumn/winter and are seen in children I year and older. In contrast there is no seasonal peak in the more tropical climates and the children are infected at a younger age (<6 months).

6.2.1 RV Disease Burden

RV is the most important cause worldwide of severe gastroenteritis in children under 5 years of age. The World Health Organization (WHO) estimated that globally the number of RV deaths in children <5 years decreased from 527,000 deaths in 2000 to 215,000 deaths in 2013 [3]. The majority (>80%) of RV gastroenteritis deaths occur in resource-limited countries, such as those found in southern Asia and sub-Saharan Africa highlighting the need for RV immunization to be introduced to national programs globally. Six of the seven countries with the highest mortality due to RV diarrhea were located in Africa and would have been eligible for GAVI support. Similarly, data generated from global rotavirus surveillance networks highlights the burden of hospitalization for young children hospitalized for RV AGE. The median detection rate for RV was 40% globally and 41% in Africa.

Without immunization most children become infected with RV during the first few years of life, regardless of hygiene, sanitation or whether they are in a high income or resource poor setting.

6.2.2 Virus Structure

RV is a non-enveloped double stranded RNA (dsRNA) virus belonging to family *Reoviridae*. RV is a complex virus that has a triple-layered protein capsid (an inner

capsid, and intermediate and outer capsid) surrounding a genome of 11 segments of dsRNA that encode proteins needed for the viral life cycle. There are at least eight different antigenic groups (A to H). The outer capsid has two proteins VP4 and VP7, the intermediate layer is formed by VP6 and the inner layer by VP2. Most human infections are caused by Group A RV (90%), and occasionally by group B or C. Subgroup specificity is determined by VP6 which characterizes the antigenic characteristics of the various RV strains. Most human RVs belong to subgroup 1 or subgroup 11. RV serotype classification is determined by the two outer capsid structural proteins VP7 (the glycoprotein (G protein)) and VP4 (the protease-cleaved protein (P protein)). The VP4 and VP7 antigens protrude through the outer capsid and are critical for virus adhesion and penetration into the intestinal cell where the virus replicates and causes damage. In addition VP4 and VP7 elicit neutralizing antibodies thought to be relevant for the induction of protective immunity [4]. Genetic reassortment often occurs in mixed infections due to the segmented structure of the viral genome.

6.2.3 Mode of Transmission

RV is a common and very contagious virus. The main mechanism of transmission is the fecal-oral route. It can also be transmitted through close person-to-person contact and fomites such as hard surfaces. The virus can survive on hands for at least 4 hours and remains viable on surfaces for days. It can also be transmitted by fecally contaminated food and water, and by respiratory droplets. RV is very infectious as transmission is aided by a short incubation period (1–2 days), a very low infectious dose of <100 viral particles, high viral concentration within the stool (10^{12} particles per gram of stool) and prolonged shedding of virus. Shedding begins a few days prior to the onset of symptoms, peaks on day 3 and decreases after 7 days, although it may continue for several weeks in young children and immunocompromised patients. The more severe, the infection the longer the period of shedding of RV particles. Asymptomatic shedding has also been described. RV particles are resistant to environmental conditions.

6.2.4 Pathogenesis

The pathogenesis of RV infection is complex. RV replication only occurs in the gut and the triple capsid protein shell protects them from gastric acid and digestive enzymes in the intestine. After ingestion RV virions attach to the epithelial surface of the small intestine and enter the mature enterocytes near the tips of the villi and replicate and the viral copies infect new enterocytes. The tips of the villi, where absorption occurs, are damaged which leads to inadequate adsorption and impaired digestion. Diarrhea is caused by malabsorption due to apoptosis of the enterocytes, activation of the enteric nervous system, constriction of villous arterioles and a RV glycoprotein non-structural protein 4 (NSP4) which acts as a potent enterotoxin.

The cause of vomiting, which is a characteristic of RV infection and occurs early on in the illness, is unclear and multifactorial. It may involve early cytokine release acting centrally, the release of serotonin from enterochromaffin cells of the small intestine or delayed gastric emptying.

6.2.5 Clinical

RV infections can occur with a variety of presentations including asymptomatic infection, mild watery diarrhea to severe dehydrating diarrhea, with fever that can lead shock and death. Symptoms of RV infection are typically associated with the triad of fever, vomiting and diarrhea. After an incubation period of 18–36 hours, there is usually an acute onset of fever (53–89%) and vomiting (89–97%). This is followed by non-bloody diarrhea, which typically lasts for 5–7 days. The presence of fever, vomiting and diarrhea occurs more commonly with RV than with other gastrointestinal viruses (61.8% vs. 38.7%). In the first 3 months of life, illness is generally mild as a result of passive transplacental transfer of RV antibody. Between 3 months and 5 years of age, there is a spectrum of disease, although disease is often most severe in young children aged 3–24 months. The duration of illness was less than a week in 80% of RV cases. RV infection in infants and young children can lead to severe dehydration, acidosis and electrolyte imbalance. Of hospitalized children, <1% had persistence of fever, vomiting or diarrhea for more than 2 weeks. At 1-month follow-up, 88% of children had returned to their usual health status and the remainder had almost regained any weight lost. Children can be sequentially infected with RV several times. Each subsequent episode of RV gastroenteritis is typically milder than the initial infection and with each infection conferring greater protection against severe disease. The majority of children are infected by 5 years of age. RV can cause febrile seizures even when the diarrhea is mild. In some settings there is a winter spring peak and in others it is in circulation all year round.

6.2.6 Immunity

The immune response to RV infection involves both humoral and cellular responses including the production of cytokines and virus specific antibodies. However, the correlates of protection against RV have not been definitively determined. Acute RV gastroenteritis in children is associated with antigenemia and viremia (e.g., antigen detected in 43–64% by enzyme immunoassay (EIA) and confirmed by reverse transcription PCR in 67–93% of children). Antigenemia is most common early on in the illness, peaking between day 1 and 3 days after symptoms start. Persistent antigenemia (up to 11 weeks) has been seen in immunocompromised children. RV antigen level in the serum was associated with fever, frequency of diarrhea, but not with disease severity. RV antigen in the stools was significantly higher than serum antigen level. Antigenemia was also found more commonly in older (>24 months) children [4]. It is thought that the first infection with RV induces a homotypic, serum

neutralizing antibody response to the virus and that further RV infections elicit a heterotypic response. Natural infection gives protection against future symptomatic RV infections. After the first natural, infection 88% of children are protected against severe RV AGE, 75% protected against RV gastroenteritis and 40% protected against asymptomatic RV infection [5]. There is some cross-protection between serotypes.

6.2.7 Laboratory Diagnosis

Laboratory testing is not usually done, although it is the only way to confirm the diagnosis. Virus identification is important in controlling outbreaks of AGE. Several tests have been developed to detect RV in stool samples and these include EM, virus isolation in cell culture, polyacrylamide gel electrophoresis of viral segments, enzyme immunoassays, agglutination tests and molecular tests (real time polymerase chain reaction, RT-PCR) [4]. Multipathogen detection kits have been developed to identify numerous enteric pathogens. The most commonly used tests are the ELISA and latex agglutination, as these assays are easy to perform and are sensitive (70–98%) and specific (71–100%) [6]. New molecular assays are being developed that are rapid highly sensitive and specific for detection and genotyping which allows detection of circulating RV wild-type and vaccines strains causing AGE. These molecular techniques are sensitive and specific and are replacing the traditional assays that are time consuming and not as sensitive or specific.

6.2.8 RV Vaccines

RV immunization is cost effective in both developed and developing countries to decrease the mortality and morbidity associated with RV infection. It prevents severe RV AGE during the first 3 years of life when RV infection is most severe.

The RV disease burden is highest in areas where routine immunization coverage is low. An effective oral vaccine does not necessarily prevent infection but decreases the severity of the disease, which is in contrast to parenteral vaccination aims to prevent infection and thus eradicate disease. Herd immunity does occur in non-vaccinated children, as vaccination decreases transmission of RV in the community.

Rotavirus vaccine development has been to the Group A rotavirus as this is RV group that causes most (>90%) of disease in humans.

In 1998, the first RV vaccine consisting of a live oral Rhesus-human tetravalent reassortant (RotaShield) was licensed in the USA. The clinical trials demonstrated protection of 57–76% against all cases of RV gastroenteritis and protection of 82–96% against severe RV gastroenteritis. It was withdrawn a few months later, following reports of an increased risk of intestinal intussusception (IS) following immunization.

There are two licensed (2006) and currently available oral live attenuated effective rotavirus vaccines: RotaRix, a monovalent human vaccine derived from a G1P strain (GlaxoSmithKline Biologicals) and RotaTeq, a pentavalent vaccine containing five human-bovine reassortant strains G1, G2, G3, G4 and P1A (Merck) (Table 6.1). Both are live vaccines that can replicate in vaccinated children and are then shed in the feces post vaccination. They have been licensed in more than 100 countries worldwide. Both vaccines have a high efficacy and a good safety profile. The RV vaccines both require a cold chain.

The use of these vaccines has been shown to decrease hospital admissions due to RV diarrhoea. In 2009 the World Health Organisation (WHO) Strategic Advisory Group of Experts (SAGE) recommended that routine RV vaccination of all infants be included in the national immunization schedule of all member states. A limited number of European countries have implemented national RV vaccination programs with coverage ranging from 90% in countries such as Austria and Belgium, 24% in Greece and below 10% in the United Kingdom and Norway.

South Africa became the first country in the WHO African region to include rotavirus vaccine in the national immunization programme in August 2009. Rotarix is the vaccine in use in the "expanded programme on immunisation" (EPI) and it is given at 6 and 14 weeks along with other routine immunizations [7]. By the end of 2015, 79 countries had introduced RV vaccines and this number will increase as the WHO is involved in enabling low income countries to purchase the vaccines from support, through GAVI Alliance. Sub-Saharan Africa and Asia are the regions that still have the highest RV mortality. Only 22 of 51 counties in sub-Saharan Africa have a national RV immunization program, and there are none in Asia [1].

Table 6.1 Licensed rotavirus vaccines

Commercial name	RotaRix™	RotaTeq
Manufacturer	GlaxoSmithKline	Merck vaccines
Licensed	2006	2006
Valency	Monovalent: RV1	Pentavalent: RV5
Strain	Human G1P1	Human G1-G4, Bovine P1A
		G1, G2, G3, G4, P1A
Titre	10^6 median cell culture infective dose CCID50 after reconstitution	2.0–2.8 × 10^6 infectious units per dose
Type	Human live attenuated	Human-bovine reassortant
Schedule		
South Africa	6 and 14 weeks	
USA	2 and 4 months	2, 4 and 6 months
Number and volume of doses	2 (1mls)	3 (2mls)
Route of administration	Oral	Oral

6.2.8.1 RV Vaccines with Restricted License or in Development

Other RV vaccines on the market for the prevention of RV include the Lanzhou lamb rotavirus (LLR) licensed in China in 2000. It is a monovalent oral vaccine based on an attenuated G10P RV strain obtained from a lamb with RV diarrhea. The schedule for immunization is peculiar with one dose annually for children 2 months to 3 years, for a total of four doses before 5 years of age. This vaccine has not undergone thorough pre- and post-licensure evaluation, has only been used in China and is not recommended for use in immunization programs.

There was a drive in India to provide more affordable RV vaccines to India and other resource poor areas where there is a high RV disease burden. India has recently licensed ROTAVAC, a monovalent vaccine from human-bovine reassortant strain (116E) of serotype G9P. This is based on using naturally occurring reassorted strains found in asymptomatic neonates. It has shown 90% seroconversion after three doses to infants at 8, 12 and 16 weeks of age. Protection against RV infection was 35%. Six cases on IS occurred in 4500 vaccines and two cases in 2300 placebo recipients, all after the third doses. This will require further evaluation.

An oral serotype G3(RV3) vaccine is undergoing development in Indonesia. Based on the findings that neonates infected with the RV3 strain were asymptomatic and were protected against severe RV gastroenteritis in infancy and childhood, a RV3 vaccine was developed.

Although Rotashield was withdrawn from the market because of the associated increased risk of IS that occurred when it was used in the recommended 2, 4 and 6 month immunization regime. The IS associated with this vaccine occurred in older children given the first dose of vaccine after 3 months. Rotashield has now been re-evaluated in Ghana as a two dose regime given at a younger age with the first dose given before 1 month and the second before 2 months. The efficacy against any severity gastroenteritis with the first year of life was 64%. There were no cases of IS but the study only had 500 participants and was not powered to determine this.

Inactivated vaccines which could be produced in large quantities a low cost are being investigated in animal studies where they have been shown to induce neutralizing antibodies when administered via the intramuscular or intradermal route or by using micro needles in a skin patch.

6.2.8.2 RV Vaccine Efficacy

Pre-licensure vaccine trials in the developed world (Europe and the Americas) had shown that both vaccines were highly efficacious (85–95%) against severe RV AGE and against RV of any severity (68–79%). In addition the trials did not detect an increased risk of IS in the month following RV immunization. Vaccine trials found that vaccine efficacy (South Africa 76%, Malawi 49%) was lower in resource poor settings. The reasons for this are not known but could be due to vitamin A deficiency or malnutrition. Despite the low efficacy in resource poor settings, the benefit of the vaccines was enormous in these regions with a high disease burden. Vaccination prevented 4.2 episodes of severe RV AGE per 100 child years in South Africa and 6.7 episodes per 100 child years in Malawi because the rate of severe RV AGE is

2.4 times greater in Malawi [8]. Future studies will need to be determined if effectiveness is sustained in older children and whether they are effective against non-vaccine genotypes.

6.2.8.3 RV Vaccine Safety

Rotashield had been recommended to be given at 2, 4 and 6 months. After immunizing >600,000 children, 15 children developed IS in the 2 weeks following the vaccine. The risk for IS was greatest within 3–14 days after the first dose of Rotashield. The overall risk equated to 1 incident of IS for every 10,000 children immunized. There is a very small vaccine attributle risk for IS with both vaccines (1:50,000). Although porcine circovirus type 1 and 2 DNA was detected in the two licensed vaccines it was found not to be harmful to humans.

Key Points

RV is a major cause of AGE in children below 5 years of age in developing and developed countries.

RotaRix and RotaTeq are both oral live attenuated vaccines recommended by the WHO for routine immunization of all infants in both developing and developed countries.

6.3 Norovirus (NoV)

6.3.1 Introduction

Human norovirus, previously known as Norwalk virus, was first identified in 1972 by Albert Kapikan in stool specimens collected during an outbreak of gastroenteritis at an elementary school in Norwalk, Ohio, USA, and was the first viral agent shown to cause gastroenteritis. Illness due to this virus was initially described in 1929 as "winter vomiting disease" due to its winter occurrence and the associated frequency of vomiting. It is an enteric pathogen that causes substantial morbidity globally in a wide range of different population groups.

In areas with successful RV immunization programs there has been a decline in severe RV AGE and norovirus has become the leading cause of acute gastroenteritis worldwide across all ages groups. Noroviruses account for 12–21% of all cases of sporadic AGE in children under the age of 5 years worldwide. The US Centers for Disease Control and Prevention (CDC) has estimated that NoV is the most common cause of AGE in the US with 21 million cases, 70,000 hospitalizations and 800 deaths annually. This equates to a person in the US having five episodes of NoV gastroenteritis in a life time, and an average lifetime risk of NoV hospitalization of 1 in 70 and death of 1 in 700. In the US the elderly (>65 years) have the greatest risk of death from NoV infection and children <5 years have the highest rates of NoV infection [9]. The burden of NoV disease is not confined to the US and studies from Europe have reported similar estimates of NoV infection, outpatient visits, hospitalization and death.

NoV gastroenteritis is a global economic problem but it has not received the attention and funding it deserves in order to prevent and control the disease burden that this pathogen causes. NoV is perceived to cause a mild self limiting gastroenteritis. Using computational modelling systems it has been estimated that globally there are 699 million episodes of NoV gastroenteritis and 219,000 deaths resulting in $4.2 billion in health care costs and $60.3 billion in societal costs annually. These costs are highest in young children <5 years and cost to society is estimated to be $39.8 billion annually [10].

The incidence of NoV infections (about 10,000 per 100,000 people) is similar in both resource poor and high income countries. Although the majority (82%) of the world population live in resource poor settings and these areas have a higher NoV disease burden than developed countries, the NoV-associated health system costs were higher in the high income countries.

Although NoVs are frequently detected in stool samples from patients with gastroenteritis, they are also often detected in stools of healthy asymptomatic individuals. This may be true asymptomatic infections or may be due to a prolonged period of viral shedding post gastroenteritis. In developed countries the detection rates in symptomatic and asymptomatic healthy individuals are 20% and approximately 4–8% respectively. The prevalence of asymptomatic NoV detections is higher (9.7%) in children from lower income countries. This could be due to higher rates of infection or repeated asymptomatic infections and therefore increased levels of postinfection shedding. Comparing detection rates of various pathogens in gastroenteritis cases and healthy controls, complicates the interpretation of diagnostic results and the etiological cause of gastroenteritis [11].

The epidemiology of these viruses is well described in developed countries, although there is a lack of data regarding the epidemiology, prevalence and diversity of NoV infections in children in Africa. NoV was found to be the most common cause of diarrhea <1 year and the second most common cause <2 years in the Malnutrition and Enteric Disease Study [12]. Mans et al. analysed data from19 studies from 14 of the 54 African countries (Fig. 6.1) and found NoV was a common infection in children with AGE as well as in asymptomatic children [11]. The prevalence of NoV infections was 13.5% (range 0.8–25.5%) in children with gastroenteritis and 9.7% (range 7.0–31.9%) in asymptomatic children. Genogroup II (GII) was the most prevalent genogroup, then G1 and G1/11 respectively accounting for 84.1%, 13.9% and 1.9% of all documented NoV infections. The most common genotypes was GII.4 (65.2%) followed by GI.7 (33.3%), and GI.3 (21.3%).

6.3.2 Structure

Noroviruses are non-enveloped, positive-sense single stranded RNA viruses of the family *Caliciviridae* and the genus, *Norovirus*. They are divided into seven genogroups (GI–GVI1) based on the amino acid sequence of the major structural protein VP1. These genogroups are further subdivided into over 40 genotypes (11 G1 and 29 G11). There are also many variants in each genotype which contribute to the diversity of NoV.

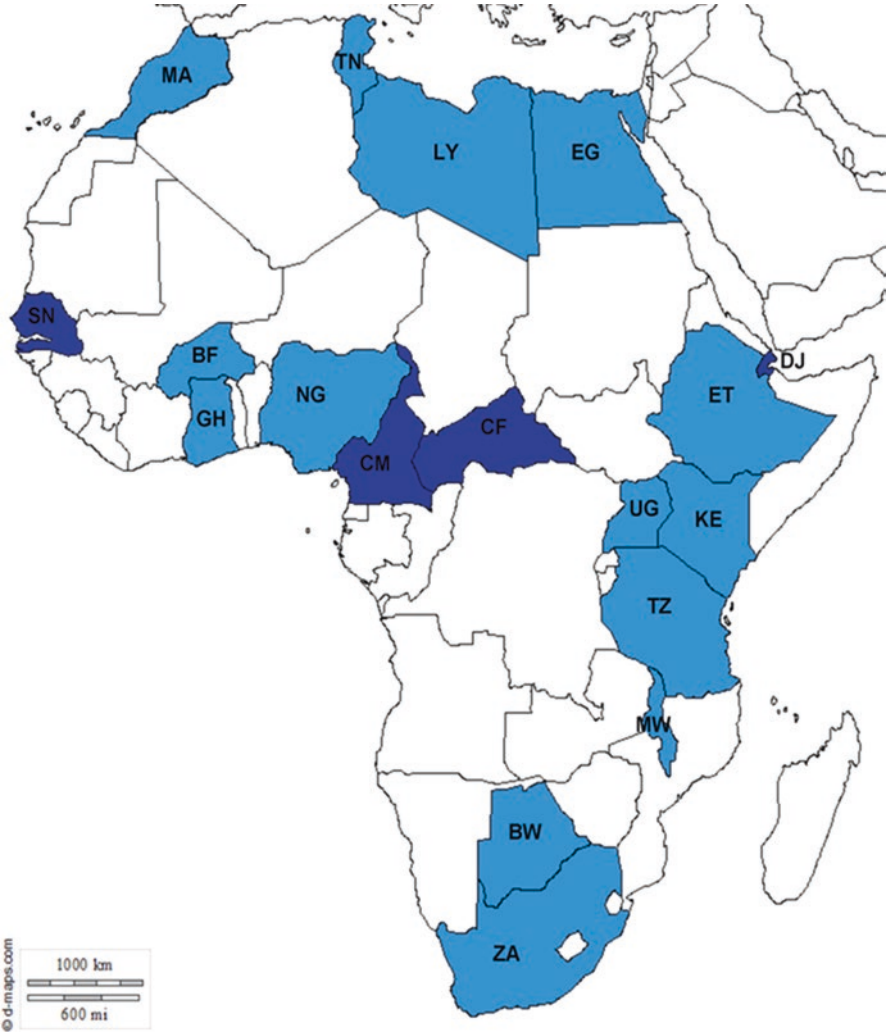

Fig. 6.1 Map of Africa indicating the countries from which prevalence and diversity data was obtained (*light blue*) and countries where NoV genotype data was available (*dark blue*). *BF* Burkina Faso, *BW* Botswana, *CF* Central African Republic, *CM* Cameroon, *DJ* Djibouti, *EG* Egypt, *ET* Ethiopia, *GH* Ghana, *KE* Kenia, *LY* Libya, *MA* Morocco, *MW* Malawi, *NG* Nigeria, *SN* Senegal, *TN* Tunisia, *TZ* Tanzania, *ZA* South Africa. Reproduced with permission from Janet Mans [11]

6.3.3 Clinical

Acute NoV infection is characterized by vomiting which occurs in almost 70% of patients and the NoV is found in most of the vomitus samples. Other nonspecific symptoms that occur are nausea, abdominal cramps, myalgias, and intense watery nonbloody diarrhea that usually resolves in 2–3 days. The incubation

period is short, around 48 hours. Children and immunocompromised individuals may have a more prolonged and severe disease course lasting for a few weeks to years. Noroviruses are highly contagious as the infectious inoculum is small (10–100 virus particles), there is prolonged viral shedding, they have an ability to survive in the environment and they are resistant to chlorine disinfectants. Transmission of NoV occurs predominantly through the fecal-oral route either by direct contact with infected individuals, via contaminated surfaces, food or water and also via vomitus droplets. Young children are more infectious than older children and adults. Contact with a symptomatic child is a major risk for NoV infection.

Of the 20 million cases of NoV gastroenteritis in the US, <1% are associated with outbreaks. NoV is the most common cause of food and water gastroenteritis outbreaks and accounts for 30–80% of these outbreaks. These outbreaks occur in a number of settings including schools, hotels, cruise ships, restaurants, schools, hospitals, old age homes, and child care facilities. Waterborne outbreaks are caused by G1 NoV whereas foodborne or person to person transmission is mainly through G11 strains. Studies from Kenya and South Africa have found significant levels of NoV (G1 and G11) contamination in river water.

NoV disease peaks in the winter in the Northern Hemisphere, but the seasonality is less defined in Africa. In North Africa the NoV peak was in the summer months, in Tunisia NoV occurred throughout the year, in Egypt the peak was in the winter months, in West Africa it was the cool dry season and in Southern Africa in the spring/early summer. NoV seasonality in these regions could be affected by humidity, temperature, rainfall, population density and the high prevelance of asymptomatic NoV infections with frequent exposure to NoV [11].

The fecal excretion of NoV in asymptomatic children is common. Studies have shown the NoV excretion in asymptomatic children ranges from 11.7% in Nicaragua, to 25% in England and 49.2% in Mexico City. Asymptomatic carriage has diagnostic and epidemiological implications.

6.3.4 Diagnosis

Diarrheal stool is the preferred specimen for NoV testing, although rectal swabs and vomitus can be used. The diagnostic yield will be higher if specimens are collected early on in the illness, within 24–72 hours of the onset of symptoms. The specimens should be kept at 4 °C (39.2 °F) prior to testing or for long term storage frozen at −20 °C (−4 °F) or −70 °C (−94 °F).

Several enzyme immunoassays are commercially available for detection of NoV G1 and G11 antigens in stool samples. These assays have a wide range of sensitivities and specificities as their performance is affected by the viral load in the sample, the viral genotype, the time into the illness that the specimen was collected, the age of the patient (<5 year vs. adult) and the type of assay kit used. These kits perform better in the of NoV outbreaks rather than in the diagnosis of NoV sporadic AGE. The sensitivity is also improved if several specimens [5–7] are collected per

outbreak. These enzyme immunoassays are easy and quick to perform but in the future will be replaced by NoV molecular tests when they become more readily available.

Several commercial RT-PCR assays are available for NoV RNA detection but the performance of these commercial kits have not been well studied. Commercial multiplex PCR/RT-PCR diagnostic assays for testing for multiple gastrointestinal pathogens have been developed. The sensitivity and specificity of these tests are greater than those of RT-PCR. In addition the TaqMan array assays are available and are highly sensitive and specific and allow for a panel of enteropathogens to be tested for in a sample. When assays using panels of multiple gastrointestinal pathogens are used, samples are often found to have several pathogens. The interpretation of these coinfections needs further investigation.

6.3.5 Immunity to NoV

The understanding of natural immunity to NoV is not fully understood. It is known that immunity is not permanently maintained and reinfections occur throughout life. Natural immunity to NoV exposure appears to be both strain and genotype specific with no or minimal cross protection between genotypes. Repeat infections by NoVs having the same genogroup are common, but repeat infections from NoVs having the same specific genotype rarely occur. It appears that the immunity to natural NoV infection is short lived and lasts for 6 months to 2 years.

There are seven NoV genogroups but only a few NoV genogroups (G1, G11, and G1V) infect humans and are associated with disease in humans. The original Norwalk virus was a G1 virus, but presently the predominant NoV genotype globally is G11, specifically G11.4 and it accounts for >80% of confirmed NoV gastroenteritis infections worldwide. Genotype data from Africa found that 84.1% of detected NoVs were Genogroup 11 and 13.9% were Genogroup 1 strains. NoV G11.4 was the most common strain identified [11]. There is extensive genetic and antigen diversity among NoV strains due to numerous point mutations and recombination events. It evolves and new G11.4 variants emerge every 2–3 years replacing the circulating strain. These novel variants have altered antigenicity and have advantages, such as being shed in higher numbers and having greater transmissibility than other genotypes. The continuing evolution of new strains will require regular epidemiologic surveillance with intermittent updating of NoV vaccines to keep up with shifting antigen changes.

There is limited cross-protection and protection against one NoV strain does not protect against infection with other strains. NoV is often detected in stool samples from patients with diarrhea but it is also found in stools from healthy individuals. Asymptomatic NoV infection occurs in approximately 4.8% of healthy people in the developed world and more frequently in children from lower income countries. This complicates the interpretation of diagnostic tests.

Carbohydrates expressed on many cells act as receptors for viruses. Histo-blood group antigens (HBGAs) recognize NoV. HBGAs are a diverse group of

carbohydrate glycans expressed on the mucosal epithelium of the gut as well as red blood cells respiratory epithelium. The pathogenesis of NoV infection is thought to involve the binding of NoV to the human HBGAs that are recognized as receptors on the epithelium of the small intestine allowing NoV attachment and entry into the cells. Variations in the expression of these HBGA binding sites affects the susceptibility to NoV infection. Three gene families expressing the ABO, secretor (fucosyltransferase FUT2) and Lewis-type (fucosyltransferase FUT3) antigens code for HBGA production. Persons with a functional FUT2 gene (secretors) are more susceptible to common viral infections including NoV.

6.3.6 Treatment and Prevention

The treatment of NoV AGE is supportive and involves correcting the dehydration and electrolyte abnormalities as well as oral zinc supplementation. Implementation of outbreak control and prevention strategies are limited to the use of disinfectants and hand sanitizers. There are no effective antiviral agents available to treat NoV infection at present. Research is focused on drugs that could inhibit infection by preventing adhesion of enteric viruses to the intestinal epithelium or by preventing viral proliferation. There are no commercially available antivirals to specifically treat NoV infection. In animal studies, nucleoside analogues ribavirin and favipiravir reduced the infectious viral load in feces. There are anecdotal case reports of ribavirin in some patients, but not in others with common variable immunodeficiency. Further development of suitable antiviral drugs is needed to treat persistent infections in chronic shedders or immunosuppressed patients and so limit the spread of NoV infection.

6.3.7 Vaccines

The global burden of NoV disease justifies the development of NoV vaccines. A NoV vaccine would be beneficial to both developed and developing countries. Licensed NoV vaccines are not yet available. Vaccine development for norovirus has been difficult. Due to the inability to culture NoV it has not been possible to produce live oral vaccines for human NoV infection, which have been so effective for RV. Therefore NoV vaccine development has focused on using inactive, nonreplicating NoV recombinant capsid proteins that lack the viral genome such as virus-like particles (VLP) and P particles. They are structurally and antigenically similar to wild virus but lack the viral genome. Several candidate vaccines are under development but are still in the clinical trial phase.

There are host and pathogen factors that complicate development of a NoV vaccine which will most likely have to be multivalent and require regular reformulations in response to the viral antigenic drift (Table 6.2).

Table 6.2 Challenges for norovirus vaccine development

Inability to culture norovirus
Incomplete understanding of natural immunity to norovirus
No known correlates of protection
Noroviruses are highly diverse viruses (genogroup and genotype)
Limited cross protection across norovirus strains
Short duration of natural norovirus immunity
Inherited human blood group antigen (HBGA) variability
Unknown efficacy in vulnerable groups (<5 years and the elderly)
Vaccine will probably require regular vaccine updating
Vaccine will need to be bivalent and include G1 and G11 VLPs

6.3.7.1 VLPs Vaccines

Vaccine trials have been conducted in adults in high income settings, but no clinical NoV vaccine trials have been conducted in children. Several adult human clinical trials have evaluated immunization with different formulations of VLPs and using several different routes of administration for protective immunity to NoV. Serological responses have been generated to VLPs given intra-nasally, intramuscularly and orally. Two recent phase 1 trials using different NoV subunit vaccines administered via different routes, have reported good tolerability and immunogenicity [13]. Intranasal vaccination in humans has been shown to provide short term protection after NoV rechallenge. Adults were given two doses of adjuvanted NoV VLP vaccine or placebo intranasally 3 weeks apart, then challenged with live virus, homotypic to the vaccine strain. The vaccine was well tolerated. There was a fourfold increase in NoV specific IgA in 70% of vaccinated adults and it provided partial protection after rechallenge against infection and reduced virus specific gastrointestinal symptoms. It was also found that recipients with a serum HBGA blocking antibody titre of >1:200 had a 72% reduction of risk of NoV gastroenteritis compared with individuals with titres less than 200. HBGA-blocking activity may prove to be a correlate of immunogenicity and protection [14].

As NoVs are highly diverse viruses, so a broadly effective vaccine would require bivalency and contain both GI and GII VLPs. A VLP bivalent (G1.1 and G11.4) vaccine intramuscularly has been evaluated in humans. Two intramuscular injections were given 1 month apart and then recipients were rechallenged 28 days later with a heterologous G11.4 strain. Vaccine recipients had reduced diarrhea and vomiting and increased virus-specific antibodies when compared to placebo recipients.

It is thought that the use of intramuscular VLP vaccination will be useful as a booster in adults who have had previous a NoV infection, but who have insufficient protective antibody levels. Whereas, mucosal VLP vaccines will be needed in infants and young children who are naïve to NoV infection.

Due to genotype specific immune responses a polyvalent vaccine will need to be developed. In addition, because of the NoV antigens variation this vaccine will need regular updating.

Viral vector-based VLPs vaccine candidates have been investigated in animal models as potential vaccine candidates. They would probably require only one dose and would give a higher inoculum of VLPs than conventional VLPs. However, there are safety concerns. Recombinant vectored VLP vaccines have been evaluated in mice and appear to elicit mucosal and systemic immune responses.

6.3.7.2 P Particle Vaccines

The capsid protein VP1 has a S (for shell) and a P (for protruding) domain which is important for binding the virus to HBGAs. P particles are also potential vaccine candidates and in animal studies they have been shown to have similar a immunogenicity and efficacy as the VLPs. P particle vaccines have not yet been evaluated in humans.

Key Points

NoVs are a leading cause of acute gastroenteritis and is the most common pathogen causing food borne gastroenteritis.

G11.4 is the predominant NoV genotype globally.

New NoV variants evolve through antigenic drift.

Histo-blood group antigens (HBGAs) are important for initiation of NoV infection.

VLPs have been developed as a candidate norovirus vaccine.

Muliplex PCR tests are sensitive and specific and can test for enteric pathogens simultaneously in stool samples.

6.4 Astrovirus (HAstV)

Human astrovirus is a common cause of mild gastroenteritis in children accounting for about 10% of all sporadic diarrhea cases. HAstV most commonly infects children <4 years old, although infections in healthy adults, the elderly and immunocompromised are reported. Although infections occur throughout the year, there is a seasonal peak in late winter and spring. HAstV-induced diarrhea is usually not severe enough to require hospitalization and resolves spontaneously. The incidence of HAstV AGE is higher in developing countries and rural areas.

6.4.1 Virus Description

Astroviruses were discovered in 1975 and are small, round non-enveloped, single stranded, positive-sense RNA viruses. They are named because of their star like appearance under the electron microscope. Eight antigenic serotypes (HAst V1 – HAst V8) have been identified, causing gastroenteritis predominantly in children. HAstV1 is the most common serotype detected worldwide.

The detection rates of HAstV2-8 have increased using the new molecular techniques. This may be due to the increase sensitivity of the assays or to new emerging serotypes.

6.4.2 Clinical Features

Clinically the infection is characterized primarily with diarrhea, although abdominal pain, vomiting (20–62%), nausea and fever (7–25%) can occur. Infections are usually self-limiting and of short duration (around 3–5 days) with a median of four stools during the first 24 hours. Dehydration was not common (0–30%) in HAstV gastroenteritis and very few (3%) children were hospitalized. Asymptomatic infections are common. HAstV diarrhea is less severe than RV AGE. Studies have documented co-infections of HAstV with RV or NoV in 13–65% of cases. Transmission is person to person via the fecal oral route. Viral shedding lasts for 5 days after the onset of symptoms, but children may shed asymptomatically for weeks after the illness. In China over 95% of HAstV infections occurred in children <2 years of age whereas in France infections were more common >3 years of age and in Spain the peak was between 2 and 4 years of age. Most children are infected with HAstV and antibodies to astroviruses can be detected in >80% of 5–10 year old children.

6.4.3 Diagnosis

Electron microscopy was the earliest method of identification of this virus. Enzyme linked immunoassays using monoclonal antibodies are now available commercially for detection of HAstV in feces but a high concentration of virus is needed for a positive reaction. These traditional detection methods lack sensitivity. The detection of HAstVs with molecular techniques using reverse transcript-polymerase chain reaction methods are sensitive and have resulted in increased levels of detection of HAstV in prevalence studies.

6.4.4 Prevention

Prevention of HAstV infections is based on control of transmission of the virus. No commercially available vaccines have been developed for HAstV.

6.5 Enteric Adenovirus

Adenoviruses are responsible for 1.5–5.4% of AGE cases in children <2 years old. Enteric adenovirus infection is a common cause of infantile diarrhea in the day care setting, but less common than RV infection and, in some settings, less common than

infection with HAstV. It can also affect adults and immunocompromised patients. Adenovirus can be excreted in the feces for weeks after AGE symptoms have resolved. Watery diarrhea is usually associated with fever and lasts 1–2 weeks.

Mesenteric adenitis and IS have been associated with nonenteric adenovirus serotypes (ie, types 1, 2, 3, 5, 6). Approximately 40% of infants with IS have positive findings from cultures of stool or mesenteric lymph nodes for nonenteric serotypes, and most have no evidence of infection with enteric strains (ie, 40, 41). The role of adenovirus in this setting is unclear. Mesenteric lymphadenitis or hyperirritable small bowel associated with nonenteric adenoviral infection has been postulated to lead to IS. However, most patients with IS have no evidence of adenoviral infection (based on culture, serology, or histopathologic viral inclusion findings); thus, IS may be related to multiple etiologies.

6.5.1 Virus Description

Adenoviruses are double-stranded non-enveloped DNA viruses. They are the only DNA viruses amongst the most common viral pathogens in children. Although there are 57 distinct adenovirus serotypes only serotypes 40 and 41 and to a lesser extent types 18, 31 and 52 that have been associated with diarrhea.

6.5.2 Diagnosis

These serotypes are difficult to culture. Electron microscopy, monoclonal antibody assays, ELISAs support the association of these strains with enteric disease.

6.5.3 Clinical Features

The incubation period of enteric adenovirus infection is 3 and 10 days. The diarrhea is characterized by mild persistent diarrhea with fever and vomiting. In infections with adenovirus 41, the duration of diarrhea is 12 days and prolonged symptoms are not uncommon, while adenovirus 40 infection generally has a more intense course with diarrhea lasting 9 days. In Infections caused by both serotypes, vomiting is mild, starting just after the onset of the diarrhea onset and lasting 2–3 days. The associated fever is mild and has a short duration.

6.5.4 Prevention

Prevention of enteric adenovirus infections is to control of transmission of the virus. There is no vaccine available to enteric adenovirus.

6.6 Sapovirus

Sapoviruses like NoVs are also part of the family *Caliciviridae*. They were first found in diarrhea stools in 1976. Sapovirus is generally associated with mild AGE and it rarely leads to death. However, more serious infections can occur in immunocompromised patients. They cause diarrhea in people of all ages, although more commonly in adults than in children and are responsible for outbreaks and sporadic cases. Sapovirus infections account for 2.2–12.7% of all gastroenteritis globally. Sapovirus infection causes milder diarrhea than either RV or NoV and has been associated with vomiting in 60% of cases. As with NoV fever is uncommon. The incubation period is 1–4 days and the infection lasts around 6 days. Sapoviruses have also been found in asymptomatic children. Outbreaks occur throughout the year. Mortality is rare but may occur in the immunocompromised or elderly. The transmission is via the fecal–oral route, but can also be foodborne. Using molecular techniques sapovirus has been detected in feces of healthy asymptomatic persons with viral loads similar to those shed by individuals with AGE.

Sapovirus is a small positive-sense nonenveloped single stranded RNA virus. There are five human genotypes (G1–GV) of Sapovirus with G1, G11, G1V, and GV all infecting humans whereas G111 infects porcine species.

6.6.1 Diagnosis

Under EM sapoviruses have a typical "Star of David" appearance. ELISAs have been developed for the detection of human sapovirus antigens but they are of low sensitivity and are not commercially available. RT-PCR and particularly real-time RT-PCR is the most sensitive and specific method us in faecal samples.

6.7 Potential Pathogenic Viruses in the GIT Tract

6.7.1 Aichi Virus

Aichi viruses are members of the *Picornaviridae* and have been identified in fecal samples from patients with diarrhea. The prevalence of Aichi viruses (0.5–1.0%) in stools was too low to determine a significant association with AGE.

6.7.2 Torovirus

Toroviruses are members of the *Coronaviridae.* They were identified in 1984 in children and adults with AGE.

6.7.3 Picornavirus

Picornaviruses are members of the *Picornaviridae*. Using sequence independent amplification methods, several novel viruses have been described in AGE e.g. cosavirus, scaffold virus, klassevirus/salivirus.

6.7.4 Other Viral Families

Three new polyomaviruses (MW polyomavirus, MX polyomavirus and STL polyomavirus) have been identified in stool samples from healthy children using next-generation sequencing assays. These new polyomaviruses do not seem to be associated with gastroenteritis.

Bufavirus, and tusavirus are both members of the *Parvoviridae* family that have been recently associated with gastroenteritis. They have been isolated in patients with diarrhea but not from healthy controls.

Recovirus is a new member of the *Calciviridae* family and has been found in diarrhea samples in one study from Bangladesch [15].

Many new viruses have been identified in the gastrointestinal tract but their role as enteropathogens is not clear. The presence of a virus in a fecal sample does not mean that the virus is replicating in the intestinal cells.

6.7.4.1 Key Points

AstV is a common cause of mild diarrhea.

New viruses are being identified in stool samples but their role as pathogens is unclear.

6.8 Conclusion

Viral pathogens play an important role in gastroenteritis in children. The disease burden of RV is substantial in both resource poor and resource rich settings. NoV has become a leading cause of acute gastroenteritis in areas universal RV immunization programs exist. Viral diagnosis is required determining the etiology of outbreaks of diarrhea and in investigating cases of gastroenteritis in infants and in severely ill patients. Antigens of RVs and adenoviruses can be detected in the feces of the patient, and the rapid tests applied have proven to possess sufficient sensitivity. Sensitivities of the antigen detection tests for NoV are poor. In addition to antigen detection tests, a RT PCR test based on the detection of NoV nucleic acids has come onto the market, being both easy to use and substantially more sensitive. In the future, multiplex PCR tests allowing simultaneous detection of several different diarrhea-causing microorganisms are expected to become more common.

Universal RV vaccination is cost effective and has been recommended by the WHO that it be included globally in national immunization programs. There is great interest in the development of enteric vaccines, especially a combined NoV VLP/rotavirus vaccine.

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Viral Hepatitis

7

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Abstract

Hepatitis is a general term, which refers to the inflammation of the liver. Hepatitis occurs as a result of infection with various pathogens, exposure to alcohol, medications, chemicals, toxins, as well as immune disorders.

7.1 Introduction

Hepatitis is a general term, which refers to inflammation of the liver. Hepatitis occurs as a result of infection with various pathogens, exposure to alcohol, medications, chemicals, toxins, as well as immune disorders.

Hepatitis in children is predominantly caused by viruses; and the incidence and etiology of viral hepatitis varies according to the immunization regime and geographical location of different countries. The hepatotrophic viruses, hepatitis A, B, C, D and E account for the majority of cases of viral hepatitis. Other viruses that commonly cause hepatitis include the herpes viruses (cytomegalovirus (CMV), Epstein–Barr virus (EBV) and herpes simplex) and the enteroviruses (coxsackie virus). There are many other viruses that can affect the liver as part of a systemic viral illness (measles, rubella, varicella-zoster virus, parvovirus B19, adenovirus) as well as the mosquito-borne viral infections (yellow fever, dengue haemorrhagic

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fever, Lassa fever, Ebola virus, Marburg virus and Rift valley fever), but they will not be discussed in this chapter.

The clinical symptoms and signs of the different viruses are often indistinguishable, but the epidemiologies are markedly different and clinically this chapter will concentrate on the liver manifestations.

Despite the availability of effective vaccines for hepatitis A, B and E; effective therapy for hepatitis B and herpes simplex infections; and curative therapy for hepatitis C; viral hepatitis remains a significant global health challenge. In May 2016, the World Health Organisation (WHO) adopted a global hepatitis strategy with the goal to eliminate viral hepatitis as a public health threat by 2030. The targets to be achieved by 2030 are ambitious and include: 90% reduction in new cases of chronic hepatitis B and C, 65% reduction in mortality due to hepatitis B and C and 80% of treatment eligible persons with chronic hepatitis B and C infections being treated.

7.2 Hepatotrophic Viruses

7.2.1 Hepatitis A

Hepatitis A (HAV) is endemic in many parts of the world and is transmitted primarily via the fecal-oral route. The prevalence of hepatitis A strongly correlates with socio-economic conditions and access to safe water and adequate sanitation and this has contributed to the endemic nature of hepatitis A.

7.2.2 Virus Structure

Hepatitis A is a small, non-enveloped, single stranded RNA virus and is a member of the family *Picornaviridae* belonging to the genus *Hepatovirus.* Human HAV has only one serotype, but can be grouped into four human genotypes (I, II, III, VII) using RNA sequencing [1–4]. The virus may persist in the environment for prolonged periods even under high levels of environmental stress, but is inactivated by boiling (at >85 °C or 185 °F for 1 min) and on exposure to household bleach (1:100 dilution in tap water) [3].

7.2.3 Epidemiology and Transmission

The global epidemiology of hepatitis A has changed markedly due to improvements in water supply, sanitation and hygiene. In highly industrialized countries, prevalence in blood donors is now <10% and cases are largely imported by individuals visiting endemic areas [3]. As endemicity patterns shift from high to intermediate levels, a larger pool of susceptible older children and adults develops and symptomatic disease with increased morbidity and mortality as well as outbreaks is more frequent [5].

HAV is highly infectious with person-to-person spread being the most common route of transmission, followed by ingestion of fecally contaminated water or food.

7.2.4 Clinical Presentations of Hepatitis A

Hepatitis A infection is usually a self-limiting disease, there is no chronic carrier state and immunity following infection is considered to be life-long. Acute hepatitis A may be a trigger for unmasking autoimmune hepatitis. The incubation period is 15–50 days (average 28 days) and viremia is transient (2–4 weeks). Individuals are most infectious 2 weeks prior to the onset of jaundice. Most individuals will remain infectious for 1–2 weeks following the onset of jaundice [1]. However, prolonged shedding of the virus in stool has been documented, thus increasing the period of infectivity [6]. The clinical presentation in an area is largely influenced by the age at which individuals become infected and the presence of underlying risk factors for severe disease [6, 7]. In areas where socio-economic standards are poor and there is inadequate access to clean water and sanitation, infection occurs early in life and produces mostly mild or asymptomatic disease. In these areas, rates of infection are higher, but morbidity considerably less. Most people in such communities are immune by adolescence and this immunity persists lifelong. In developing countries, most children are infected before the age of 9 years [3].

In areas where exposure to HAV in childhood is less likely due to improved living conditions, infection will occur less frequently, but will present in adolescents and adults and is more likely to be symptomatic. Thus, morbidity associated with disease in this setting is considerably greater.

The overall mortality is 0.3% in icteric cases and 0.1% in children <15 years of age.

The different clinical presentations include:

- ***Asymptomatic infection***: Most children <4 years of age are completely asymptomatic
- ***Symptomatic hepatitis without jaundice***: 90% children aged 4–6 years are anicteric
- ***Symptomatic hepatitis with jaundice***: 40–70% individuals >15 years of age of age, present with jaundice [4]. A prodromal illness usually precedes the jaundice in 85% individuals and includes:
  - Loss of appetite, fatigue and malaise
  - Flu-like symptoms: fever, cough, coryza, pharyngitis, photophobia and headache
  - Arthralgia and myalgia
  - Nausea, vomiting and abdominal discomfort
  - Diarrhea.

The symptoms of the prodrome usually decline with the onset of jaundice.

7.2.5 Complications of Hepatitis A

1. ***Fulminant hepatitis with acute liver failure***: Although there is an increased risk in adults >40 years of age, it can also occur in very young children. The severity of the liver injury is often underestimated in children, as encephalopathy is often

a late and terminal presentation in children <5 years of age. Mortality rates are 70–95% unless liver transplantation is performed, where 65% survival rates have been achieved.
2. ***Cholestatic hepatitis***: An uncommom complication characterized by prolonged jaundice with marked pruritus, more common in adolescents. Steroids should not be used to treat cholestatic hepatitis A.
3. ***Relapsing hepatitis***: This is uncommon, occurring in 3–20% of symptomatic individuals. It may occur 4–15 weeks after the initial symptoms have resolved. Illness manifests with a relapse of symptoms and liver function abnormalities. In addition, HAV is shed in the stool and patients are again infectious. The vast majority will recover fully, but this may take up to 12 months. It tends to occur if individuals return to active sport too early.

7.2.6 Diagnosis of Hepatitis A

Viral hepatitis cannot be distinguished clinically or biochemically but requires a serological diagnosis. Elevated transaminases (ALT and AST usually 10–100 times upper limit of normal) confirm the presence of hepatitis.

- ***Acute hepatitis A***: Positive anti-HAV IgM. Levels decline over 3–6 months following infection
- ***Previous exposure to hepatitis A or post HAV vaccination***: Positive anti-HAV IgG.

7.2.7 Prevention of Hepatitis A

Pre-exposure prevention includes good personal hygiene, adequate sanitation and access to safe food and drinking water. Hepatitis A vaccination (a single dose with a booster at 6–12 months) provides long-term protection. It is not part of the expanded program of immunization (EPI) in many developing countries; but with changing socio-economic demographics and potential transition towards a lower hepatitis A endemicity level in many developing countries; EPI policies may need to be reevaluated. A West African seroprevalence study in urban children has indicated that the midpoint of population immunity has shifted to school-aged children suggesting a transition to lower levels of hepatitis A endemicity, and greater risk of symptomatic disease [8].

Hepatitis A vaccination is recommended in high-risk groups i.e. children with chronic liver disease, immune-compromised children including solid organ transplant recipients and children on immunosuppression. HAV vaccination should be considered in children >2 years of age if affordable.

Vaccination is now the preferred post-exposure approach in children >2 years of age. HAV vaccine must be given early, preferably within 72 hours of exposure, but can be administered up to 14 days post-exposure.

Immune globulin is still recommended as post-exposure prophylaxis for immune-compromised children due to the reduced vaccine immunogenicity and more severe disease.

7.2.8 Treatment of Hepatitis A

There is no specific antiviral treatment for hepatitis A infection and treatment is supportive. Children with severe symptomatic disease (jaundice and associated nausea and vomiting) should be hospitalized and liver transplantation must be considered in patients presenting with fulminant liver failure.

7.2.9 Hepatitis B

Hepatitis B is an entirely vaccine-preventable disease, but it remains endemic in many regions of the world. In a recent systematic review based on observational studies performed in the general population, amongst blood donors, health-care workers and pregnant women between 1965 and 2013, the number of hepatitis B surface antigen (HBsAg) positive individuals was highest in the Western Pacific (95.3 million, prevalence estimate 5.26%) and Africa (75.6 million, prevalence estimate 8.83%) regions, which together included nearly 70% of the global burden Hepatitis B virus. This is most likely an underestimate due to under-reporting and exclusion of high-risk groups [9]. In endemic countries, hepatitis B virus (HBV) endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged 5–9 years and adults [10]. Globally, there are ten genotypes (A–J) [11, 12] and the HBV genotypes influence the spectrum of disease, the risk of hepatocellular carcinoma and the response to antiviral treatment.

7.2.10 Virus Structure

HBV is an enveloped partially dsDNA virus and is a member of the *Hepadnaviridae* family. It has a compact genomic structure (±3.2 kb) with four overlapping open reading frames that encode four sets of viral proteins: HBsAg, HB core Ag, viral polymerase and HBx protein.

Ultrastructurally, there are three distinct morphological forms found in the sera of infected patients: small non-infectious spherical particles (17–25 nm), tubular filamentous forms of various lengths and the complex, spherical, double shelled particle (42 nm).

The virus circulates in serum as a 42-nm, double-shelled particle, with an outer envelope component of HBsAg and an inner nucleocapsid component of hepatitis B core antigen (HBcAg). HBV DNA can be detected in serum and is used to monitor viral replication. HBeAg, unlike HBsAg and HBcAg, is not particulate, but rather is detectable as a soluble protein in serum.

HBV is found in blood and all body fluids and survives in dried blood for prolonged periods (weeks) and is stable on environmental surfaces for at least 7 days at 25 °C (77 °F). Hepatitis B virus is stable at temperatures below 60 °C (140 °F): stable at 37 °C (98.6 °F) for 60 min and 56 °C (132.8 °F) for 30 min, and stable for years at −70 °C (−158 °F). HBV is stable at pH 2.4 for up to 6 hours (some infectivity is lost). HBV is susceptible to inactivation by many disinfectants including 1% sodium hypochlorite, 2% alkalinized glutaraldehyde and formaldehyde.

7.2.11 Transmission of Hepatitis B

HBV is a 100 times more infectious than HIV and 10 times more infectious than HCV. HBV is transmissible via perinatal, percutaneous or sexual exposure to HBV-infected body fluids including serum, saliva, semen and vaginal fluids.

All HBsAg positive individuals are infectious; but HBeAg positive individuals are more infectious as they have higher rates of HBV replication.

7.2.11.1 Horizontal Transmission

This is the main route of HBV transmission in sub-Saharan Africa, usually occurring in children between the ages of 6 months and 5 years [13–16], from unapparent percutaneous exposure to infected blood or body fluids. Modes of acquisition include close non-sexual person-person contact over a long period with infected older siblings and playmates; sharing of personal items e.g. toothbrushes, razors, hairclippers and traditional scarification practices.

7.2.11.2 Perinatal Transmission

This occurs mainly at birth and is the main route of transmission in South-East Asia where mothers are usually HBeAg positive in the immune tolerant phase of chronic infection. There is an increased risk of perinatal transmission associated with HBV DNA levels >200,000 IU/mL [17–22]. In-utero transmission is rare and transmission through breast milk is controversial [23]. The risk of chronic HBV infection at 6 months in the absence of any intervention is 70–95% in babies born to HBeAg-positive women and <10% in babies born to HBeAg-negative women.

Risk of transmission from women acutely infected in the first or second trimester is low, but increases to approximately 60%, if acute infection occurs in the third trimester.

Maternal HIV/HBV coinfection increases the risk of perinatal transmission up to 2.5-fold as HIV/HBV coinfected pregnant women are twice as likely to test positive for HBeAg, three times more likely to test positive for HBV DNA and have higher HBV DNA levels, thereby increasing the risk of mother-to-child transmission (MTCT) [10, 24].

7.2.11.3 Sexual Transmission

HBV is efficiently transmitted sexually, but the exact risk of transmission per sexual contact is unknown. Sexually active adolescents who have not been vaccinated are at risk.

7.2.11.4 Percutaneous Transmission: Needle-Stick Injuries [25]

The risk of HBV transmission from needlestick injury is:

- 30–60% from exposure to HBeAg-positive blood
- 10–30% with HBeAg-negative blood
- Injection drug use poses a high risk of HBV transmission.

7.2.12 Clinical Presentations of Hepatitis B

The clinical manifestations of acute and chronic HBV infections are variable.
The risk of chronicity is dependent on the age of acute infection:

- 70–95% for infants exposed perinatally (HBeAg positive mother)
- 25–50% for children aged 1–5 years
- 6–10% for 5–20 years
- 1–3% for adults >20 years.

7.2.13 Acute Hepatitis B

The incubation period ranges between 1 and 4 months and clinical manifestations of acute hepatitis B depend on the age of acquisition:

- Anicteric, asymptomatic infection in about 70% individuals, especially if infected during early childhood
- Symptomatic, icteric illness in 30%
- Fulminant hepatitis occurs in 0.5–1%.

Acute HBV infection in children under the age of 10 is usually asymptomatic, but in adolescents it is usually symptomatic, has various phases and is associated with a full clinical recovery.

7.2.13.1 Early Prodromal Phase

In symptomatic individuals, the illness may be heralded by a serum sickness-like syndrome which precedes jaundice by 14–21 days and disappears with the onset of jaundice. The prodromal symptoms include fever, urticaria, arthralgia and arthritis.

7.2.13.2 Preicteric Phase

The abrupt or insidious onset of non-specific constitutional symptoms or an influenza-like illness may occur and include malaise and fatigue; myalgia; anorexia, nausea and vomiting; epigastric or right upper quadrant discomfort.

Physical examination may be unremarkable or may reveal a tender hepatomegaly and splenomegaly. Hepatosplenomegaly is usually mild (liver palpable 2–3 cm below the costal margin and spleen tipped).

7.2.13.3 Icteric Phase

With the onset of jaundice approximately a week after the preicteric phase; fever and constitutional symptoms subside. Anorexia, nausea and vomiting may transiently worsen. The presence of dark urine and pale stools often raises the clinical concern of obstructive jaundice. Pruritic scratch marks maybe present, if jaundice is severe or prolonged. Weight loss is common.

7.2.13.4 Convalescent Phase

Jaundice tends to wane rapidly over days in adolescents, but tends to persist longer (6 weeks or more) in adults. The preicteric phase symptoms disappear, pruritus abates and the hepatosplenomegaly gradually resolves.

7.2.14 Fulminant Hepatitis B

This syndrome is characterized clinically by jaundice, hepatic encephalopathy and coagulopathy (international normalized ratio (INR) > 1.5), which generally occurs within 8 weeks of the onset of the acute illness. This is the result of massive cellular immune-mediated lysis of infected hepatocytes which explains the frequent lack of detectable viral replication in such patients.

Although the majority of infected infants become chronically infected, infants born to HBsAg positive, HBeAg negative mothers may develop fulminant hepatitis within the first 12 weeks of life [26]. The increased incidence of fulminant hepatitis B at this age is due either to partial immunity (as the mother may have circulating anti-HBe) or due to vaccine failure. However, the majority of cases are associated with the transmission of a pre-core mutant virus from mother to child [27]. Although, fulminant hepatitis B may be effectively prevented by vaccination of all infants of hepatitis BsAg positive mothers, this depends on antenatal screening and effective prevention of MTCT.

7.2.15 Chronic Hepatitis B

Chronic Hepatitis B is defined as the persistence of HBsAg positivity ≥6 months. It is frequently a clinically silent disease and is often identified incidentally.

Physical examination may reveal no or few signs. Peripheral stigmata of chronic liver disease (spider naevi and palmar erythema) and signs of portal hypertension (distended abdominal veins, caput medusa, ascites and splenomegaly) may be present depending on the phase of chronic infection. Weight loss, jaundice and a rapidly enlarging, tender, hard nodular liver together with a systolic bruit raises the concern of a hepatocellular carcinoma (HCC).

7.2.15.1 Natural History

The natural history of chronic infection is determined by the interplay between host immunity, and viral replication. There are five different phases of chronic

infection: Immune tolerant, immune clearance, immune control, immune escape and occult hepatitis B [28, 29].The clinical outcome is determined by the age of acquisition and the phase of the infection at the time of arrest of viral replication by host immunity or antiviral treatment [30]. HBV DNA levels, ALT levels and HBeAg status are important determinants of the risk of cirrhosis [31, 32], whereas HBV DNA >2000 IU/mL, HBeAg status and cirrhosis are key predictors of HCC risk [31–34].

Following acute exposure, HBV enters the hepatocyte via binding to the receptor sodium taurocholate cotransporting polypeptide and translocates to nucleus. The partially doubled-stranded DNA is repaired to form a circular extra-chromosomal molecule called the covalently closed circular DNA (cccDNA), which is the transcriptional template for the viral messenger RNAs (mRNAs) [35]. HBV replicates its DNA genome by reverse transcription of an RNA intermediate via the viral reverse transcriptase within the cytoplasm.

Cytoplasmic viral capsids containing mature viral DNA are either transported to the nucleus, thereby replenishing cccDNA, or bind to HBsAg that have accumulated in the endoplasmic reticulum, bud through the cellular membranes and are secreted from the hepatocyte non-cytopathically as virions.

Hence, even if the individual clears HBsAg, the hepatocyte still harbours intranuclear cccDNA and this determines the chronicity and the inability to cure hepatitis B with present day therapies. HBV DNA can also integrate into the hepatocyte genome during chronic infection. This integrated DNA plays no role in viral replication, but plays an important and ill-defined role in the development of HCC.

The natural history of chronic hepatitis B is dynamic and complex, and may progress non-linearly through the five recognizable phases [28, 29, 36]. These phases are of variable duration, are not necessarily sequential and not every individual with chronic hepatitis B will evolve through all the phases. Some individuals will be in a "gray zone" where their ALT and HBV DNA levels fall into different phases and thus longitudinal follow-up of ALT and HBV DNA levels +/− liver histology or fibroscan is necessary to establish the phase of chronic infection [29].

The clearance of HBsAg, whether spontaneous or after antiviral therapy, reduces the risk of hepatic decompensation and improves survival. Approximately 0.5% of individuals in the immune control phase will spontaneously clear HBsAg annually and develop anti-HBs. Most children chronically infected with hepatitis B will be completely asymptomatic and only develop complications when they reach adolescence or adulthood. However, in the setting of immunosuppression, they are at risk of hepatitis flares and decompensation. The risk of HCC increases as children reach adolescence. In untreated adults with chronic hepatitis B, the cumulative 5-year incidence of cirrhosis is 8–20%, and amongst those with cirrhosis, the 5-year cumulative risk of hepatic decompensation is 20%, and the risk of HCC is 2–5% [30, 36, 37].

The cumulative 5-year survival for compensated cirrhosis is 85% and for decompensated cirrhosis is 14–35% [38].

7.2.16 Extrahepatic Manifestations

Extrahepatic manifestations may be the presenting features of both acute and chronic HBV infection [39, 40].

Acute infection: Serum sickness-like syndrome, more common in adolescents.

Chronic infection (10–20% patients): Polyarteritis nodosa, membranous glomerulonephritis and membranoproliferative glomerulonephritis.

7.2.17 HIV/HBV Co-infection

HIV co-infection promotes an accelerated natural history of progression: Increased HBV replication and rates of HBV reactivation; increased rates of acute liver failure, chronicity of newly acquired HBV infections and occult HBV; accelerated progression to fibrosis and cirrhosis with HCC occurring at a younger age and an increased risk of ART hepatotoxicity [41–58].

7.2.18 Diagnosis of Acute and Chronic Hepatitis B

Hepatitis B surface antigen (HBsAg) is the key marker in the diagnosis of HBV infection. Careful interpretation of transaminases, HBV serological markers, HBV DNA levels and liver biopsy or non-invasive markers of fibrosis helps to distinguish between acute infection, resolution of acute infection, fulminant hepatitis, different phases of chronic infection and vaccination status.

Successful vaccination: Positive anti-HBs, protective titre >10 mIU/mL.

Previous exposure to HBV: Positive IgG anti-HBc +/− positive anti-HBs.

Acute Hepatitis B: HBsAg positive, IgM anti-HBc positive, elevated ALT.

Fulminant hepatitis: Maybe HBsAg negative, but IgM anti-HBc positive, HBV DNA detectable, elevated ALT with synthetic dysfunction (elevated ammonia and prolonged INR >1.5).

Chronic Hepatitis B: HBV serology, ALT and HBV DNA levels depend on phase of chronic infection:

- ***Immune tolerant***: HBsAg positive, HBeAg positive, anti-HBe negative, high HBV DNA levels (usually >200,000 IU/mL, typically >1 million IU/mL) and normal ALT
- ***Immune clearance (Chronic Hepatitis B eAg-positive hepatitis)***: HBsAg positive, HBeAg positive, anti-HBe negative, HBV DNA ≥20,000 IU/mL, elevated ALT
- ***Immune control***: HBsAg positive, HBeAg negative, anti-HBe positive, HBV DNA <2000 IU/mL, normal ALT
- ***Immune escape (Chronic Hepatitis B eAg-negative hepatitis)***: HBsAg positive, HBeAg negative, anti-HBe positive, HBV DNA ≥2000 IU/mL, fluctuating elevated ALT levels. Hepatitis B IgM core antibody maybe low positive with a flare
- ***Occult HBV infection***: HBsAg negative, anti-HBs negative, IgG anti-HBc positive, HBV DNA <200 IU/mL, normal ALT.

7.3 Management of Hepatitis B Infection

7.3.1 Acute Hepatitis B [28, 29, 59]

Treatment is largely supportive as more than 95% immunocompetent adolescents will spontaneously recover, clear HBV and seroconvert to anti-HBs. Interferon therapy is contraindicated as this exacerbates hepatic necro-inflammation and can precipitate acute liver failure, particularly in individuals with synthetic dysfunction. The use of nucleoside/tide analogues (lamivudine, tenofovir and entecavir) is not routinely advised.

Nucleoside/tide analogues (NUC) therapy is currently recommended in acute liver failure (jaundice, encephalopathy and INR > 1.5) as patients can stabilise and NUCs prevent reinfection of the liver graft. NUC therapy (lamivudine, tenofovir or entecavir) should be continued for at least 3 months after seroconversion to anti-HBs; 12 months after anti-HBe seroconversion without HBsAg loss and indefinitely, if the individual undergoes liver transplantation.

7.3.2 Chronic Hepatitis B

It is important to establish the phase of chronic hepatitis B and the need for therapy depending on disease activity, the presence of cirrhosis or the use of immunosuppressive therapy.

Assessment of liver disease and need for therapy:

- Establish phase of chronic infection
- Detailed clinical history and physical examination
- Assessment of the severity of the liver disease
  - Liver profile: total bilirubin, conjugated bilirubin, ALT, AST, ALP, gamma-glutamyltransferase (GGT)
  - Full blood count (FBC) including a differential count
  - Albumin and INR to assess synthetic function
- Look for other co-factors
  - Viral co-infection: HIV, HCV
  - Alcohol
  - Non-alcoholic fatty liver disease
  - Iron overload
  - Drug/toxin-induced liver injury
- Serological assessment
  - HBsAg, anti-HBs, HBeAg and anti-HBe ± IgM anti-HBc (low positive with a flare)
  - Hepatitis B IgG core antibody positive (if assessing for occult HBV or previous cleared infection)
  - Anti-HAV IgG to assess need for HAV vaccination
- Virological assessment
  - Serum HBV DNA quantification
  - HBV genotype is useful when deciding on potential efficacy of interferon therapy

  - Precore and basal core promoter mutations help predict risk of HCC
  - Previous exposure to Lamivudine and concerns regarding resistance: YMDD mutations can be measured
- Alpha-fetoprotein
- Ultrasound of the liver and dopplers
- Endoscopy to assess for varices in cirrhotic individuals
- Liver biopsy:
  - Determining the severity of liver disease (necro-inflammation and fibrosis)
  - Excluding other contributing factors to the development of acute or chronic liver disease
- Non-invasive markers of fibrosis
  - APRI Score = (AST/ULN) × 100)/platelet count (10^9/L)

An ***APRI Score > 2 identifies patients with cirrhosis (F4) and in need of antiviral therapy***

  - Fibroscan.

7.3.3 Goals of Therapy

1. ***Prevention of long-term complications of chronic hepatitis B:***
   - Cirrhosis
   - Liver failure
   - Hepatocellular carcinoma.
2. ***Prevention of reactivation in the setting of immunosuppression/biologicals/chemotherapy***
3. ***Ensure HBV viral suppression in acute liver failure***

A virological cure defined as viral eradication with elimination of cccDNA is not yet possible with the presently available treatment options. At present, the ideal endpoint of treatment is a functional immunological cure with sustained HBV DNA suppression and sustained HBsAg loss, with/without seroconversion to anti-HBs, as HBsAg is a surrogate marker for transcriptionally active cccDNA.

7.3.4 Indications for Treatment

1. **Patients who must be treated:**
   - Acute liver failure
   - Compensated or decompensated regardless of ALT levels, HBeAg status or HBV DNA levels
   - Patients receiving chemotherapy, rituximab or immunosuppressive therapy (all phases of chronic infection).
2. **Patients who should be considered for therapy and the appropriate therapy and timing of therapy discussed:**
   - Chronic HBeAg-positive hepatitis B (Immune clearance phase)
   - Chronic HBeAg-negative hepatitis B (Immune escape phase).

3. **Patients who do not require immediate therapy, but should be monitored:**
   - Patients in the immune tolerant phase
   - Patients in the immune control phase.

Chronic hepatitis B in children is typically benign, as children are usually in the immune tolerant phase. Liver biopsy is helpful in guiding the need for therapy in children with abnormal liver profiles. Treatment is recommended in HBeAg positive children with persistently elevated ALT (>30 IU/mL). As the HBV DNA is usually $>10^6$ IU/mL, there is no recommended HBV DNA threshold for treatment in children. If HBV DNA $<10^4$ IU/mL, defer therapy until other causes of liver disease, or spontaneous HBeAg seroconversion are excluded.

7.3.5 Treatment Options

- ***Lamivudine and Entecavir*** are approved for children ≥2 years of age, but long-term use of lamivudine is associated with the development of resistance (70% at 5 years)
- ***Lamivudine***: The recommended dosage for children is 3 mg/kg/day with a maximum dosage of 100 mg/day. A liquid formulation is available for children
- ***Tenofovir is*** approved for children ≥12 years of age
- ***Standard interferon alpha-2b*** is approved for children ≥1 year of age and the duration of treatment is 24 weeks. The recommended dosage for children is 6 MU/m^2 3 times a week with a maximum dosage of 10 MU 3 times a week
- ***Pegylated interferon-alpha-2a*** (180 μg/1.73 m^2 body surface area, maximum 180 μg weekly) is not approved for children with Hepatitis B, but has been approved for children ≥5 years of age with chronic hepatitis C.

7.3.5.1 Treatment Recommendations [60]

- Entecavir in children ≥2 years of age and weighing at least 10 kg. The oral solution should be given to children with a body weight up to 30 kg and is dosed according to body weight. Children who are treatment naïve with a body weight of ≥30 kg should receive 0.5 mg or 10 mL entecavir daily
- Tenofovir 300 mg daily in children ≥12 years of age and weighing at least 35 kg
- Treatment with NUCs is continued until HBeAg seroconversion followed by an additional 12 months of consolidation therapy [29]
- On stopping therapy, need to monitor every 3 months for at least 1 year for hepatitis B flares and clinical decompensation.

7.3.6 Prevention of Hepatitis B

The WHO recommended the incorporation of the HBV vaccine into the Expanded Program of Immunization (EPI) in 1991 as the most effective way to reduce the global burden of HBV. To date 194 countries worldwide and 45 in WHO Africa region have incorporated hepatitis B vaccination into the EPI.

A systemic review from 1990 to 2005 confirmed that HBV seroprevalence has decreased in many regions of the world as a result of universal HBV vaccination and it is estimated to have prevented more than 1.3 million deaths [61].

In 2009, WHO recommended a Hepatitis B birth dose (HepB-BD) vaccine for all countries, even those with a low HBV prevalence [62]. A monovalent HBV vaccine should be administered within 24 hours of delivery and preferably within 12 hours. However, in 2014, only 96 of 194 countries (49%) reported offering HepB-BD vaccine as part of their national immunization programs and <38% of babies born worldwide received HepB-BD within 24 hours after birth [63, 64].

7.3.6.1 The Efficacy of Universal HBV Vaccination

This has proved exemplary in Taiwan, where universal vaccination, introduced in 1984, together with a catch-up vaccination programme and improved maternal screening, resulted in a decrease in the prevalence of HBsAg positivity in children aged <15 years from 9.8% in 1984 to 0.3% in 2009 [65–67]. The infection rate (antiHBc seropositive rate) deceased from 38% in 1984 to 4.6% in 2009 [68]. Furthermore, the average annual incidence of HCC in children aged 6–14 years decreased from 0.7 per 10,000 children in 1981–1986 to 0.36 per 100,000 children in 1990–1994 [69, 70]. Incomplete vaccination has been shown to be an important risk predictor of HCC with a hazard ratio (HR) of 2.52 ($p = 0.0094$) [71].

A similar decline in HBsAg seroprevalence rate and in the incidence of HCC has been seen in other hepatitis B endemic countries that have implemented universal HBV vaccination [72].

7.3.6.2 Prevention of Mother to Child Transmission

It is essential that all pregnant women be screened for HBsAg. Neonates born to HBsAg positive mothers should receive 0.5 mL (200 IU) HBIG and HBV monovalent vaccine within the first 24 hours, but preferably within 12 hours of delivery at different injection sites (anterolateral thigh). Thereafter, the same immunization schedule is followed as for other infants. Combined immunoprophylaxis with HBIG and HepB-BD vaccine fails in 10–30% of infants born to mothers with HBV DNA levels >6$\log_{10}$ copies/mL [21, 73–78]. In addition, HBIG is expensive and is not easily accessible in many developing countries.

A number of studies have suggested that antiviral therapy with lamivudine or telbivudine or tenofovir during the third trimester of pregnancy could be clinically and cost effective in reducing the vertical transmission of hepatitis B infection when compared to no treatment or placebo.

AASLD recommends the initiation of tenofovir 300 mg daily at 28–32 weeks of pregnancy if HBV DNA >200,000 IU/mL to further reduce risk of perinatal transmission and EASL suggests antiviral therapy in third trimester if HBV DNA >10^{6-7} IU/mL [28, 29].

Infants born to HBsAg positive mothers should be offered post-vaccination testing for HBsAg and anti-HBs at 9–18 months of age. Children with anti-HBs ≥10 mIU/mL are protected and need no further management. Those who have

anti-HBs <10 mIU/mL should be given a second course of vaccination as they may be at risk of exposure in the household. Children who are HBsAg positive should be referred for clinical management.

7.3.6.3 Post-exposure Prophylaxis (PEP)

PEP is indicated following exposure to blood or body fluids of a known or potential HBsAg positive source if the exposed individual does not have protective anti-HBs ≥10 mIU/mL or if anti-HBs status is unknown and testing will delay administration of HBV vaccination or HBIG.

Exposures in which HBV post-exposure prophylaxis should be given include:

- Percutaneous (e.g. bite or needlestick) or mucosal exposure to blood or body fluids of a known or potential HBsAg positive source
- Neonates born to HBV infected women
- Sex or needle sharing contact of a HBsAg positive person or a person of unknown HBsAg status
- Victims of sexual assault/abuse by a perpetrator who is HBsAg positive or of unknown HBsAg status.

7.3.6.4 Effectiveness of PEP

- A combination of HBIG and active HBV vaccination is highly effective in preventing transmission after exposure to HBV
- HBIG provides passively acquired anti-HBs which is immediately protective and lasts for 3–6 months
- HBIG is approximately 75% effective in preventing clinical HBV infection if administered soon after HBV exposure
- PEP effectiveness decreases with increasing delay in administration following exposure and is unlikely to be effective >7 days after perinatal and needle stick exposures and >14 days after sexual exposure
- HBIG alone does not confer long-lasting protection against HBV
- HBIG is the primary means of protection of non-responders to vaccination.

7.4 Hepatitis C

Prior to the discovery of Hepatitis C (HCV) and the use of anti-HCV in the early 1990s as a marker of exposure to exclude infected blood and organ donors; most HCV infections were acquired through transfusions or inadequately sterilized needles or instruments. Children were frequently affected following repeated administration of blood and blood products for hemoglobinopathies, hemophilia or cancer therapy. Perinatal mother-to-child transmission accounts for 95% of all cases of hepatitis C in children born after 1990 in developed countries. Unfortunately in many regions of the world, post-transfusional hepatitis C remains a hazard as does unsafe injection practices.

7.4.1 Virus Structure

HCV is an enveloped, ribonucleic acid (RNA) virus that was identified and sequenced in 1989 [79]. It is classified as a separate genus (*Hepacivirus*) within the *Flaviviridae* family. Approximately 10^{12} viruses are produced daily and given the lack of an RNA proofreading polymerase, many mutations develop with the formation of so-called viral quasispecies in a single host [80].

There are six clinically relevant HCV genotypes and >80 subtypes. Genotype prevalence varies according to geographic region and route of acquisition [79].

7.4.2 Transmission of Hepatitis C

HCV remains viable on environmental surfaces at room temperature for at least 16 hours, but typically no longer than 4 days [81] and transmission occurs via parenteral and non-parenteral routes. The major route of HCV infection in the pediatric age group is vertical, with infection occurring in up to 5% of infants born to mothers positive for HCV-RNA.

7.4.2.1 Parenteral Transmission

HCV is most efficiently transmitted through parenteral inoculation. The predominant risk is in people who inject drugs (PWID) through the sharing of syringes and needles. The risk is as high as 90% after 5 years in PWID. Other parenteral transmission routes include tattooing, body piercing and needle-stick injuries.

7.4.2.2 Non-parenteral Transmission

This is less well defined and includes:

- **Mother-to-child transmission**: This only occurs in 1–5% of infants born to HCV infected women. Risk factors shown to increase the possibility of HCV vertical transmission include coinfections with human immunodeficiency virus (HIV), intravenous drug use and elevated maternal HCV viral load. Vertical transmission risk increases to ~20% in HIV/HCV coinfected mothers [82]
- **Sexual transmission** especially in the setting of high risk sexual practices and in men who have sex with men (MSM).

7.4.2.3 Household Transmission

- Percutaneous/mucosal exposure to blood, and sharing of contaminated personal items such as razors, toothbrushes and nail-grooming equipment is described, but is uncommon.

7.4.3 Clinical Presentations of Hepatitis C

Variation in disease progression is characteristic of HCV infection and contributing factors include environmental, host genetic and immunological factors.

Hepatitis C usually has an incubation period of 4–16 weeks and most individuals who develop acute hepatitis C are completely asymptomatic. Jaundice is uncommon and fulminant liver failure complicating acute HCV infection is rare. Anti-HCV antibodies can take 12–16 weeks, from the time of first infection to develop. However, HCV RNA is detectable in serum as early as 1–3 weeks after exposure. The persistence of HCV RNA beyond 24 weeks after acute infection marks the onset of chronic infection [83].

The natural course of HCV infection in children is characterized by a high rate of spontaneous clearance, an asymptomatic clinical course, and normal or mild histologic changes. Cirrhosis is reported in 1–2% of children, and progression to severe chronic liver disease and HCC occurs 20–30 years after infection. Only a few cases of HCC have been reported in adolescents.

Approximately 25–40% children with vertically acquired HCV, will undergo ALT normalization and loss of HCV-RNA by the age of 2–3 years [84–86]. Spontaneous resolution can be achieved in up to 6–12% of infected children, as late as 7 years of age [84–87].

High ALT levels are associated with increased chance of biochemical remission and viral clearance [85, 88]. HCV clearance is also significantly higher in infants infected with HCV genotype 3 [89].

In children infected via the parenteral route, HCV-RNA clearance is highly variable. In long-term follow-up studies of 25–30 years, clearance ranged from 11% in a cohort of infants infected by an HCV-RNA-positive blood donor [90] to 30–45% in cohorts similarly infected in early infancy via contaminated blood products during surgery [91, 92]. Eighty percent children who do not clear HCV spontaneously will be asymptomatic with normal or mildly elevated transaminases. Ten to twenty percent of HCV-infected children will have persistent elevation of transaminases and may manifest clinical signs of liver disease.

Histology reveals that most children have no or only mild fibrosis, but there is evidence of insidious progression of liver disease on follow-up liver biopsies.

Risk factors for more severe disease include obesity, alcohol consumption and intravenous drug use, childhood cancer, immunosuppression and liver transplantation, congenital anemia requiring chronic transfusions, and co-infection with HIV/hepatitis B virus [93–97].

7.4.4 Extrahepatic Manifestations of Hepatitis C

Hepatitis C has been associated with several extra-hepatic manifestations:

- Autoimmune (e.g. Sjögren's syndrome, cryoglobulinemia, polyarteritis nodosa)
- Porphyria cutanea tarda
- Lymphoproliferative diseases (e.g. B-cell non-Hodgkin's lymphoma)

- Insulin resistance: Progressive insulin resistance, impaired fasting glucose (IFG) and/or type 2 diabetes mellitus (DM) is higher in chronic HCV patients (50%) than in the general population (14.5%) [98].

7.4.5 HIV/HCV Co-infection

HIV coinfection significantly alters the natural history of hepatitis C and is regarded as a priority for HCV treatment given that there is:

- Accelerated fibrosis and progression to cirrhosis
- Increased HCC risk
- Increased HCV infectivity risk, especially MTCT of HCV
- Increased risk of ART and TB drug induced liver injuries
- Reduced response to interferon-based therapy.

7.4.6 Diagnosis of Hepatitis C

- ***Anti-HCV***: Detects anti-HCV in 80% infected individuals within 6 weeks of primary infection and has >95% sensitivity
- ***Quantitative HCV PCR (Viral load quantification)***: Confirms active viraemia
- ***Genotype testing***: This is required to choose correct treatment.

7.4.7 Pretreatment Clinical Evaluation

Medical evaluation includes:

- Clinical history and physical examination
- Assessment of the liver disease
  - Liver profile: Total bilirubin, conjugated bilirubin, albumin, ALT, AST, ALP, GGT
  - FBC and differential count
  - INR to assess synthetic function
  - Fibrosis assessment: Liver histology or non-invasive methods
- HBV and HAV serology to assess need for vaccination
  - Anti-HAV IgG negative: Needs HAV vaccination - HBsAg and anti-HBs negative - vaccinate against HBV
- HCC screening: Alpha-fetoprotein and ultrasound of the liver (6–12 monthly).

7.4.8 Prevention

There is no immunoglobulin and no vaccine available.

7.4.9 Treatment of Hepatitis C

As there is a high spontaneous clearance rate in infancy and early childhood and most children have no or only mild fibrosis, it is recommended that children not be treated before the age of 5–6 years [99].

The aim of treatment is to achieve a sustained virological response (SVR) that results in:

- Reduced necro-inflammation and progression to fibrosis, cirrhosis and end stage liver disease
- Reduction in risk of HCC
- Improved liver-related morbidity and mortality
- Improved all-cause mortality.

Treatment prioritization i.e. patients who need to be treated first:

- Significant fibrosis (F3) or F4/cirrhosis (including compensated cirrhosis)
- HIV or HBV coinfection
- Liver transplant
- Extra-hepatic manifestations.

Treatment with pegylated interferon (Peg-IFN) and ribavirin for 24 weeks results in 90–100% SVR12 in children with HCV genotypes 2 or 3, but only 45–55% SVR12 in those infected with genotypes 1 or 4 treated for 48 weeks [100–102]. Treatment is associated with adverse effects ranging from flu-like symptoms, myalgia, anemia and thrombocytopenia, to less commonly observed thyroid-related symptoms, alopecia, neuropsychiatric manifestations and possible long-term effects on growth.

No all-oral, direct-acting antiviral regimens have been approved as yet for children with chronic hepatitis C. A phase 2, multi-centre, open-label study evaluating the efficacy and safety of ledipasvir-sofosbuvir in adolescents with chronic HCV genotype 1 infection has been performed. One hundred adolescents aged 12–17 years (median age 15 years) received a combination tablet of 90 mg ledipasvir and 400 mg sofosbuvir once daily for 12 weeks. Eighty percent were HCV treatment naïve, and 84% were infected through perinatal transmission. One patient had cirrhosis and 42 did not; in 57 patients the degree of fibrosis was unknown. Overall, 98% (98/100; 95% CI, 93–100%) of patients reached SVR12. No patient had virological failure. The two patients who did not achieve SVR12 were lost to follow-up either during or after treatment. The three most commonly reported adverse events were headache (27% of patients), diarrhea (14%), and fatigue (13%) [103].

As the natural history of Hepatitis C is mild and the side-effects of pegylated interferon and ribavirin are significant, the decision to treat should be based on evidence of active disease progression. Most children with chronic hepatitis C will be able to wait for the availability of all-oral, direct-acting antiviral regimens and preferably a pangenotypic regimen. Such new therapies are under investigation and new agents are being registered and used in some countries.

7.5 Hepatitis D

HDV is a unique RNA virus that is dependent on hepatitis B for survival. HDV does not encode its own replicase and is dependent on HBV providing HBsAg to coat its virion in order to replicate. Thus, there are no viral replicative enzymes for drugs to target.

7.5.1 Epidemiology and Transmission

HDV is found worldwide, but the prevalence varies in different geographical areas. It is commonly encountered in the Mediterranean basin, the Far East, certain regions in South America and in Africa [104]. Eight HDV genotypes have been identified and are associated with variable clinical courses: Genotype 1 is found worldwide (range of liver disease severity); Genotype 2 occurs in Japan, Taiwan, Russia (milder disease); Genotype 3 occurs in the northern countries of South America (more severe disease including fulminant presentations) and Genotype 4 occurs in Japan and Taiwan (milder disease). Genotypes 5–8 have been identified in African patients and are associated with HBV genotypes A–E, but little is known about the clinical course of the liver disease. In Africa, where HBV is endemic, documented HDV seroprevalence rates vary geographically from low rates in countries south of the Equator (0–0.6%) to high rates north of the Equator (3–67%). Transmission is parenteral, but risk of perinatal transmission is low [104].

7.5.2 Clinical Presentations [105]

- ***Acute HBV/HDV coinfection*** (including fulminant hepatitis)
- ***Acute HDV super-infection of an individual with chronic HBV infection***: This can present as an acute hepatitis in a previously asymptomatic HBsAg carrier or result in further clinical deterioration in individuals with established HBV disease
- ***Chronic HDV infection***: HBV replication is usually suppressed (low or undetectable HBV DNA) and HBeAg is negative. Hepatitis D becomes chronic in 70–90% individuals with superinfection and there is more rapid progression to cirrhosis and decompensation, especially in injecting drug users where end-stage liver disease can occur in <2 years. There is also an increased risk of HCC.

7.5.3 Diagnosis

- ***Acute HBV/HDV co-infection***: Positive anti-HDV IgM and HDV RNA; HBsAg positive and Hepatitis B IgM core antibody positive
- ***Acute HDV super-infection of patient with chronic HBV infection***: Positive anti-HDV IgM and HDV RNA; HBsAg positive
- ***Chronic HDV infection***: Positive anti-HDV IgG and HDV RNA; HBsAg positive.

7.5.4 Prevention and Treatment

There is no immunoglobulin available and no specific HDV vaccine. HBV vaccination is effective prophylaxis against HDV. The currently recommended treatment is Peginterferon alfa given weekly for 48 weeks, leading to HDV RNA clearance in 17–47% of infected individuals [106].

7.6 Hepatitis E

Hepatitis E virus (HEV) is a major etiologic agent of enterically transmitted non-A, non-B, non-C hepatitis worldwide [107–111].

7.6.1 Virus Structure

HEV is a spherical, non-enveloped, small single stranded, positive-sense RNA virus that measures approximately 27–34 nm. HEV is classified as the sole member of the genus *Hepevirus* under the family *Hepeviridae*. Four genotypes (1–4), but only one serotype have been identified [112, 113] and there are clear differences in the epidemic potential of the various genotypes [110].

7.6.2 Epidemiology and Transmission

Hepatitis E is a food-borne and water-borne disease. Compared to hepatitis A, HEV is less resistant to environmental conditions such as temperature; and prolonged excretion of HEV in stool following symptomatic/asymptomatic infections is rare.

The modes of transmission vary dependent on the HEV genotype. Genotypes 1 and 2 have fecal-oral and waterborne transmission and are associated with epidemics. Epidemics of hepatitis E have been reported in Central and South-East Asia; North, West and Central Africa; Mexico and in sub-Saharan Africa. Genotypes 3 and 4 have food-borne transmission. Parenteral transmission has also been described via blood transfusions and perinatal transmission.

7.6.3 Clinical Presentations

The incubation period following exposure to HEV ranges from 15 to 60 days, with a mean of 40 days. The period of infectivity following acute infection has not been determined. HEV-RNA can be detected in stool from 1 week prior to the onset of symptoms and virus excretion in stools has been demonstrated up to 14 days after onset of illness [114]. The clinical presentation is modulated by the underlying epidemiological pattern of a particular region, by genotype; and the immune status and age of the individual. Symptoms tend to increase with age. The overall mortality is

0.5–4% with increased mortality in certain groups: 5–8% in children <3 years [115, 116], 25% in pregnant women in the third trimester [117, 118] and 75% in individuals with chronic liver disease [119].

The different clinical presentations include:

1. ***Mild subclinical illness***: Asymptomatic infections tend to be more common in children and the symptomatic to asymptomatic ratio for children is 1:12 compared with 1:3 for adults [120].
2. ***Self-limiting acute hepatitis resembling hepatitis A***: Attack rate is highest in men aged 15–40 years (10–30%). Symptomatic acute hepatitis occurs in up to 15% during an outbreak.
3. ***Severe disease*** occurs in pregnant women in the third trimester and individuals with chronic liver disease.

Chronic hepatitis defined as HEV RNA positivity in stool or serum persisting for >6 months. This occurs in solid organ transplant recipients, HIV patients and haematological malignancies and has only been documented with Genotype 3 infections [121–125]. The transaminitis is usually mild in the range of 100–300 U/L, and patients are usually not jaundiced. Progression to chronicity occurs in approximately 60% immunosuppressed solid organ transplant recipients as a result of impaired specific T-cell responses. Rapid progression to cirrhosis can occur. Tacrolimus therapy is the main predictive factor for the development of chronic hepatitis.

7.6.4 Diagnosis

Acute Hepatitis E: Positive anti-HEV IgM (Wantai ELISA).
Previous exposure to hepatitis E: Positive anti-HEV IgG (Wantai ELISA).
Chronic Hepatitis E: Positive anti-HEV IgG and a positive HEV PCR for >6 months.

7.6.5 Prevention and Treatment

Hepatitis E prevention and control strategies are generally as for hepatitis A, but also need to consider zoonotic transmission. In endemic areas, improving sanitation, ensuring safe water supplies and maintaining good hygienic practices e.g. washing hands with soap can prevent spread. In non-endemic areas, avoid intake of raw uncooked meat to prevent zoonotic transmission. An effective vaccine is available, but this has not been tested in children or pregnant women. There is no protective immunoglobulin currently available.

Clinical management of hepatitis E is supportive. Ribavirin therapy for 3 months can be considered in children presenting with acute hepatitis and impaired synthetic function; and in immune-compromised children with chronic hepatitis.

7.7 Herpes Viruses

The herpesvirus family contains five important human pathogens: herpes simplex virus types 1, 2 and varicella-zoster virus, cytomegalovirus, and Epstein–Barr virus.

Herpesviruses are noted for their ability to cause latent infections where the acute infection is followed by an asymptomatic period during which the virus remains in a quiescent or latent state. On exposure to a trigger event such as immunosuppression, reactivation occurs and clinical symptoms may be similar to the initial infective episode or different as in varicella-zoster infections.

7.7.1 Herpes Virus Structure

All herpesviruses are structurally similar with an icosahedral core surrounded by a lipoprotein envelope. They are large, linear double-stranded DNA viruses ranging from 120 to 200 nm in diameter. The virion does not contain a polymerase and replication occurs in the nucleus. They are the only viruses that obtain their envelopes by budding from the nuclear membrane.

7.8 Herpes Simplex Viruses (HSV) 1 and 2

Herpes simplex viruses (HSV-1 and HSV-2) are endemic worldwide, can cause disease at any age and result in lifelong infection. HSV-1 and HSV-2 are structurally and morphologically indistinguishable, but can be differentiated by the restriction endonuclease patterns of their genome DNA and by type-specific monoclonal antisera. Humans are the natural hosts of both HSV-1 and HSV-2.

After entry into the cell, the virion is uncoated and the genome DNA enters the nucleus. Early virus messenger RNA is transcribed by host cell RNA polymerase and then translated into early, non-structural proteins in the cytoplasm. Two of these early proteins, thymidine kinase and DNA polymerase, are important because they are targets for antiviral drugs e.g. acyclovir. As the initial containment of HSV infection requires intact cellular immunity, immunocompromised patients are at risk for more frequent and severe/disseminated HSV infections.

7.8.1 Epidemiology and Transmission

HSV-1 is transmitted primarily by saliva, whereas HSV-2 is transmitted by sexual contact. Most primary HSV-1 infections are asymptomatic. Only 20–25% patients with HSV-1 antibodies and 10–20% of those with HSV-2 antibodies have a history of oral-labial or genital infections. Viral shedding can lead to unsuspected transmission to others via contact with secretions or mucous membranes.

7.8.2 Clinical Presentations

HSV-1 typically causes acute gingivostomatitis, herpes labialis, keratoconjunctivitis, and encephalitis, whereas HSV-2 causes genital herpes, neonatal herpes and aseptic meningitis. Both HSV-1 and HSV-2 can cause hepatitis [126].

7.8.2.1 Hepatitis

Herpes simples virus (HSV) hepatitis is a rare complication of both HSV-1 and HSV-2 infection and usually occurs in immunocompromised patients. Those at risk include neonates, patients taking steroids, HIV-infected patients, liver transplant recipients and oncology patients, but HSV-related hepatitis can also occur in immunocompetent young individuals. HSV hepatitis frequently presents as a fulminant disease with a high mortality (>80%), if left untreated. HSV accounts for 0.8% of acute liver failure and 2–4% of acute viral hepatitis cases. Mucocutaneous lesions occur in less than 40% of patients and clinical symptoms are often non-specific and include fever (82%), headache (80%), anorexia with nausea and/or vomiting (18%), abdominal pain (33%), leukopenia (43%), and coagulopathy (20%). Jaundice is frequently absent. Patients with HSV hepatitis are moderately ill for 3–10 days, and then deteriorate rapidly with hepatic necrosis resulting death within 1 week. HSV hepatitis is a difficult diagnosis to establish. It should be considered in the differential diagnosis of any case of severe hepatitis with or without jaundice. It is important to recognize the entity and start specific treatment early in the course of the illness.

7.8.3 HSV Diagnosis

Early diagnosis may be difficult as the characteristic vesicular rash is absent in up to 40% of the neonates who acquire the infection. Early symptoms are often non-specific and the majority of their mothers lack a history of genital herpes infection.

The diagnosis of HSV infection can be made by a variety of techniques including liver biopsy, PCR assays or serology.

Liver biopsy: This was historically the "gold standard" investigation for HSV hepatitis. Histology may reveal HSV-type intranuclear inclusions and immunostaining for HSV can be performed.

Serology: Serological testing for HSV-1 and 2 (IgG and IgM) is limited by a high rate of false-positive and false-negative tests. IgM antibodies may be useful in diagnosing neonatal infections, which appear during the first 4 weeks of infection and persist for months. In immunocompromised children, there is often a delay in the development of IgM antibodies leading to a delay in diagnosis and treatment of acute HSV hepatitis.

Polymerase chain reaction: HSV serum PCR is both a highly sensitive and specific test, can be quantitative and allows for a rapid diagnosis and earlier initiation of therapy.

7.8.4 Treatment and Prevention

The high mortality (80%) of untreated HSV hepatitis is greatly reduced to 33% with early treatment with intravenous acyclovir (10 mg/kg 8 hourly for 14–21 days) which inhibits viral replication. Immunocompromised patients may have a more severe and protracted course and may require longer therapy [127]. If the diagnosis is suspected, treatment with intravenous acyclovir should be started immediately, whilst awaiting confirmation of the diagnosis with HSV PCR.

Liver transplantation has been carried out successfully in a few reported neonates with fulminant hepatic failure associated with disseminated neonatal HSV disease [128, 129].

There is no currently licensed, effective vaccine or immunoglobulin against HSV-1 or HSV-2 infection.

7.9 Cytomegalovirus (CMV)

CMV is a ubiquitous human herpes virus that causes a lifelong persistent infection. CMV is a well-recognized cause of hepatitis. It occurs more commonly in immunocompromised children, particularly in organ transplant recipients and HIV-infected children. CMV hepatitis can occur during a primary infection or following reactivation of latent CMV infection especially in the setting of immunosuppression. Symptomatic CMV infection in immunocompetent children typically has a benign, self-limited course, but there are numerous reports of severe clinical CMV disease in immunocompetent patients.

7.9.1 Virus Structure

CMV is an icosahedral shaped, encapsulated, double-stranded DNA β-herpes virus about 200 nm in diameter. The complete virion consists of an inner core of DNA genome, surrounded by capsid, which in turn is surrounded by a proteinaceous tegument and an outer lipid envelope. During infection, the virus replicates in hepatocytes and cholangiocytes. It is uncertain whether the pathogenesis of hepatic disease is related to the direct cytopathic effect of the virus or to the immune response of the host.

7.9.2 Epidemiology and Transmission

Social and environmental factors are determinants in the age of acquiring CMV infection. Most children in resource-poor settings are infected with CMV during infancy and early childhood and that is in contrast to resource-rich countries where the primary CMV infection occurs later at an older age. Transmission can occur

perinatally or with close contact of infected blood and tissues or sexually. The incubation period is 4–6 weeks. The natural immune response of the host to primary CMV infection does not clear the virus completely and it persists in a latent or non-lytic state.

7.9.3 Clinical Presentation [130]

The clinical presentation of acute CMV hepatitis usually includes jaundice and vague abdominal pain, but may be non-specific and present with vomiting and prolonged unexplained fever and headaches. Liver function test abnormalities are characterized by a transaminitis and an elevated lactate dehydrogenase. The bilirubin is often only mild-to-moderately elevated, but can be entirely normal. Portal vein thrombosis has also been described as a rare complication of acute CMV-associated hepatitis.

7.9.4 CMV Diagnosis

There are several diagnostic investigations to determine CMV infection.

Viral Culture: CMV can be cultured in secretions (saliva, urine, breast milk) and blood. This is a direct culture system with human fetal lung fibroblasts used to prove CMV infection by visualizing typical cytopathic effects of the virus. It can take up to 21 days to visualize these changes. This technique lacks sensitivity and is rarely used.

Histopathological diagnosis of CMV: The gold standard of diagnosing CMV disease is to detect cytomegalic cells on histology. Typical CMV-infected cells increase in size and contain cytomegalic inclusion bodies with a halo, which gives the cell an owl's eye appearance. The sensitivity of CMV detection in tissue specimens has been improved with immunoperoxidase or immunofluorescence staining for CMV antigens using monoclonal antibodies and/or in situ DNA hybridization.

Serology: CMV infection is diagnosed by comparing the IgG antibody titre at the acute stage with the titre of the recovery stage. Paired serum samples obtained at least 2–4 weeks apart are necessary. It is not sensitive and CMV-specific IgG does not distinguish CMV reactivation from CMV carriers so is not useful in the diagnosis of CMV hepatitis. CMC IgM antibodies can also be measured, but there can be a delay in detection in immunocompromisd individuals.

CMV antigenemia: The CMV antigenemia method has a sensitivity of 60–100% and a specificity of 83–100%. The detection of antigen (pp65)-positive cells in peripheral blood cells reflects reactivation of CMV; however, the positive finding of CMV antigenemia does not necessarily reflect CMV disease and is not useful in the diagnosis of CMV hepatitis.

CMV polymerase chain reaction (PCR) analysis: Standardized commercial qualitative and quantitative PCR assays are available to detect CMV-DNA in the urine, stool, blood, and tissues. The PCR analysis is sensitive for diagnosing CMV

infection and monitoring the viral load. However, the high sensitivity of the PCR assay may result in low specificity for diagnosing active CMV infection because very few copies of CMV-DNA can be detected, which may have no clinical significance but only point towards a local low level reactivation.

Quantitative CMV PCR is useful in monitoring the response to therapy.

7.9.5 Treatment and Prevention

Antiviral treatment is indicated in CMV hepatitis in all immunocompromised patients, but in an immunocompetent patient, treatment will depend on the clinical course and the viral load level. Treatment is with either intravenous ganciclovir (5 mg/kg 12 hourly) or oral valganciclovir for a minimum of 3 weeks.

There is as yet no effective vaccine against CMV.

7.10 Epstein–Barr Virus (EBV)

EBV or human herpesvirus 4 is a gamma herpesvirus that infects more than 95% of the general population by the age of 20 years [131]. EBV is structurally and morphologically identical to other herpesviruses, but is antigenically different. There are two strains of EBV (EBV-1 and EBV-2) and they can simultaneously infect individuals causing identical acute illnesses. Human are the natural hosts and EBV infects mainly lymphoid cells, primarily the B lymphocytes. EBV infection is associated with the development of B-cell lymphomas, T-cell lymphomas, Hodgkins lymphoma and nasopharyngeal carcinoma in certain individuals [132].

7.10.1 Epidemiology and Transmission

Epstein–Barr virus is present in oropharyngeal secretions and is most commonly transmitted through saliva. Early asymptomatic infection tends to occur in children in lower socio-economic groups. Clinically apparent infectious mononucleosis, however, is more common in individuals who are exposed to the virus later in life.

After initial inoculation, the virus replicates in nasopharyngeal epithelial cells. Cell lysis is associated with a release of virions, with viral spread to adjacent structures, including salivary glands and oropharyngeal lymphoid tissues. EBV viremia leads to infection of the lymphoreticular system, including the liver, spleen, and peripheral B lymphocytes. The host immune response to the viral infection includes CD8+ T lymphocytes with suppressor and cytotoxic functions, the characteristic atypical lymphocytes found in the peripheral blood. The T lymphocytes are cytotoxic to the Epstein–Barr virus-infected B cells and eventually reduce the number of Epstein–Barr virus-infected B lymphocytes to less than 1 per 10^6 circulating B cells.

The humoral immune response involves the development of IgM antibody to the viral capsid antigen (VCA), followed by the IgG antibody to VCA and this persists for life. In addition to the EBV-specific antibodies, nonspecific heterophile antibodies that are directed against cell membrane constituents also occur. These heterophile antibodies are not specific for the EBV infection and usually disappear after 6 weeks. After acute EBV infection, latently infected B lymphocytes and epithelial cells persist and are immortalized as EBV DNA is integrated into the cell genome.

7.10.2 Clinical Presentations

The incubation period in adolescents is 30–50 days, but tends to be shorter in young children. EBV infection is usually subclinical during early childhood. Symptomatic acute infectious mononucleosis is more common in adolescents and is characterized primarily by fever, sore throat, lymphadenopathy, and splenomegaly. Anorexia and lethargy are prominent. Hepatitis is frequent with 80–90% patients demonstrating a moderate, but transitory elevation of liver enzymes [132]. Encephalitis occurs in some patients. Spontaneous recovery usually occurs within 2–3 weeks in immunocompetant individuals. Splenic rupture is a rare complication. In the setting of immunosuppression, chronic EBV infection or a severe, often fatal EBV infection may occur.

EBV Hepatitis: A mild, self-limiting cholestatic hepatitis is seen in immunocompetant children with liver involvement during acute EBV infections. A severe hepatitis is uncommon in immunocompetant individuals [133]. ALP, AST, and bilirubin levels peak 5–14 days after onset, and GGT levels peak at 1–3 weeks after onset.

Occasionally, GGT levels remain mildly elevated for as long as 12 months, but most liver enzymes are normal within 3 months. Lactic acid dehydrogenase (LDH) levels are increased in approximately 95% patients. Serum ferritin can also be increased.

The cholestasis may be functional due to impaired activity of sinusoidal and canalicular transporting systems associated with the production of systemic and intrahepatic pro-inflammatory cytokines or due to direct infection of biliary epithelial cells. Chronic hepatitis is rare [134]. Fifty percent of fatal infectious mononucleosis cases are due to liver failure [135].

7.10.3 Diagnosis

The diagnosis of infectious mononucleosis is based on three criteria: Lymphocytosis, ≥10% atypical lymphocytes and positive EBV serology.

Full blood count and differential: An absolute lymphocytosis occurs and usually 20–40% of the lymphocytes are atypical. These “atypical lymphs” are larger with a lobulated less dense nucleus, a lower nuclear-to-cytoplasmic ratio and a

vacuolated, basophilic cytoplasm. Most of these atypical lymphocytes are polyclonal-activated CD8 cytotoxic-suppressor T lymphocytes, although CD4 helper T cells and CD11 natural killer cells are also present.

Serology: The heterophile antibody test is useful for the early diagnosis of infectious mononucleosis as it is usually positive by week 2 of the illness. The heterophile antibody tests are recommended as screening tests in adolescents and adults, but not in children. The antibody titre declines after recovery and so is not useful for detection of prior infection. These heterophile antibodies agglutinate cells from other species and are not directed against Epstein–Barr virus. These antibodies are the basis of the Paul-Bunnell and the Monospot test. The Monospot test is more sensitive, more specific, and cheaper than the tube agglutination test.

The EBV-specific antibody test is used primarily in diagnostically difficult cases, atypical presentations or the immunocompromised. Early antigen (EA) are expressed early in the lytic cycle, whereas VCA and membrane antigens are structural viral proteins expressed late in the lytic cycle. Ebstein–Barr virus nuclear antigen (EBNA) is expressed in latently infected cells.

The IgM VCA antibody response can be used to detect early illness and the IgG VCA antibody response detects prior infection. Antibodies to EA and EBNA can be useful diagnostically. Antibody to EBNA appears 3–4 weeks after infection and persists for life.

Primary acute Epstein–Barr virus infection is associated with positive VCA-IgM, and VCA-IgG antibodies; and absent EBNA antibodies.

Recent EBV infection (3–12 months): positive VCA-IgG and EBNA antibodies, negative VCA-IgM antibodies, and, usually, positive EA antibodies. After 12 months EA antibodies are negative.

EBV polymerase chain reaction (PCR) analysis: Quantitative PCR is useful in investigating EBV-associated disease in the context of immunosuppressed or immunodeficient patients where acute serology is often negative. Quantitative PCR can be used to measure EBV DNA in plasma during acute infectious mononucleosis. Levels decline during convalescence and are rarely measurable in latently infected individuals. EBV DNA in serum is detectable with PCR during EBV reactivation.

Histology: Viral inclusions may be detectable. Certain EBV-associated tumors have characteristic histology (eg, Reed Sternberg Cells). In situ testing with DNA probes or immunohistochemistry for viral proteins can be done to further demonstrate infection.

7.10.4 Treatment

The mainstay of treatment for individuals with infectious mononucleosis and other manifestations of primary EBV disease is supportive care. Acetaminophen or non-steroidal anti-inflammatory drugs are recommended for the treatment of fever, throat discomfort, and malaise. Provision of adequate fluids and nutrition is also recommended.

Antiviral therapy including acyclovir, gangciclovir and foscarnet, have not been shown to be of proven efficacy for treatment of EBV infections, but are frequently used in imunocompromised patients and in the setting of severe disease in immunocompetant individuals [136, 137]. Foscarnet, a pyrophosphate analog, has been reported to be active against acyclovir- or ganciclovir-resistant herpes family viruses including EBV. Corticosteroids are not recommended for uncomplicated cases. Corticosteroids are reserved for severe complications of mononucleosis such as impending airway obstruction, acute hemolytic anaemia, severe thrombocytopenia, and severe clinical disease. Intravenous immunoglobulin is used to modulate immune function in the presence of autoantibodies and has been used successfully in the treatment of immune thrombocytopenia associated with infectious mononucleosis [138]. Avoidance of contact sports for at least 1 month is recommended in individuals with enlarged spleens to decrease the risk of splenic rupture.

7.10.5 Prevention

Currently, there is no commercially available vaccine for EBV-related disease and no immunoglobulin directed against EBV.

7.11 Coxsackie Virus

Coxsackie viruses belong to the family *Picornaviridae* and the genus Enterovirus. Coxsackie virus infections occur throughout the world [139].

7.11.1 Virus Structure

Coxsackie viruses are nonenveloped viruses with linear single-stranded RNA. Coxsackie viruses are divided into two groups: group A and group B viruses. At least 23 serotypes (1–22, 24) of group A and 6 serotypes (1–6) of group B are recognised.

In general, group A coxsackie viruses tend to infect the skin and mucous membranes and group B coxsackie viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myocarditis, pericarditis, and hepatitis.

7.11.2 Epidemiology and Transmission

Coxsackie virus infections occur in all age groups, but are more common in young children and infants. Children are at higher risk of infection during the first year of life. The rate of illness decreases greatly following the first decade of life.

Coxsackie viruses are transmitted primarily via the fecal-oral route, respiratory droplets and less commonly via fomites. The viruses replicate in the upper respiratory tract and in the distal small bowel. They have been found to persist in the respiratory tract for up to 3 weeks after initial infection and in feces up to 8 weeks after initial infection. Spread to target organs occurs following a secondary viremia. Immunity is thought to be predominantly humoral.

7.11.3 Clinical Presentation

In general, group A coxsackie viruses tend to infect the skin and mucous membranes and group B coxsackie viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myocarditis, pericarditis, and hepatitis. Coxsackie B is a rare cause of isolated hepatitis in an immunocompetent person. The hepatitis is clinically indistinguishable from other causes of viral hepatitis.

7.11.4 Laboratory Diagnosis

Serology: Antibody testing is available for coxsackie virus group B. A fourfold increase in the IgG titre in acute and convalescent serum or a single titre greater than 1:320 is diagnostic of a recent infection.

7.11.5 Prevention and Treatment

There is no specific treatment for coxsackie virus group B hepatitis and no immunoglobulin or vaccine available against coxsackie infections.

7.12 Conclusions

Viral hepatitis remains a global health problem with significant associated morbidity and mortality. It is not possible to distinguish biochemically between the different forms of viral hepatitis and diagnosis is dependent on appropriate serological and virological testing in order to implement therapeutic and preventative measures.

Development and implementation of National Guidelines for the Prevention and Treatment of Viral Hepatitis will be important to combat this increasing global health problem. It is essential to ensure access to affordable diagnostics, preventative vaccines and therapeutics. This will enable early identification and linkage to appropriate care.

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