Infections of the Ears, Nose, Throat, and Sinuses

Marlene L. Durand
Daniel G. Deschler
Editors

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ISBN 978-3-319-74834-4 ISBN 978-3-319-74835-1 (eBook)
https://doi.org/10.1007/978-3-319-74835-1

Library of Congress Control Number: 2018938660

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Dedication

With love and gratitude to:

My husband, Dr. Brooke Swearingen, our daughters, Jennifer and Laura Swearingen, and my parents, Leslie and Marjorie Durand.

– Marlene L. Durand, M.D.

My wife, Dr. Eileen E. Reynolds, our sons, Jack and Will Deschler, and my parents, Robert and Doris Deschler.

– Daniel G. Deschler, M.D.

Foreword (Dr. Rochelle P. Walensky)

Rarely does the demand for a modern medical text date back to the Founding Fathers of the United States. At 67 years old, George Washington succumbed to a 40-h illness characterized by sore throat, hoarseness, fever, and dyspnea—an illness that medical historians attribute to fulminant acute epiglottitis. While today the first president of the U.S. would have benefited from bactericidal antibiotics and a surgical airway, his precipitous demise is a reminder of the aggressive nature of infections in the small vulnerable regions of the head and neck. Such infections traverse and penetrate tissue planes, compromising these structures and spaces often within hours and sometimes right before our eyes. The management of ear, nose, and throat (ENT) infections mandates anatomical mastery, a reflexive menu of anticipated pathogens, a command of the expected antibiotic penetration into these spaces, a strong collaboration between medical and surgical specialties, and a deep respect for the potential of these infections to rapidly become life-threatening.

For decades, Monday morning Infectious Disease Case Conference at Massachusetts General Hospital (MGH) has been a working consultation where those attending on clinical service receive much-sought wisdom and advice from colleagues on their most challenging cases of the week. A common query on Monday morning at MGH is, "Is Marlene here today?" With over 20 years of experience in the treatment of ENT infections as both an infectious disease physician at MGH and the Director of the Infectious Disease Service at Massachusetts Eye and Ear Infirmary (MEEI), Dr. Durand has long been the go-to resource for many complex ENT infectious disease cases at MGH, MEEI, and around the country. Her co-editor, Dr. Deschler, has been a practicing ENT surgeon for over 20 years and is Vice Chair for Academic Affairs at MEEI as well as a professor of otolaryngology at Harvard Medical School. The senior authors of the chapters are otolaryngologists or infectious disease specialists with expertise and experience treating the infections discussed; many are chairs of their respective departments and divisions. The resulting textbook from this medical and surgical collaboration is masterful and will be a valuable resource to primary care providers, infectious disease specialists, and otolaryngologists around the world.

I offer my profound congratulations and gratitude to Drs. Durand and Deschler for the provision of a much-needed comprehensive update on the management of ENT infections. This textbook, *Infections of the Ears, Nose,*

Throat, and Sinuses, offers a window into their collective acumen—and that of their esteemed colleagues in the field—and reminds us of the required medical/surgical trusted partnership with which these infections must be managed.

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Foreword (Dr. D. Bradley Welling)

The world of medicine changes at an increasingly rapid pace. In the dynamic fields of otolaryngology and infectious diseases, it is surprising that there have been no textbooks updating information relevant to infectious diseases of the head and neck in the past two decades. These infections are among the most common of all medical problems encountered and can quickly lead to morbidity and mortality when unrecognized or inadequately treated.

Knowledge of the microbiome's influence on disease processes of the ear, sinuses, and aerodigestive tract has evolved in important ways. Techniques for precision diagnostics have helped in understanding the balance among pathogenic, colonizing, and commensal organisms. Treatment paradigms and resistance profiles constantly change in common and rare infections alike. The role of viruses in head and neck neoplasms, the state of adaptive and innate immunity, and the unique conditions associated with immunosuppression are all areas of critical understanding to the primary care physician and specialist.

Drs. Durand and Deschler are to be congratulated for responding to meet the unmet demands in infectious diseases and otolaryngology with this text that includes contributions from many of the world's authorities. It is the best I've seen in the field and is essential to the many clinicians who daily encounter these infections. Advances in our ability to render better care for our patients require treatment paradigms based upon sound evidence. This text affords the reader a valuable resource to quickly find, weigh, and use such information with up-to-date recommendations for diagnostic and treatment options.

In summary, *Infections of the Ears, Nose, Throat, and Sinuses* is a clear, concise, and comprehensive resource that beautifully fills the void for a reference in the field.

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Preface

Infections of the ears, nose, throat, and sinuses include some of the most common infections worldwide. Many of these infections are self-limited, while others require immediate treatment to prevent complications or even death. Understanding the clinical presentation, diagnosis, and treatment of various common and rare infections in otolaryngology will lead to better patient care, and it is our hope that this textbook will add to that understanding.

The purpose of the textbook is to serve as a comprehensive and useful resource to clinicians who see patients with ear or upper respiratory tract infections. To that end, the chapters include focused discussions and many helpful tables, references, diagrams, illustrations, and clinical photographs. The intended audience includes primary care practitioners, internists, ears, nose, and throat (ENT) specialists, and infectious disease specialists.

The authors of the individual chapters are experts in the field, and senior authors include department chairs and staff members of over 20 different institutions on four continents. The textbook begins with a discussion of antibiotics, resistant bacteria, and biofilms (Chaps. 1–3), followed by a discussion of various infections of the ears (Chaps. 4–10), sinuses (Chaps. 11–15), nose (Chap. 16), throat (Chaps. 17–21), mandible (Chap. 22), salivary glands (Chaps. 23 and 24), lymph nodes (Chaps. 25 and 26), and deep neck spaces (Chap. 27). The final chapters pertain to human papillomavirus-related conditions (head and neck cancers, Chap. 28, and recurrent respiratory papillomatosis, Chap. 29), and the textbook concludes with a discussion of antibiotic prophylaxis in ENT surgery (Chap. 30). Some chapters are devoted to common infections, such as acute otitis media, pharyngitis, and sinusitis, while others focus on rare but important ENT infections such as malignant external otitis and Lemierre's syndrome. Infections that have caused outbreaks, such as mumps and diphtheria, are also discussed.

We are grateful to the chapter authors for their expertise and their contributions to this textbook. We would also like to acknowledge the help of Lorraine Coffey, developmental editor at Springer International Publishing Company. Finally, we would like to thank our families and friends (Marlene: Brooke, Jennifer, and Laura Swearingen, James Van Strander, Taki Bitounis, Diane, Bob, and Jessica Rosenberg, Becky and Brad Renick; and Dan: Eileen Reynolds, Jack and Will Deschler, Sharon Derosa, and Theresa Wilson) for their ongoing encouragement and support.

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1 Antibiotics in Otolaryngology: A Practical Approach

Alyssa R. Letourneau

Introduction

This chapter provides an overview of common antibiotics encountered in otolaryngology with a summary of microbial spectrum, clinical indications, and adverse effects. A clinical approach to choosing antibiotics is outlined. Antibiotic stewardship, with an emphasis on appropriate use of antibiotics, is highlighted.

There is a current worldwide focus on antibiotic stewardship. Antibiotic stewardship programs aim to improve patient care and patient safety by ensuring that the correct antibiotic is given only when it is needed, at the correct dose and for the shortest duration for best clinical outcome [1]. Antibiotic stewardship is the responsibility of all antibiotic prescribers. Efforts should be made to understand when and why an antibiotic is needed as well as when it can be stopped.

Multidrug-resistant infections have become more common. The Centers for Disease Control and Prevention (CDC) defines a multidrug-resistant organism (MDRO) as one that is resistant to one or more classes of antibiotics. Antibiotic resistance is an emerging local, national, and international issue. The CDC, the World Health Organization, and the United Nations have all made antibiotic resistance a top priority and are supporting programs to combat the emergence of resistance. Antibiotic research and development continue to lag behind the need for novel agents.

The CDC estimates that each year in the United States, two million people develop infections due to MDROs and that at least 23,000 people die of these infections [2]. The use of antibiotics is the single most important risk factor leading to MDROs [2]. Inappropriate use of antibiotics is estimated to affect 13–39% of hospitalized patients and up to 30% of outpatients [3, 4]. About one-third of prescribed outpatient antibiotics are for otitis media, sinusitis, and pharyngitis, and narrow spectrum antibiotics are recommended as first-line therapy by national guidelines [4]. In the United States from 2010 to 2011, only 52% of prescriptions for these conditions were for first-line, narrow spectrum agents [5]. Improving appropriate antibiotic use will help to decrease antibiotic resistance.

General Considerations

Antibiotic Selection

Selecting an appropriate antibiotic depends on several factors: (1) the suspected infection (e.g., otitis media, pneumonia, abscess); (2) the likely

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_1

organisms and antibiotic susceptibilities; (3) host factors (e.g., immunosuppression, antibiotic allergies); and (4) antibiotic properties (e.g., dose, route of administration, potential toxicities).

Initial antibiotic therapy is usually empiric and broad-spectrum, covering a wide variety of organisms that are likely to cause a specific infection. For example, a patient with sepsis from an unknown source may be started on vancomycin, cefepime, and metronidazole to treat empirically for Gram-positive, Gram-negative, and anaerobic bacteria. Microbiologic specimens should be obtained prior to starting antibiotics whenever possible, to increase the likelihood of isolating a causative pathogen. Antibiotics should be tailored once culture results are available.

Local antibiograms can help guide initial empiric antibiotic choices, especially in critically ill patients. The antibiogram provides susceptibilities of common pathogens at a given institution or at the local or regional level. Risk factors for MDROs also should be considered for each patient. Risk factors for MDROs have been studied in patients admitted to the intensive care unit and those admitted with pneumonia [6, 7]. These MDRO risk factors include receipt of intravenous antibiotics within the preceding 90 days, residence in a nursing home, and an extended hospital stay within the previous 6 months [6, 7].

Gram stain of fluids can provide early clues to the etiology of an infection. Culture and susceptibility testing may take several days. Polymerase chain reaction testing can be useful for rapid identification of some pathogens (e.g., respiratory viruses). Antibiotics should be adjusted (directed therapy) as clinical and microbiologic data become available. Anti-bacterial agents should be stopped if a non-bacterial diagnosis is made.

Antibiotic Susceptibilities and Site of Infections

Antibiotic susceptibility testing is often performed on the bacterial isolates in positive cultures. The microbiology laboratory tests bacteria for susceptibility to a variety of antibiotics likely to be effective. Susceptibility testing guidelines are standardized by the Clinical and Laboratory Standards Institute and are commonly reported as minimum inhibitory concentration (MIC) with an interpretation of susceptible, intermediate, or resistant. The MIC is the lowest concentration of antibiotic needed to inhibit growth of the bacteria. The MIC varies by organism and by antibiotic and is not necessarily directly comparable across antibiotics.

Antibiotics are only effective if they are delivered adequately to the site of infection and this varies by agent and by dose. Antibiotics penetrate and achieve different concentrations in different bodily fluids. For example, patients with *Staphylococcus aureus* meningitis should not be treated with cefazolin because this antibiotic does achieve therapeutic concentrations in cerebrospinal fluid. Similarly, a patient with an undrained neck abscess may not improve on antibiotics alone because of poor penetration of the antibiotics into the abscess.

Antibiotic Dosing

Antibiotic dosing may be based on age, weight, renal function, the location of the infection, the targeted organism, and its susceptibility profile (if known). Some antibiotics should be avoided, if possible, at the extremes of age due to an increased risk of toxicity [8, 9]. Weight-based dosing of antibiotics is recommended in children and sometimes in overweight or underweight adults. Weight-based dosing is also recommended for certain antibiotics, such as vancomycin.

Many antibiotics need to be adjusted for renal function. Dosing should be based on estimated creatinine clearance. Some antibiotics can cause renal dysfunction and need close monitoring of electrolytes, creatinine, and drug levels during use (e.g., vancomycin and the aminoglycosides).

Antibiotics are nearly always given intravenously when a patient presents with a serious illness or is critically ill. As the patient improves, oral antibiotics may be suitable alternatives

depending on the clinical syndrome. Antibiotic bioavailability varies. Some antibiotics, such as fluoroquinolones, linezolid, azithromycin, clindamycin, doxycycline, metronidazole, and trimethoprim-sulfamethoxazole, have very good oral bioavailability while others, such as penicillins and cephalosporins, do not. Of note, oral bioavailability may be altered by food or other medications (e.g., antacids or iron supplements), and the prescribing clinician should be aware of such interactions.

Comorbid Conditions

Comorbidities may change the differential diagnosis of pathogens causing a clinical syndrome. Patients who are immunosuppressed (e.g., patients with HIV, organ or bone marrow transplant, cancer receiving chemotherapy, rheumatologic disease receiving immunosuppressive therapy) are susceptible to infection from a broader spectrum of pathogens than are immunocompetent hosts. For example, patients receiving TNFα (tumor necrosis factor alpha) inhibitors such as infliximab, adalimumab, or etanercept have an increased risk of tuberculosis and fungal infections [10]. Patients with diabetes are susceptible to invasive otitis externa by *Pseudomonas* even if their diabetes is in good control, and patients with diabetes out of control are susceptible to rhinocerebral mucormycosis. Exposures to sick contacts, animals, and travel, both recent and remote, should be considered when evaluating a patient as these factors can also alter the likely organisms causing disease.

Pregnancy and Lactation

Pregnancy and lactation need to be considered when selecting an antibiotic. Safety for both the pregnant mother and fetus or breastfeeding mother and infant must be considered [11]. Antibiotic concentrations in the placental tissue and breast milk vary. Dosing also varies as the pregnancy-related increase in glomerular filtration rate may clear antibiotics faster. Reviewing antibiotic selection and dosing with the patient's obstetrician or the infant's pediatrician is essential. The U.S. Food and Drug Administration (FDA) also has a description of the safety of various antibiotics during pregnancy and lactation.

Adverse Reactions and Allergies

Antibiotic complications are common and include hypersensitivity reactions, drug toxicity, and development of MDRO infections. In the U.S., 16% of emergency room visits for adverse drug events are due to antibiotics and this rate increases to 56% for children 5 years of age or younger and 32% for children ages 6–19 years [12]. Decreasing inappropriate antibiotic use would reduce the risk of adverse reactions requiring emergency room visits.

Antibiotic allergies should be confirmed prior to antibiotic prescribing. Antibiotics cause a variety of reactions including maculopapular rash, hives, Stevens-Johnson Syndrome, drug fever, and anaphylaxis. True allergic reactions should be distinguished from antibiotic-related side effects such as mild gastrointestinal upset, for example. Approximately 10% of the general population reports an allergy to penicillin (15.6% in some series) [13]. However, up to 90% of these individuals are not truly allergic to penicillin and were labeled as such unnecessarily [14]. Beta-lactams are the preferred antibiotics for many infections and substitution with broader-spectrum, non-beta-lactam therapies may result in poorer outcomes, higher rates of MDRO and *Clostridium difficile* infections, and longer lengths of stay [14–16]. A test dose or "graded challenge" procedure may allow many patients who report a penicillin or cephalosporin allergy to safely receive beta-lactam antibiotics. A test dose protocol introduced at a large teaching hospital in Boston resulted in an increase in the use of beta-lactams and a decrease in the use of some alternative antibiotics (vancomycin, fluoroquinolones, aminoglycosides, aztreonam) but without an increase in adverse drug events [17].

Drug toxicities and side effects vary by antibiotic and may be dose related (Table 1.1). Diarrhea may occur during or after an antibiotic course and may be either a side effect of the antibiotic or due to *C. difficile* infection. Antibiotics alter the normal microbiome of the gastrointestinal tract

Table 1.1 Antibiotic toxicities and side effects[a,b]

Antibiotic	Toxicities and side effects
Aminoglycosides	Renal dysfunction, vestibular and auditory toxicity, neuromuscular blockade.
Penicillins, cephalosporins, carbapenems	Allergic reactions, rash, diarrhea, central nervous system toxicity (e.g., seizure risk with high-dose penicillin), neutropenia with high doses or prolonged use
Clindamycin	Nausea, vomiting, diarrhea (not including *Clostridium difficile* infection), rash
Fluoroquinolones	Central nervous system toxicity (especially in the elderly), tendinopathy and tendon rupture (increased risk if >60 years old, using corticosteroids, or solid organ transplant recipient), QT prolongation on electrocardiogram.
Macrolides (azithromycin, clarithromycin, erythromycin)	Nausea, vomiting, diarrhea, abdominal pain, QT prolongation on electrocardiogram
Metronidazole	Metallic taste, adverse reaction (severe vomiting) with alcohol; prolonged use can lead to peripheral neuropathy
Trimethoprim-sulfamethoxazole	Nausea, vomiting, diarrhea, rash, nephrotoxicity, bone marrow suppression, aseptic meningitis, hyperkalemia, rare but severe skin reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis, hemolytic anemia in patients with G6PD deficiency
Tetracyclines (doxycycline, minocycline, tetracycline)	Gastrointestinal upset, sun sensitivity, discolored teeth in children <8 years old, affects growing bones in fetus
Vancomycin	Nephrotoxicity (increased risk with higher serum concentrations), ototoxicity. "Red man syndrome" (infusion reaction with itching, flushing, hypotension) usually can be avoided with slower infusions.

G6PD = glucose-6-phosphate dehydrogenase

[a]This table is not all-inclusive (does not list all antibiotics or all potential toxicities)

[b]Some antibiotics within a given antibiotic class cause fewer side effects than others (e.g., azithromycin has fewer gastrointestinal side effects than erythromycin); see the text for details

allowing overgrowth of *C. difficile*, whose toxin can cause frequent watery diarrhea, fever, leukocytosis, and in severe cases, toxic megacolon, intestinal perforation, and death. Each year in the U.S. approximately 250,000 people develop *C. difficile* infections, resulting in 14,000 deaths [2]. Half of these infections occur in hospitalized or recently hospitalized patients, while approximately half occur in residents of nursing homes or patients recently cared for in doctors' offices or clinics [2]. Many infections are associated with current or recent antibiotic use. Some antibiotic classes carry a higher risk than others. Clindamycin, fluoroquinolones, and cephalosporins carry the highest risk of community-acquired *C. difficile* infection, increasing the risk by 20-fold, six-fold, and four-fold, respectively, over no antibiotics [18]. A recent study from the United Kingdom found that decreasing fluoroquinolone use nationally resulted in a national decline of *C. difficile* infection [19]. Appropriate antibiotic use focusing on narrow spectrum agents for the shortest duration with best therapeutic effect can also help decrease *C. difficile* infection.

Duration of Therapy

Duration of therapy varies by the type of infection, causative pathogen, and antibiotic used. Society guidelines should be reviewed for duration of therapy including those from the Infectious Diseases Society of America (IDSA), available at www.idsociety.org/IDSA_Practice_Guidelines. Shorter antibiotic durations seem to be as effective as longer durations for urinary tract infections, community and hospital-acquired pneumonia, and drained intra-abdominal infections [7, 20–22]. One recent example of failure of shorter course antibiotic therapy, however, was for acute otitis media in children 6–23 months of age: 5 days of therapy resulted in less favorable outcomes than 10 days of therapy [23]. Longer duration of antibiotics is associated with increased adverse effects including toxicities of the drug, development of antibiotic resistance, and increased risk for *C. difficile* infection [2].

De-escalation of Therapy

In hospitalized patients receiving empiric antibiotic therapy, the need for antibiotic therapy should be re-evaluated at the 48–72-h mark. This timeframe allows for microbiologic data to mature and for an assessment of the clinical situation and potential response or nonresponse to antibiotic therapy. Antibiotics should be narrowed, if possible. "Response to therapy" should not be the only reason for antibiotic continuation if another explanation is likely. Additionally, culture data should be interpreted critically including the potential for positive cultures to represent colonization instead of infection. For example, a stable patient with a tracheostomy may grow highly resistant bacteria from tracheostomy cultures. Treatment of these bacteria may not be necessary in a patient who has no signs or symptoms of active infection.

Surgical Antibiotic Prophylaxis

Antibiotic prophylaxis for surgery targets bacteria that may contaminate the wound at the time of surgery. Antibiotic prophylaxis is recommended for nearly all clean-contaminated surgeries and for some clean surgeries. Skin flora, especially *Staphylococcus aureus*, and streptococci, especially Group A *Streptococcus*, are the primary targets of prophylaxis for clean surgeries. For clean-contaminated surgeries, broader-spectrum antibiotics are indicated since these must also cover the flora of the respiratory or gastrointestinal tract. Antibiotics should be started within 1 h prior to surgical incision (or within 2 h for vancomycin and fluoroquinolones) to be most effective [24, 25]. Antibiotics may need to be redosed intraoperatively for longer procedures [24]. Continuation of prophylactic antibiotics beyond skin closure has not been shown to improve outcomes [24], and the CDC recommends stopping prophylactic antibiotics after the incision is closed in the operating room, even in the presence of a drain [26]. Surgical prophylaxis in otolaryngology is discussed further in Chap. 30.

Antibacterial Agents

Beta-Lactam Antibiotics

Beta-lactam antibiotics include the penicillins, cephalosporins, carbapenems, and monobactams. Beta-lactam antibiotics have a four-member core ring structure (Fig. 1.1) and are bactericidal. They inhibit bacterial cell wall synthesis. Table 1.2 provides a summary of commonly used beta-lactam antibiotics, their general spectrum of activity, and common indications.

Penicillins. Penicillin was first used to treat a patient in Oxford, England, in 1941. It was initially effective against *S. aureus* in addition to streptococci, but resistance in staphylococci quickly developed. Group A *Streptococcus*, however, never developed resistance to penicillin. Methicillin was developed in 1961 as a penicillin derivative with efficacy against *S. aureus*, but this was subsequently replaced by less toxic alternatives, nafcillin and oxacillin. The name "methicillin" remains in "methicillin-susceptible *S. aureus*" (MSSA) and "methicillin-resistant *S. aureus*" (MRSA), and signifies susceptibility or resistance to beta-lactam antibiotics such as oxacillin, nafcillin, ampicillin-sulbactam, cefazolin, cefuroxime, ceftriaxone, and cefepime.

Cephalosporins. The first cephalosporin was isolated in Oxford, England, in 1961 and the first clinically useful cephalosporin, cephalothin, was marketed in 1964. Subsequent development of multiple cephalosporins has led to their classification in "generations" (Table 1.2). Clinically important features that distinguish various cephalosporins include their activity against *S. aureus* (e.g., cefazolin, cefuroxime, cefepime), *S. pneumoniae* (e.g., ceftriaxone), anaerobes (e.g., cefoxitin), and Gram-negative bacilli. All cephalosporins have activity against Gram-negative bacilli, but the number of susceptible pathogens generally increases as the generation of cephalosporin increases. The few cephalosporins (e.g., ceftazidime, cefepime) with activity against *Pseudomonas* are noteworthy. None of the cephalosporins had activity against MRSA until the

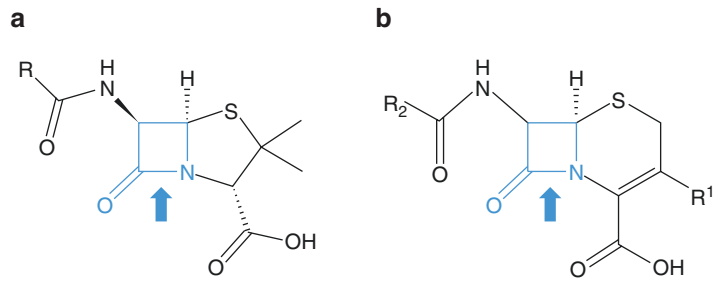

Fig. 1.1 Beta-lactam antibiotics, core structure. (**a**) Penicillins; (**b**) Cephalosporins. The "R" is a variable group. The beta-lactam ring is in blue. The arrow points to the site of action of bacterial beta-lactamase enzymes

advent of the fifth generation cephalosporins, ceftobiprole and ceftaroline.

Carbapenems. Carbapenems provide broad antibacterial therapy treating Gram-positive cocci, Gram-negative bacilli, and anaerobes. They are also active against most bacteria that have an extended-spectrum β-lactamase (ESBL) or an AmpC beta-lactamase (bacterial mechanisms of resistance). They are administered intravenously and include doripenem, ertapenem, imipenem-cilastatin, and meropenem. They are not active against MRSA or *Stenotrophomonas maltophilia*. Ertapenem is not active against *Pseudomonas* or *Acinetobacter*. Carbapenems have good penetration into many tissues, including into the central nervous system, and are valuable agents because of their broad-spectrum of activity. As with all antibiotics, resistance can emerge while on therapy and these agents should only be used when narrower spectrum antibiotics are not an option.

Monobactams. The only FDA-approved monobactam to date is aztreonam, an antibiotic with a similar spectrum of activity as gentamicin and other aminoglycosides, but with significantly less toxicity. Aztreonam is effective against Gram-negative bacteria, including *Pseudomonas*, but has no activity against Gram-positive bacteria or anaerobes. Aztreonam is used primarily for treatment of Gram-negative infections in patients with severe penicillin or cephalosporin allergies, because nearly all patients with beta-lactam allergies can tolerate aztreonam [27, 28]. Aztreonam has a similar side chain as ceftazidime and should be used cautiously in patients with ceftazidime allergy [29]. Aztreonam can be used to treat a variety of infections including bacteremia, urinary tract infections, bone and joint infections, and skin and soft tissue infections. In can be used in combination with a Gram-positive antibiotic in cases requiring broad-spectrum therapy.

Aminoglycosides

Aminoglycosides (e.g., amikacin, gentamicin, tobramycin) are often used in combination with beta-lactam antibiotics to treat some types of bacterial endocarditis and Gram-negative infections. Aminoglycosides have activity against nearly all Gram-negative bacilli, including *Pseudomonas aeruginosa*, and act synergistically with ampicillin to treat serious infections due to susceptible enterococci. Some aminoglycosides (e.g., streptomycin) are used as part of a regimen to treat multidrug-resistant mycobacterial infections. Clinical use of aminoglycosides is largely reserved for the treatment of drug-resistant organisms because renal dysfunction and ototoxicity are significant side effects. Renal function and serum peak and trough aminoglycoside levels should be monitored frequently. Patients should be alerted to the possibility of ototoxicity, and hearing and vestibular function should be monitored unless the aminoglycoside course is expected to be very brief. Ototoxicity can affect hearing and/or vestibular function and usually begins with high-frequency sensorineural hearing loss. This may not be appreciated by the patient but can be detected on hearing tests. Vestibular toxicity may be more prevalent that auditory toxicity. One study of 71 cystic fibrosis patients who had received courses of aminoglycosides for the treatment of *Pseudomonas*

Table 1.2 Select beta-lactam antibiotics and their common uses[a]

Antibiotic[a]	Usual spectrum of activity[a]	Common uses (for susceptible bacterial isolates)[a]
Penicillins		
Penicillin G (IV) Penicillin VK (PO) Benzathine penicillin G (IM) for syphilis	Group A *Streptococcus* Group B *Streptococcus* *Streptococcus anginosus* group viridans streptococci (most) *Streptococcus pneumoniae* (not penicillin-resistant strains) *Arcanobacterium* species Most Gram-positive anaerobes *Actinomyces* species *Treponema pallidum*	Pharyngitis *Actinomyces* infection Oral and periodontal infections Necrotizing fasciitis Syphilis (IV/IM)
Nafcillin (IV) Oxacillin (IV) Dicloxacillin (PO)	Methicillin-sensitive *Staphylococcus aureus* (MSSA)	Cellulitis MSSA bacteremia (IV) MSSA endocarditis (IV)
Ampicillin (IV) Amoxicillin (PO)	*Enterococcus faecalis* *Streptococcus* species (penicillin-susceptible isolates only) *Haemophilus influenzae* (beta-lactamase-negative strains only) *Listeria monocytogenes* *Escherichia coli* *Proteus mirabilis* Most Gram-positive anaerobes (similar to penicillin)	Acute otitis media *Listeria* bacteremia or meningitis (IV) *Haemophilus influenzae* meningitis and epiglottitis (IV) (ampicillin-susceptible strains only) Endocarditis due to susceptible enterococci (IV, in combination with aminoglycoside or ceftriaxone)
Ampicillin-sulbactam (IV) Amoxicillin-clavulanic acid (PO)	*Enterococcus faecalis* *Enterococcus faecium* MSSA *Streptococcus* species *Arcanobacterium* species *Listeria monocytogenes* *Escherichia coli* *Proteus mirabilis* *Haemophilus influenzae* (including beta-lactamase-positive isolates) *Moraxella catarrhalis* Most anaerobes including *Bacteroides fragilis* Sulbactam has activity against *Acinetobacter baumanii*	Bacterial sinusitis Acute otitis media Bite wounds Urinary tract infections Community-acquired pneumonia Community-acquired abdominal infections (e.g., diverticulitis) Skin and skin-structure infections
Piperacillin-tazobactam (IV)	Similar to ampicillin-sulbactam plus *Pseudomonas aeruginosa*	Pseudomonal infections Nosocomial infections including pneumonia Intra-abdominal infections
Cephalosporins		
First generation		
Cefazolin (IV) Cefadroxil (PO) Cephalexin (PO)	MSSA Group A *Streptococcus* Some community-acquired Gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella* species, *Proteus mirabilis*)	Cellulitis MSSA bacteremia (IV) Peri-operative prophylaxis (IV)
Second generation		
Cefaclor (PO) Cefprozil (PO) Cefuroxime (IV or PO)	MSSA *Streptococcus* species *Escherichia coli* *Klebsiella* species *Proteus mirabilis* *Haemophilus influenzae* *Moraxella catarrhalis*	Acute otitis media Bacterial sinusitis Community-acquired pneumonia

(continued)

Table 1.2 (continued)

Antibiotic[a]	Usual spectrum of activity[a]	Common uses (for susceptible bacterial isolates)[a]
Cefotetan (IV) Cefoxitin (IV)	MSSA *Streptococcoccus* species *Escherichia coli* *Klebsiella* species *Proteus* species Anaerobes including *Bacteroides fragilis*	Peri-operative prophylaxis for gastrointestinal and pelvic surgeries, however use has decreased due to increased resistance of *Bacteroides*
Third generation		
Cefdinir (PO) Cefditoren pivoxil (PO) Cefixime (PO) Cefotaxime (IV) Cefpodoxime proxetil (PO) Ceftriaxone (IV)	MSSA *Streptococcus* species *Escherichia coli* *Klebsiella* species *Proteus* species *Neisseria* species *Haemophilus influenzae* *Moraxella catarrhalis* *Borrelia burgdorferi*	Upper respiratory tract infections, including otitis media, and some lower respiratory tract infections Urinary tract infections IV ceftriaxone is commonly used as part of a regimen to treat community-acquired meningitis, community-acquired pneumonia, some types of complicated Lyme disease infections (e.g., neuroborreliosis), and as part of a regimen to treat gonorrhea.
Ceftazidime (IV)	Gram-negative bacilli including *Pseudomonas aeruginosa* Some activity against Gram-positive bacteria (less active against MSSA than most other cephalosporins)	*Pseudomonas* infections including meningitis Nosocomial infections including pneumonia and bacteremia
Fourth generation		
Cefepime (IV)	MSSA *Streptococcus* species Gram-negative bacilli including *Acinetobacter* species *Citrobacter* species *Enterobacter* species *Proteus* species *Pseudomonas aeruginosa* *Serratia* species	Broad Gram-positive and Gram-negative therapy (empiric) *Pseudomonas* infections Nosocomial infections including pneumonia Bacteremia
Fifth generation		
Ceftaroline (IV)	MSSA MRSA *Group A Streptococcus* *Streptococcus pneumoniae* *Haemophilus influenzae* *Escherichia coli* *Klebsiella* species	Skin and skin structure infections (e.g., complicated cellulitis) Community-acquired pneumonia

IV = intravenous, PO = per os (oral), IM = intramuscular, MSSA = methicillin-susceptible *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*

[a]This table is not all-inclusive, nor is it intended to guide therapy for a particular infection. In addition, the indications for use by the U.S. Food and Drug Administration (FDA) may be more limited, or in some cases broader, than those listed under "Common Uses". Some common uses for antibiotics are "off label," and some pathogens are not among those for which the antibiotic has an FDA-approved use. Some of the pathogens listed may have isolates that are resistant to the corresponding antibiotic. Some of the common uses noted for a given antibiotic may apply only when that antibiotic is used in combination with another antibiotic.

infections found that 79% had vestibular dysfunction while 23% had hearing loss (some had both) [30]. Ototoxicity, which is usually irreversible, may start either during or even weeks after completing a course of aminoglycosides.

Clindamycin

Clindamycin is active against susceptible *S. aureus* and *Streptococcus* species as well as many anaerobic Gram-positive cocci such as *Peptostreptococcus*. It has no activity against Gram-negative bacilli, and increasingly poor activity against anaerobic Gram-negative bacilli such as *Bacteroides fragilis*. Clindamycin is often used to treat MRSA skin and soft tissue infections, although MRSA resistance to clindamycin is significant (20–25%) in some regions of the U.S. [31, 32]. Clindamycin is also used to treat some *S. aureus* (MSSA) and streptococcal infections in penicillin-allergic patients, but increasing clindamycin resistance in these pathogens is also a concern. A recent study of Group A streptococcal pharyngitis in children in Wisconsin reported a clindamycin resistance rate of 15% [33]. Clindamycin has excellent oral bioavailability but patients usually tolerate much higher doses of intravenous than oral clindamycin. Clindamycin is cleared by the liver and should be dose adjusted in liver dysfunction.

Daptomycin

Daptomycin, FDA-approved in 2003, is a lipopeptide. It is available only intravenously and has activity solely against Gram-positive bacteria. It is active against most Gram-positive bacteria, including resistant bacteria such as MRSA and vancomycin-resistant *Enterococcus* (VRE). It is approved for treating complicated skin and soft tissue infections, *S. aureus* bacteremia and for right-sided endocarditis. It should not be used for pneumonia and other pulmonary infections as it is ineffective in the presence of surfactant. Daptomycin dosing is weight-based and the drug is generally well tolerated. Creatinine phosphokinase (CPK) should be followed weekly to monitor for treatment-related myopathy.

Fluoroquinolones

Fluoroquinolones are broad-spectrum agents that have excellent oral bioavailability, with oral and intravenous doses achieving similar serum levels in patients with normal gastrointestinal absorption. Oral medications, such as some antacids and dietary supplements that contain divalent and trivalent cations (magnesium, aluminum, iron, or calcium), may significantly reduce oral quinolone absorption and should be given at least 2 h before the quinolone. Quinolones have excellent penetration into tissues including bone. Ciprofloxacin is primarily active against Gram-negative bacteria including enteric Gram-negative bacilli and *Pseudomonas aeruginosa*. Levofloxacin has additional activity against streptococci, including *S. pneumoniae*, and atypical pathogens such as *Legionella* and *Mycoplasma*, making it useful for treatment of community-acquired pneumonia. Moxifloxacin is similar to levofloxacin but has some activity against anaerobes and much less activity against *Pseudomonas*.

Widespread use of the fluoroquinolones has led to increasing resistance and providers should be thoughtful about their use [34, 35]. Additionally, in 2016 the FDA issued a safety announcement about the serious adverse effects of quinolones including tendinitis, tendon rupture, paresthesias, muscle and joint pain, and central nervous system effects [36]. The FDA stated that systemic fluoroquinolones should not be used in patients with other treatment options for acute bacterial sinusitis, acute bronchitis, and uncomplicated urinary tract infections [36].

Linezolid and Tedizolid (Oxazolidinones)

Linezolid was the first FDA-approved (2003) member of a new class of antibiotics, the oxazolidinones. Tedizolid is a second-generation

oxazolididone (FDA-approved 2014) and is more potent than linezolid against staphylococci and enterococci. Both antibiotics are available intravenously and orally, and are used to treat infections due to Gram-positive bacteria, including resistant Gram-positive bacteria such as MRSA and VRE. They also have activity against some mycobacteria, and may be used (off label use) as part of a combination regimen for mycobacteria. They have good oral bioavailability and tissue penetration. Linezolid can be used to treat bacteremia, pneumonia, and complicated skin and soft tissue infections due to Gram-positive bacteria. Use of linezolid can cause cytopenias, particularly thrombocytopenia, which is less likely to occur with tedizolid [37, 38]. Long-term use of these antibiotics can cause peripheral neuropathy and rarely, optic neuropathy. Tedizolid is currently approved only for treating skin and soft tissue infections.

Macrolides

The macrolides, including erythromycin, clarithromycin, and azithromycin, are used primarily to treat community-acquired pneumonia and are often used to treat pharyngitis in penicillin-allergic patients. Clarithromycin and azithromycin are active against susceptible *S. pneumoniae* (although resistance has been increasing), *Legionella pneumophila*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. Approximately 15% of Group A streptococcal pharyngitis isolates are resistant to macrolides [33], and macrolides are ineffective against *Fusobacterium necrophorum*, an important cause of pharyngitis in adolescents and young adults and the primary cause of Lemierre's syndrome. Azithromycin is available both intravenously and orally, is given once daily, and is better tolerated than the other macrolides. Clarithromycin is only available orally. Erythromycin is usually poorly tolerated due to gastrointestinal side effects, and it is often used as a gastrointestinal motility agent in the intensive care unit. Azithromycin and clarithromycin are important components of the treatment regimen for nontuberculous mycobacteria infections. Gastrointestinal upset with nausea, vomiting, abdominal pain, and diarrhea is a common side effect (less so with azithromycin) and QT prolongation can occur while on therapy.

Metronidazole

Metronidazole is active against nearly all Gram-negative anaerobes including *Clostridium*, *Bacteroides*, and *Fusobacterium* species. It has poor activity against many Gram-positive anaerobes (see Chap. 2) and no activity against aerobic bacteria. Oral metronidazole is well absorbed. It is often used in combination with antibiotics active against Gram-positive and Gram-negative aerobic bacteria to provide broad-spectrum coverage. It has been used as initial therapy for *C. difficile* infections for many years, but recent evidence suggests that oral vancomycin is superior [39–41]. Metronidazole can cause a metallic taste and when used for extended courses, peripheral neuropathy.

Tetracyclines

Tetracyclines are active against both Gram-positive and Gram-negative bacteria as well as atypical agents such as *Mycoplasma*, rickettsia, and *Borrelia burgdorferi* (the major cause of Lyme disease in the U.S.). Doxycycline is available intravenously and orally and is more commonly prescribed than tetracycline in the U.S. Tetracyclines can be used for the treatment of atypical pneumonia caused by *Mycoplasma* or *Chlamydia pneumoniae*. These agents are also used to treat skin and soft tissue infections caused by MRSA, although many MRSA isolates are resistant. Sun sensitivity (sunburn) can occur with the use of the tetracyclines and patients should be advised to wear sunscreen. Tigecycline is a tetracycline derivative, available only intravenously, that was FDA-approved in 2005. However, tigecycline received an FDA "black box warning" in 2010 due to increased all-cause mortality observed in patients treated with tigecycline versus comparator drugs. The cause of

the higher mortality rate in the tigecycline-treated patients is unknown. Tigecycline has broad-spectrum activity and is used primarily to treat those MDRO infections that are resistant to other antibiotics. It is not active against *Pseudomonas*. Tigecycline does not achieve high serum concentrations and should not be used for bacteremia.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole is active against *Staphylococcus* species as well as Gram-negative bacteria including *H. influenzae*, *Escherichia coli*, *Proteus mirabilis*, and *Stenotrophomonas*. It has excellent bioavailability. It is a first-line agent for urinary tract infections due to susceptible pathogens and can be used to treat susceptible MRSA skin and soft tissue infections. It is important to understand the local susceptibilities of MRSA to be sure trimethoprim-sulfamethoxazole provides adequate therapy. It is also used as prophylaxis to prevent *Pneumocystis jivorecii* pneumonia in HIV patients with low CD4 counts and in solid organ and hematopoetic stem cell transplant recipients.

Vancomycin and Other Glycopeptides

Vancomycin. Vancomycin, FDA-approved in 1958, has activity only against Gram-positive bacteria. Intravenous vancomycin is primarily used to treat infections due to resistant *Staphylococcus* species, *Streptococcus* species, and *Enterococcus* species, while oral vancomycin is used to treat *C. difficile* infections. Oral vancomycin is not absorbed so cannot be used to treat systemic infections. Intravenous vancomycin is the drug of choice for susceptible MRSA infections including bacteremia and pneumonia. Vancomycin can be used for treating *S. aureus* (MSSA) infections in patients who cannot tolerate beta-lactam therapy, but beta-lactam antibiotics clear MSSA bacteremia more quickly. Dosing is based on renal function and weight. Serum vancomycin trough levels should be monitored to achieve therapeutic drug concentrations and minimize toxicity. Renal toxicity can occur with high doses. "Red man syndrome" is a vancomycin infusion reaction due to histamine release that presents with rash, itching, flushing, and sometimes hypotension. It typically occurs with rapid infusion of the antibiotic and can usually be avoided with slower infusion rates.

Other glycopeptides. Telavancin, dalbavancin, and oritavancin are lipoglycopeptides that were FDA-approved in 2009 (telavancin) and 2014 (dalbavancin, oritavancin). They are in the same antibiotic class as vancomycin and have similar activity, but these newer agents have the advantage of once-daily dosing (televancin) or once-weekly dosing (dalbavancin and oritavancin). The once-weekly regimens are only approved for skin and soft tissue infections. Use of these agents should be with guidance from an infectious disease specialist.

Miscellaneous Antibiotics for Urinary Tract Infections

Fosfomycin and nitrofurantoin. Fosfomycin and nitrofurantoin are oral agents available for the treatment of uncomplicated urinary tract infections. Fosfomycin can be administered as a one-time dose. Nitrofurantoin can only be given to those with relatively normal renal function as it requires adequate excretion into the urine to be effective. These agents, along with trimethoprim-sulfamethoxazole, are excellent treatments for uncomplicated urinary tract infections due to susceptible bacteria [20].

Treatment of Infections Due to Multidrug-Resistant Organisms

For MDRO infections, consultation with an infectious disease specialist is recommended. Several of the antibiotics discussed above, such as linezolid, are approved for the treatment of infections caused by resistant Gram-positive bacteria including MRSA and VRE. For treating

infections due to resistant Gram-negative bacilli, there are several options but treatment should be guided by results of susceptibility testing. Ceftolozane-tazobactam and ceftazidime-avibactam have been recently approved (2014, 2015 respectively) for treatment of urinary tract infections and intra-abdominal infections. Ceftolozane-tazobactam was developed to treat highly resistant *Pseudomonas aeruginosa*. It also has activity against many other MDRO Gram-negative bacilli but not those with carbapenamases. Ceftazidime-avibactam is active against resistant Gram-negative bacilli including some that produce carbapenemases.

Other antibiotics used for highly drug-resistant organisms include tigecycline and polymyxins (e.g., colistin). These are primarily drugs of last resort and should be used with guidance from an infectious disease specialist.

Antifungal Agents

Fungal infections are generally divided into yeast infections and mold infections. Most yeast infections in otolaryngology are due to *Candida* species. Mold infections, such as those due to *Aspergillus* and the agents of mucormycosis, are much more difficult to treat than *Candida* infections. In general, antifungal antibiotics with activity against molds also treat *Candida*, while the reverse is not true. Results of antifungal susceptibility testing for *Candida* species are clinically meaningful (correlate with response to therapy), but the same is not true for molds. For treatment of invasive mold infections, results of clinical trials using various antifungal agents have proven to be most reliable in guiding therapy.

Amphotericin. Amphotericin B treats nearly all molds and *Candida* species but has significant toxicities, including renal. Liposomal amphotericin is at least as effective as amphotericin B and has significantly less renal toxicity, but is much more expensive. Both the agents are only available intravenously.

Azoles. The major azoles available in the U.S. are fluconazole, itraconazole, voriconazole, posaconazole, and most recently isavuconazonium sulfate (metabolized to isavuconazole). Azoles have high bioavailability so oral and intravenous formulations often achieve similar serum levels. Fluconazole achieves excellent tissue penetration and is effective against nearly all strains of *Candida albicans*, although some other *Candida* species may be resistant. Fluconazole is not effective against molds. Itraconazole has some activity against molds but therapeutic serum drug levels are difficult to achieve, and itraconazole is less effective against *Aspergillus* than voriconazole. Voriconazole, available orally and intravenously, is the treatment of choice for invasive *Aspergillus* infections. It also has activity against some other molds (e.g., *Fusarium*) although not against the molds that cause mucormycosis (e.g., *Rhizopus*, *Mucor*). Oral voriconazole has excellent bioavailability. Posaconazole has activity against fungi that cause mucormycosis and is available orally and intravenously. Posaconazole is FDA-approved only for the treatment of refractory oropharyngeal candidiasis and for prophylaxis of invasive *Aspergillus* and *Candida* infections in high-risk patients, such as immunocompromised hosts. Posaconazole is frequently used as step-down oral therapy in invasive mold infections such as mucormycosis after an initial course of treatment with amphotericin or liposomal amphotericin. Isavuconazonium sulfate (metabolized to isavuconazole) is available both intravenously and orally and has broad-spectrum antifungal activity, including against both *Aspergillus* and the agents of mucormycosis. See Chap. 15 for discussion of invasive fungal sinusitis. Hepatotoxicity is an important side effect of azoles and liver function tests should be monitored. All azoles, except for isavuconazonium sulfate, can prolong the QTc interval and this should be monitored closely while on therapy. Isavuconazonium sulfate can shorten the QTc interval. Azoles are metabolized through the CYP3A4 pathway of the liver and therefore have many drug-drug-interactions. Healthcare providers should evaluate potential interactions with a

patient's other medications before prescribing azoles.

Echinocandins. Echinocandins, including caspofungin and micofungin, are primarily used to treat serious infections due to *Candida* species that are resistant to fluconazole. Echinocandins are generally well tolerated but are available only intravenously.

Conclusion

The discovery of sulfa drugs in 1932 and the first clinical use of penicillin in 1941 ushered in the modern antibiotic era. The introduction of each new antibiotic, however, has been followed by the development of microbial resistance to that antibiotic. Many bacteria are now resistant to multiple classes of antibiotics. It is important for clinicians to use antibiotics appropriately and prudently, as unnecessary antibiotic use contributes to the selection of increasingly resistant organisms.

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2 Antibiotic-Resistant Pathogens in Ear, Nose, and Throat Infections

Itzhak Brook

Introduction

The management of ear, nose, and throat (ENT) infections requires an accurate clinical and bacteriological diagnosis, followed by an initial empiric antimicrobial therapy that may be adjusted once the identification of the causative organism(s) is available. The increasing antimicrobial resistance of many respiratory tract bacterial pathogens has made the treatment of these infections more challenging [1, 2].

The microflora of the upper airways, including the oral cavity, nasopharynx, and oropharynx, is complex and contains many types of aerobic, facultative, and obligate anaerobic bacteria [3]. The ratio of anaerobic to aerobic bacteria in saliva is approximately 10:1. The total count of anaerobes in the saliva and elsewhere in the oral cavity reaches 10^7–10^8 bacteria/ml.

Table 2.1 lists the major pathogens that cause various ENT infections. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are the predominant aerobic pathogens recovered in acute respiratory tract infections. Their resistance to antimicrobials has significantly increased in the past 30 years. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and endogenous oropharyngeal anaerobes are commonly recovered in chronic head and neck infections, some of which can be life-threatening [4]. Because anaerobes are difficult to isolate, they are often overlooked. Furthermore, their exact role is difficult to ascertain from many past reports because of the inconsistent methodologies used for their isolation and identification in many of these studies [5, 6]. Isolation and identification of anaerobes require appropriate methods of collection, transportation, and cultivation of specimens. Treatment of anaerobic infections is complicated by their polymicrobial nature and the growing antimicrobial resistance and slow growth of these bacteria [5, 6].

Antibiotic Resistance Mechanisms

Antibiotics are naturally produced by many bacteria and fungi, and antibiotic-producing microbes are resistant to the antibiotics they produce. Antibiotic resistance therefore preceded the advent of antibiotics by many millennia. Antibiotic resistance genes have been found within bacteria contained in samples of 30,000-year-old permafrost. Selective pressure by human use of antibiotics over the past 80 years has led to rapid expansion in antibiotic resistance in clinically important pathogens. Multidrug-resistant organisms,

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_2

Table 2.1 Some of the aerobic and anaerobic bacteria isolated in upper respiratory tract and head and neck infections

Type of infection	Aerobic and facultative organisms	Anaerobic organism
Otitis media: acute	*Streptococcus pneumoniae*	*Peptostreptococcus* spp.
	Haemophilus influenzae[a]	
	Moraxella catarrhalis[a]	
Otitis media: chronic, and Mastoiditis	*Staphylococcus aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.
	Escherichia coli[a]	*Bacteroides* spp.[a]
	Klebsiella pneumoniae[a]	*Fusobacterium* spp.[a]
	Pseudomonas aeruginosa[a]	*Peptostreptococcus* spp.
Peritonsillar and retropharyngeal abscess	*Streptococcus pyogenes*	*Fusobacterium* spp.[a]
	S. aureus[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	S. pneumoniae	
Recurrent tonsillitis	*S. pyogenes*	*Fusobacterium* spp.[a]
	H. influenzae[a]	
	S. aureus[a]	
Suppurative thyroiditis	*S. pyogenes*	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	S. aureus[a]	
Sinusitis: acute	*H. influenzae*[a]	*Peptostreptococcus* spp.
	S. pneumoniae	
	M. catarrhalis[a]	
Sinusitis: chronic	*S. aureus*[a]	*Fusobacterium* spp.[a]
	S. pneumoniae	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	H. influenzae	
Cervical lymphadenitis	*S. aureus*[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Mycobacterium spp.	*Peptostreptococcus* spp.
Postoperative infection disrupting oral mucosa	*Staphylococcus* spp.[a]	*Fusobacterium* spp.[a]
	Streptococcus spp.[a]	*Bacteroides* spp.[a]
	Enterobacteriaceae[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Pseudomonas[a]	*Peptostreptococcus* spp.
Deep neck space	*Streptococcus* spp.[a]	*Bacteroides* spp.[a]
	Staphylococcus spp.[a]	*Fusobacterium* spp.[a]
		Peptostreptococcus spp.
Odontogenic complications	*Streptococcus* spp.[a]	Pigmented *Prevotella* and *Porphyromonas* spp.[a]
	Staphylococcus spp.[a]	*Peptostreptococcus* spp.
Oropharyngeal: Vincent's angina	*Streptococcus* spp.[a]	*Fusobacterium necrophorum*[a]
Necrotizing ulcerative gingivitis	*Staphylococcus* spp.[a]	*Spirochetes*, *Prevotella Intermedia*, *Fusobacterium* spp[a]

[a]Organisms that have the potential of producing beta-lactamase

defined as those organisms with resistance to one or more classes of antibiotics, are now prevalent.

Bacteria can be genetically resistant to an antibiotic or acquire resistance through mutation or acquisition of foreign DNA (e.g., uptake of naked DNA left by dying bacteria, or acquisition of a plasmid carrying resistance genes). Plasmids, small circular strands of DNA that replicate independently of chromosomes, are commonly found in bacteria. Plasmids can be transferred from one bacterium to another in several ways, including during bacterial conjugation and via a bacterial

virus (bacteriophage). Resistance genes may be continuously expressed ("constitutive"), or expressed only when needed ("inducible"). Resistance usually costs the bacterium energy so inducible resistance is more common.

Bacteria have several mechanisms of resistance (Table 2.2). These include permeability barriers, inactivating enyzmes, target site alteration, overproduction of the target, and efflux mechanisms. An example of a permeability barrier is that of Gram-negative bacilli to penicillin. Gram-negative bacilli have a lipopolysaccharide outer membrane that envelops the cell wall. This outer membrane is absent in Gram-positive bacteria. The outer membrane is hydrophobic, and hydrophilic antibiotics such as nafcillin do not penetrate. Hydrophilic antibiotics may penetrate the outer membrane through their porins (permeability channels), but loss of favorable porins will lead to resistance. This may occur during imipenem treatment of *Pseudomonas*, for example. Another common mechanism is alteration of the target site of the antibiotic. Penicillin acts by attaching to penicillin binding protein (PBP), a bacterial enzyme that is used in cell wall synthesis. *Staphylococcus aureus* can acquire a gene (*mecA*) which encodes for an altered PBP (PBP2a) that does not bind penicillin. Acquisition of the *mecA* gene by *S. aureus* results in MRSA (methicillin-resistant *S. aureus*), a bacterial species resistant to all beta-lactams except fifth generation cephalosporins.

Table 2.2 Some common mechanisms of bacterial resistance and examples of antibiotics affected

Mechanism	Example
Permeability barrier to antibiotic	Outer membrane of Gram-negative bacteria serves as a barrier to nafcillin
Enzymatic inactivation of antibiotic	Beta-lactamases (e.g., *Staphylococcus aureus* inactivation of penicillin by a beta-lactamase)
Alteration of target site for the antibiotic	(1) Alteration of the bacterial enzyme, penicillin binding protein, in MRSA so that penicillin cannot bind (2) Alteration of the ribosomal target site by methylation so erythromycin or clindamycin cannot bind
Overproduction of the target	Overproduction of the target bacterial enzyme (dihydropteroate synthase) involved in folate production
Efflux pumps to pump antibiotic out of cell	Efflux of tetracycline by some Gram-negative bacilli, resulting in low intracellular concentrations

MRSA methicillin-resistant *Staphylococcus aureus*

Beta-Lactamase Production

A major resistance mechanism is inactivation of the antibiotic by a bacterial enzyme. Beta-lactamases are the most important examples of such enzymes, and these include penicillinases, cephalosporinases, carbapenemases. Some are produced by the bacterial chromosome and some by a plasmid within the bacterium. Beta-lactam antibiotics have a four-member beta-lactam ring, and beta-lactamases hydrolyze this ring, rendering the antibiotic ineffective (Fig. 2.1).

Beta-lactamase production is an important mechanism of antimicrobial resistance of both aerobic bacteria (e.g., *Staphylococcus aureus*, *H. influenzae*, and *M. catarrhalis*), and anaerobic Gram-negative bacilli (e.g., pigmented *Prevotella* and *Porphyromonas*). Beta-lactamase-producing bacteria can play an important role in respiratory infections [7]. They can cause the infection as well as have an indirect effect through their ability to produce the beta-lactamase [8]. These bacteria may not only survive penicillin therapy but can also, as was demonstrated in vitro [9], in vivo [10, 11], and in clinical [12] studies, protect other penicillin-susceptible bacteria from penicillin by releasing the free enzyme into their environment [8].

Aerobic Bacteria

Haemophilus influenzae

About 40% of *H. influenzae* resist beta-lactam antimicrobials through production of beta-lactamases. Increased prevalence of nontypeable *H. influenzae* strains that resist ampicillin and/or other beta-lactams was noted in the

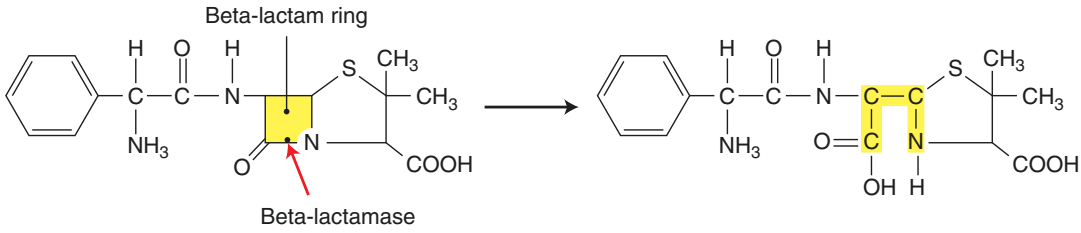

Fig. 2.1 Inactivation of ampicillin by beta-lactamase. The red arrow points to the chemical bond that is hydrolyzed by beta-lactamase

past decade [13]. Ampicillin resistance is usually due to plasmid-mediated production of beta-lactamase so it can be overcome by beta-lactam, beta-lactamase inhibitor combination antibiotics (e.g., amoxicillin-clavulinate). However, *H. influenzae* resistance to beta-lactams has expanded to include production of an altered penicillin binding protein (PBP3) [14]. This type of resistance cannot be overcome by a beta-lactamase inhibitor, so amoxicillin-clavulinate and similar antibiotics will be ineffective. The frequency of non-beta-lactamase resistance in *H. influenzae* has increased. In a retrospective study that evaluated 465 *H. influenzae* isolates from the blood or cerebrospinal fluid from patients in Sweden between 1997 and 2010, a significant increase in beta-lactam–resistant isolates was observed over the course of the study period. Ninety-one isolates (20%) were resistant to one or more beta-lactam antibiotics (including penicillin, ampicillin, a cephalosporin, or a carbapenem), and nearly half of the resistant bacteria were beta-lactamase-negative [15].

Beta-lactamase–negative, ampicillin-resistant *H. influenzae* strains are being recovered in greater frequency worldwide. The prevalence of such strains has increased in Japan (by 34%) [16], Spain (by 56%) [17], and in other parts of Europe and Canada [18]. Prevalence in the U.S. has remained low (3%) [19]. Possible explanations for this discrepancy include inadequate vaccination against *H. influenzae* type b in some regions, increased use of cephalosporins, and underdosing of ampicillin [16, 17]. These types of ampicillin-resistant, beta-lactamase-negative *H. influenzae* strains are still susceptible to ceftriaxone [20], which may be a good choice for treatment of clinical infections due to these organisms.

Moraxella catarrhalis

Over 90% of *M. catarrhalis* produce a beta-lactamase and are therefore resistant to ampicillin. Nearly all strains express beta-lactamase from a chromosomal locus. Three types of beta-lactamases, BRO-1, BRO-2, and BRO-3, that are inducible and intracellular were identified and characterized [21]. *Moraxella catarrhalis* acquired beta-lactamase in the 1970s and the 1980s, and its antimicrobial susceptibility has remained relatively stable. However, recent macrolide and tetracycline-resistant strains were recovered from the Asia Pacific region and China [22].

The oral antibiotics that are active against *M. catarrhalis* as well as *H. influenzae* are amoxicillin-clavulanate, fluoroquinolones, extended-spectrum cephalosporins, newer macrolides, trimethoprim-sulfamethoxazole (TMP-SMX), and tetracyclines. Parenteral antimicrobials effective against these organisms include second and third-generation cephalosporins, aminoglycocides, ticarcillin, and piperacillin. The *M. catarrhalis* strains are resistant to penicillin, ampicillin, and clindamycin [23].

Streptococcus pneumoniae

Resistance of pneumococci to many antimicrobials has increased in the past two decades [23]. Pneumococcal resistance has increased to beta-lactams (penicillins, cephalosporins, and carbapenems), macrolides (erythromycin, azithromycin, clarithromycin), lincosamides (clindamycin), tetracyclines, folate inhibitors (TMP-SMX), and fluoroquinolones (ciprofloxacin, levofloxacin, gemifloxacin, and moxifloxacin). Most

strains of penicillin-resistant *S. pneumoniae* are also resistant to other antimicrobials. Resistance to antimicrobials is determined genetically. The resistance to beta-lactam antimicrobials is through changes in penicillin binding proteins, to chloramphenicol through inactivating enzymes, and to fluoroquinolones through decreased drug permeability [24]. Macrolide resistance is due to efflux pump, and binding blockage. The latter mechanism also blocks clindamycin. There is no resistance to vancomycin or linezolid. Although vancomycin resistance is not known in *S. pneumoniae*, the phenomenon of vancomycin tolerance has been observed in a few strains [25]. Risk factors for the acquisition of antibiotic-resistant pneumococcal strains include recent antibiotic use; previous time spent in daycare (for children), in an institutional setting, or a shelter for the homeless (for adults); and recent respiratory infections [26–28].

The affinity of beta-lactams for one or more of the penicillin binding proteins is lowered in pneumococcal strains that have reduced susceptibility to penicillins [29]. Decreased susceptibility of pneumococci to beta-lactams can frequently be overcome with higher doses of penicillins, cephalosporins, and carbapenems. Whether in-vitro resistance to macrolides [30] or the fluoroquinolones [31] can be overcome by increased doses is controversial. Resistance to folate inhibitors or tetracyclines cannot be overcome by increasing the antibiotic dose [32]. Non-susceptible isolates are divided into intermediate and resistant strains. The penicillin breakpoints for non-meningitis pneumococcal infections are: susceptible minimum inhibitory concentration (MIC) ≤2 mcg/mL, intermediate (MIC = 4 mcg/mL), and resistant (MIC ≥8 mcg/mL) [33]. For meningitis, the penicillin breakpoints are much lower and there is no intermediate category: susceptible MIC ≤ 0.06 mcg/mL, resistant MIC ≥ 0.12 mcg/mL.

There has been a recent decrease in penicillin-resistant pneumococcal strains. This is probably due to both the change in definition of resistance and the widespread use of pneumococcal conjugate vaccine, which has greatly reduced the prevalence of resistant strains in the population. Among isolates obtained in the U.S. from normally sterile sites such as blood culture, pleural fluid, and cerebrospinal fluid (CSF), 95.5% were found to be susceptible, 2.5% intermediate, and 2.2% resistant [34].

Staphylococcus aureus

Staphylococcus aureus can resist beta-lactam antimicrobials through the production of beta-lactamase. It can also resist methicillin which is defined as an oxacillin MIC ≥ 4 mcg/mL Isolates resistant to oxacillin or methicillin also resist all beta-lactam agents, including cephalosporins (with the exception of the fifth-generation cephalosporins, ceftobiprole and ceftaroline).

The prevalence of infection and colonization with MRSA is increasing [35] in all infections including head and neck. A 16.3% increase in the rate of pediatric *S. aureus* head and neck infections occurred between 2001 and 2006 in a study of 21,009 patients [36]. The highest rate of MRSA infections was in otological (34%), followed by sinonasal (28.3%), and oropharynx/neck (14.2%) infections. The association between previous antimicrobial use and increased isolation of MRSA was noticed in various infections [37, 38], including sinusitis [39, 40]. Brook et al. [39] and Gerencer [40] found that most patients with chronic sinusitis due to MRSA, who were previously treated with antimicrobials, had been treated with either a fluoroquinolone or macrolides.

Methicillin resistance is mediated by the mecA gene that encodes for low-affinity penicillin binding protein, PBP2a. This gene is located on a mobile genetic element called staphylococcal cassette chromosome (SCCmec). Most MRSA strains isolated during the 1960s originated most likely from a single clone; by 2002, five major MRSA clones emerged throughout the globe [41].

Oral Antibiotics Active Against MRSA. Oral antibiotics that can be used for the treatment of MRSA infections include clindamycin, TMX-SMT, tetracyclines (such as doxycycline or minocycline), and linezolid. Because resistance to these agents is rising, their use should be supported by susceptibility testing whenever

possible and by clinical response. Clindamycin inhibits bacterial production of toxins, including Panton-Valentine leukocidin and other virulence factors, and has excellent tissue, bone, and abscess penetration [42]. The agent should not be administered empirically when local MRSA resistance rates to clindamycin are >15% [43]. Clindamycin-susceptible isolates that are resistant to erythromycin may become resistant to clindamycin in its presence [44]. Inducible clindamycin resistance can be detected with D testing in the microbiology laboratory [45]. Trimethoprim-sulfamethoxazole and tetracyclines are not advisable for empiric management of infections that may be due to group A streptococci. Resistance of MRSA to fluoroquinolones may emerge during therapy [46]. Oxazolidinones (linezolid or tedizolid) are effective for the treatment of MRSA-related head and neck infections [47]. Their use is limited by cost and toxicity.

Parenteral Agents Active Against MRSA. Parental agents for treating MRSA infections include vancomycin, daptomycin, linezolid, ceftaroline, telavancin, dalbavancin, oritavancin, tedizolid, tigecycline, teicoplanin, and quinupristin-dalfopristin. Some of these are limited by toxicity concerns, as discussed in Chap. 1. The greatest cumulative clinical experience for the treatment of MRSA infections is with the glycopeptide vancomycin. It is still an important agent for treating these infections despite the overall decrease in the in-vitro susceptibility. Its tissue penetration is variable and increases with inflammation. Daptomycin, a cyclic lipopeptide, is inhibited by pulmonary surfactant and should not be used for the treatment of MRSA pneumonia [48]. Previous exposure to vancomycin can increase resistance to daptomycin [49]. Linezolid, a synthetic oxazolidinone, has excellent tissue distribution, and inhibits toxin production [50]. Linezolid resistance has emerged among MRSA isolates, mostly in healthcare associated strains. The mechanism of resistance is via the bacterial cfr gene located in a potentially mobile genetic element [51]. Linezolid use is limited because of safety concerns, including thrombocytopenia, anemia, lactic acidosis, peripheral neuropathy, serotonin toxicity, and ocular toxicity (rare cases of optic neuropathy with treatment beyond 2 weeks).

Ceftaroline, a fifth-generation cephalosporin, is active against Gram-positive organisms (including MRSA, vancomycin-intermediate *S. aureus*) as well as Gram-negative pathogens (including *Enterobacteriaceae* but not *Pseudomonas* species or extended-spectrum beta-lactamase producers) [52]. Telavancin, a semisynthetic lipoglycopeptide, has a half-life of 7–9 h, allowing once-daily dosing. Oritavancin, a semisynthetic glycopeptide, has a half-life of 100 h. Dalbavancin, a semisynthetic lipoglycopeptide, has a half-life of 6–12 days, permitting once-weekly dosing. Teicoplanin, a glycopeptide, can be administered once daily. Quinupristin-dalfopristin, a streptogramin, use is limited by adverse effects (e.g., hyperbilirubinemia, myalgias, arthralgias, and nausea). Tigecycline, a glycylcycline, is active in-vitro against many Gram-positive cocci (including MRSA, vancomycin-resistant enterococci, and penicillin-resistant *S. pneumoniae*), aerobic and facultative Gram-negative bacilli (except *Pseudomonas* and *Proteus* spp.), anaerobes, and atypical bacteria. However, the U.S. Food and Drug Administration (FDA) issued "boxed warnings" in 2011 and 2013 because of increased risk of death in patients treated with tigecycline compared with other antibiotics.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is commonly found in chronic otitis media and external otitis [53, 54]. *Pseudomonas* possesses intrinsic resistance to several antimicrobials and can attain resistance during therapy. Some strains are highly drug-resistant, resisting three or more classes of antibiotics [55]. Only a small number of antimicrobials possess reliable efficacy against *P. aeruginosa*. These include some penicillins (ticarcillin-clavulanate, piperacillin-tazobactam), cephalosporins (ceftazidime, cefepime, cefoperazone), monobactams (aztreonam), fluoroquinolones (ciprofloxacin, levofloxacin), carbapemens (imipenem, meropenem, doripenem), aminoglycosides (gentamicin, tobramycin, amikacin), and

polymixins (colistin, polymyxin B). All of these antimicrobials are administered parentally except for the fluoroquinolones that can be given also orally [56]. Monobactams require higher dosing. Aminoglycosides are generally not used as single agents because of inadequate clinical efficacy. Polymixins are administered only in the setting of resistance to other antimicrobials because of their toxicity. A combination of anti-*Pseudomonas* antimicrobials can be administered for serious infections due to *P. aeruginosa* [57].

Anaerobic Bacteria

Anaerobic bacteria predominate in the oropharyngeal mucous membranes, and are therefore a common cause of bacterial infections of endogenous origin of upper respiratory tract and head and neck [5, 6]. These infections include chronic otitis media, mastoiditis and sinusitis, pharyngotonsillitis, peritonsillar, retropharyngeal and parapharyngeal abscesses, suppurative thyroiditis, cervical lymphadenitis, parotitis, siliadenitis, and deep neck infections including Lemierre's Syndrome. The recovery from these infections depends on prompt and proper medical and when indicated also surgical management. Because anaerobes generally are isolated mixed with aerobic bacteria, the antimicrobial(s) used should cover these organisms.

The most effective antimicrobials against anaerobic organisms are: metronidazole, the carbapenems (imipenem, meropenem, dorapenem, ertapenem), chloramphenicol, the combinations of a penicillin and a beta-lactamase inhibitor (e.g., amoxicillin plus clavulinate, ampicillin plus sulbactam, ticarcillin plus clavulanate, piperacillin plus tazobactam), tigecycline, cefoxitin and clindamycin. Table 2.3 lists the susceptibility of various anaerobes to antimicrobial agents.

Beta-Lactams and Anaerobes

Penicillins. Penicillin is used when the infecting strains are susceptible. Most *Clostridium* strains and *Peptostreptococcus* spp. are susceptible to penicillin. *Bacillus fragilis* group anaerobes are resistant to penicillin. Other strains that may show penicillin resistance are growing numbers of anaerobic Gram-negative bacilli commonly found in head and neck infections (e.g., pigmented *Prevotella* and *Porphyromonas* spp.,

Table 2.3 Susceptibility of common anaerobes to various antibiotics (includes intermediate resistant strains) [58, 74, 80, 108]

Anaerobe	Ampicillin-sulbactam (%)	Amoxicililin-clavulinate (%)	Piperacillin-tazobactam (%)	Clindamycin (%)	Moxifloxacin (%)	Imipenem (%)
Anaerobic Gram-positive cocci[a]	100	94–100	97–100	73–95	64–97	100
Clostridium species	100	95–100	100	75–84	47–93	85
Fusobacterium species		89–100	100	69–82	75–90	96
Prevotella species	100	81–100	≥99	67–87	58–89	94–100
Bacteroides fragilis[b]	89–97	63–96	95–100	58–90	59–90	93–99.7
Bacteroides thetaiotaomicron[b]	85–95	63–88	88–100	40–60	25–87	93–100
Bacteroides fragilis group[b]		80–90	92–100	48–68	43–86	≥99

Susceptibility breakpoints (MIC μg/ml), *S* = susceptible, *R* = resistant: ampicillin-sulbactam ($S \leq 8/4$, $R \geq 32/16$); amoxicillin-clavulinate ($S \leq 4/2$, $R \geq 16/8$); piperacillin-tazobactam ($S \leq 32/4$, $R \geq 128/4$); clindamycin ($S \leq 2$, $R \geq 8$); moxifloxacin ($S \leq 2$, $R \geq 8$), imipenem ($S \leq 4$, $R \geq 16$)

Metronidazole is not listed but >99% of anaerobic Gram-negative bacilli are susceptible

[a]Includes *Peptostreptococcus* species and others

[b]These comprise the majority of *Bacteroides* isolates found in infections above the neck [108]

Prevotella oralis, *Prevotella bivia*), *Bacteroides disiens*, strains of clostridia, *Fusobacterium* spp. (*Fusobacterium varium* and *Fusobacterium mortiferum*), and microaerophilic streptococci. Some of these strains show MIC of 8–32 units/mL of penicillin G. In these instances, administration of very high dosages of penicillin G (for non-beta-lactamase producers) may be effective [58]. Ampicillin and amoxicillin have activity equal to penicillin G, but nafcillin or oxacillin are either not active or have unpredictable activity [59]. Penicillin and ampicillin/amoxicillin are of limited utility because of the production of beta-lactamases by many oral anaerobes [59–61], but beta-lactam/beta-lactamase inhibitor combinations are effective. Carboxy-penicillins (carbenicillin, ticarcillin) and ureidopencillins (piperacillin, azlocillin, mezlocillin) generally are administered in large quantities to achieve high serum concentrations [62].

Cephalosporins. Cephalosporins have limited utility because many anaerobes produce cephalosporinases [63]. The activity of cephalosporins against the beta-lactamase-producing anaerobic Gram-negative bacilli varies. The antimicrobial spectrum of the first-generation cephalosporins against anaerobes is similar to penicillin G, although on a weight basis, they are less active. Most strains of the *B. fragilis* group and many *Prevotella*, *Porphyromonas*, and *Fusobacterium* spp. are resistant to these agents [64]. Cephalosporinases have little or no hydrolytic activity for the second-generation cefoxitin (a cephamycin), making it the most effective cephalosporin against the *B. fragilis* group. However, susceptibility to cefoxitin may vary by geographic location and is generally directly related to its clinical use. Cefoxitin is relatively inactive against most species of *Clostridium*, including *Clostridium difficile*, with the exception of *Clostridium perfringens* [64–66]. With the exception of moxalactam (not available in the U.S.), the third-generation cephalosporins are not as active against *B. fragilis* group.

Carbapenems. The carbapenems (imipenem, meropenem, ertapenem, doripenem) have excellent activity against anaerobes [67]. Imipenem is effective against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms including *B. fragilis* group [68, 69] It is also effective against most *Enterobacteriaceae* and about 5–15% of *Pseudomonas* spp. are resistant [70]. To overcome the problem of renal metabolism of imipenem, it is combined at a 1:1 ratio with an inhibitor of the renal dipeptidase, cilastatin. Imipenem is an effective single agent for the therapy of mixed aerobic-anaerobic infections. Meropenem possesses antibacterial activity similar to imipenem. However, it is less active against staphylococci and enterococci, and provides better coverage of aerobic and facultative Gram-negative bacteria [71, 72]. Ertapenem also has a broad antibacterial spectrum [73] but it is not active against *Pseudomonas*, *Enterococcus* spp., and *Acinetobacter* spp. Doripenem has a similar antimicrobial spectrum to meropenem and imipenem [69]. Resistant *P. aeruginosa* mutants appear to be harder to select in vitro with doripenem than with other carbapenems. Doripenem is not FDA-approved to treat pneumonia. Recent reports have noted the emergence of some carbapenem resistance among anaerobes [74] ranging from 1.1% to 2.5% in a multicenter U.S. survey. Higher resistance was noted in a small number of isolates from Taiwan [75].

Resistance of Anaerobes to Beta-Lactam Antibiotics. Anaerobes exhibit three major resistance mechanisms to beta-lactam antibiotics: inactivating enzymes, mainly beta-lactamases, which include penicilliniases and cephalosporinases; low affinity penicillin binding proteins (PBPs); and decreased permeability through alterations in the porin channel [76]. The production of beta-lactamases is the commonest mechanism, especially among the *B. fragilis* group and *Prevotella* spp. [77]. The cephalosporinases are most often of the 2e class type and can be inhibited by three beta-lactamase inhibitors, clavulanic acid, sulbactam, and tazobactam. Each individual cephalosporin may have either a class or specific inhibitor enzyme capable of inactivating it. Carbapenemases are active against the carbapenems as well as all beta-lactam antibiotics.

Carbapenem resistance was found in <1% of U.S. isolates, and up to 3% of *Bacteroides* strains harbor one of the genes that is expressed at a very low level.

With some exceptions among some *Clostridium* spp., strains of *Clostridium*, *Porphyromonas*, and *Fusobacterium* can express resistance through one or more beta-lactamases. Beta-lactamase-producing *Fusobacterium* and *Clostridium* spp. express enzymes that are usually inhibited by clavulanic acid [78]. Resistance to beta-lactam antibiotics through changes in the outer membrane porin channels, decreased PBP affinity, and efflux pumps [79] have not been well studied. *Bacteroides fragilis* group species are generally resistant to penicillins (average 90%), and less often to piperacillin (25%) cefoxitin (25%), cefotetan (30–85%), and third-generation cephalosporins (14–57%) [80, 81].

Beta-lactam/beta-lactamase inhibitor antibiotics and carbapenems have maintained their excellent antibacterial activity against anaerobes, including against members of the *B. fragilis* group [80]. However, species-to-species variation in susceptibility occurs [40]. *Bacteroides fragilis* group resistance rates for piperacillin-tazobactam are generally <1% [82], although one member of the group (*Parabacteroides distasonis*) has relatively high (20%) resistance. The carbapenems are very effective against all the members of the *B. fragilis* group, and resistance is <0.1% [79, 82, 83]. Some members of the *B. fragilis* group have lower MICs for imipenem and meropenem than for ertapenem [80]. Half of *Prevotella* spp. may produce beta-lactamases, causing penicillin resistance, and a multicenter survey [68] also detected penicillin resistance in *Fusobacterium* spp. (9%), *Porphyromonas* spp. (21%), and *Peptostreptococcus* spp. (6%). No resistance was found to cefoxitin, cefotetan, beta-lactam/beta-lactamase combinations, and carbapenems in that survey, with the exception of *Peptostreptococcus* spp. (4%) and *Porphyromonas* spp. (5%). Beta-lactamases were identified in several *Prevotella* and *Porphyromonas* spp. recovered from pediatric intra-abdominal infections [62].

Chloramphenicol and Anaerobes

Chloramphenicol, a bacteriostatic agent, is active against most anaerobic bacteria but is rarely used in the U.S. [6] due to potentially significant toxicity. The risk of fatal aplastic anemia with chloramphenicol is approximately one per 25,000–40,000 patients treated. This complication is unrelated to the reversible, dosage-dependent leukopenia. Other side effects include the production of the potentially fatal "gray baby syndrome" when given to neonates, hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and optic neuritis in those who take the agent for a prolonged time. Chloramphenicol has a unique property of lipid solubility that permits penetration across lipid barriers. Levels in the cerebrospinal fluid (CSF), with or without meningitis, usually are one-third to three-fourths the serum concentrations. Levels in brain tissue can be substantially higher than serum levels [83].

Macrolides (Erythromycin, Azithromycin, Clarithromycin) and Anaerobes

The macrolides have moderate to good in vitro activity against anaerobic bacteria other than *B. fragilis* group and fusobacteria [58, 64]. They are active against microaerophilic streptococci, Gram-positive non-spore-forming anaerobic bacilli, and certain clostridia. They are less effective against *Peptostreptococcus* spp. [84]. Macrolides have relatively good activity against *C. perfringens* and poor or inconsistent activity against anaerobic Gram-negative bacilli. Clarithromycin is the most active of the macrolides against Gram-positive oral cavity anaerobes, including *Actinomyces* spp., *Propionibacterium* spp., *Lactobacillus* spp., and *Bifidobacterium dentium*. Azithromycin is slightly less active than erythromycin against these species [84]. Azithromycin is the most active macrolide against *Aggragatibacter actinomycetemcomitans*, including those isolates

resistant to erythromycin. Clarithromycin possess similar activity to erythromycin against most anaerobic Gram-negative bacilli [85]. Emergence of erythromycin-resistant organisms during therapy has been documented [86, 87].

Clindamycin and Anaerobes

Clindamycin has a broad activity against anaerobes, is well absorbed from the gastrointestinal tract [88–90], and rapidly penetrates into most body tissues and fluids [52] although not the central nervous system (CNS). Clindamycin should not be administered in CNS infections. The side effect of most concern is *C. difficile* associated colitis [91]. Because *B. fragilis* resistance to clindamycin is increasing worldwide (over 33%) it is no longer recommended as empiric therapy for intra-abdominal infections [65, 74, 80, 92]. Resistance to clindamycin has also increased for other anaerobes. Up to 10% resistance was noted for *Prevotella*, *Fusobacterium*, *Porphyromonas*, and *Peptostreptococcus* spp., with higher rates for some *Clostridium* spp. (especially *C. difficile*) [68]. Clindamycin has lost some of its activity against anaerobic Gram-positive cocci (i.e., *Finegoldia magna*-30% resistant), and *Prevotella* spp. (*P. bivia*, 70% resistant, *P. oralis* and *Prevotella melaninogenica* both 40% resistant), although its activity against *Fusobacterium* and *Porphyromonas* spp. remains good. Among the other resistant anaerobes are various species of clostridia especially *C. difficile*. About 20% of *Clostridium ramosum* are resistant to clindamycin, as are a smaller number of *C. perfringens*.

Metronidazole and Anaerobes

Metronidazole and tinidazole are nitroimidazoles with similar in vitro activity against anaerobic bacteria. Metronidazole has excellent in vitro efficacy against most obligate anaerobic bacteria, such as *B. fragilis* group, other species of *Bacteroides*, fusobacteria (including *F. necrophorum*, the etiology of Lemierre's Syndrome), other anaerobic Gram-negative bacilli, and clostridia [93]. These agents have excellent penetration into the CNS. Resistance to metronidazole among *B. fragilis* group is uncommon [65, 94]. Resistance of anaerobic Gram-positive cocci is rare and resistance of nonsporulating bacilli is common. Most microaerophilic streptococci, *P. acnes*, and *Actinomyces* spp. are resistant [94]. Aerobic and facultative anaerobes are usually highly resistant. Because of its lack of activity against aerobic bacteria, an antimicrobial effective against these organisms (e.g., a cephalosporin, a fluoroquinolone) needs to be added when treating a polymicrobial infection. Adverse reactions to metronidazole include gastrointestinal side effects, central nervous system toxicity, and peripheral neuropathy. Possible mutagenic activity found in mice given large doses of metronidazole [95] was not confirmed by experiments in rats and hamsters [96], and no evidence of mutagenicity was ever found in humans [97].

Tetracyclines and Anaerobes

The tetracycline analogues, doxycycline and minocycline, are more active than the parent compound [58]. However, because of the significant resistance to these drugs, they are useful only when susceptibility tests show efficacy or in less severe infections in which a therapeutic trial is feasible. The use of tetracyclines is not recommended before 8 years of age because of the adverse effect on teeth; tetracyclines are also contraindicated in pregnancy. Tigecycline is a direct analog of minocycline with broad-spectrum activity including anaerobes and some drug-resistant pathogens [98, 99]. Resistance of members of the *B. fragilis* group varies from 3.3% to 7.2% [100]. As noted above, tigecycline carries an FDA boxed warning about increased mortality rates compared with other treatments for various infections.

Fluoroquinolones and Anaerobes

Of the systemic quinolones available in the U.S. (ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, gemifloxacin), moxifloxacin is the most effective against anaerobes [101]. Quinolones

with the greatest in vitro activity against anaerobes include clinafloxacin and sitafloxacin [102], but these are not available in the U.S. Quinolones' use is restricted in growing children because of possible adverse effects on the cartilage. In addition, in July 2016, the FDA issued a boxed warning on the use of quinolones for less serious infections, such as acute bacterial sinusitis, due to concern for serious and potentially irreversible side effects on "tendons, muscles, joints, nerves, and the central nervous system" [103]. Increasing resistance to quinolones in *B. fragilis* group as well as anaerobic Gram-positive cocci has been reported. *Bacteroides* spp. resistance to fluoroquinolone has been attributed to either an alteration in efflux of the antibiotic or a mutation in gyrase A gene (gyrA) [104]; high-level resistance can be caused by both the mechanisms.

Other Agents Active Against Anaerobes

Bacitracin is active in vitro against pigmented *Prevotella* and *Porphyromonas* spp. but is inactive against *B. fragilis* and *Fusobacterium nucleatum* [58]. Vancomycin and daptomycin are effective against all Gram-positive anaerobes, but are not active against anaerobic Gram-negative bacilli [105]. Quinupristin/dalfopristin exhibits antibacterial activity against *C. perfringens*, *Lactobacillus* spp., and *Peptostreptococcus* spp. [106]. Linezolid is effective against *Fusobacterium* spp. (including *Fusobacterium nucleatum*) and *Porphyromonas*, *Prevotella*, and *Peptostreptococcus* spp. [84, 85]. However, there is little clinical experience in the treatment of anaerobic infections using these agents.

Treating Infections in Otolaryngology

Infections in otolaryngology are often polymicrobial, so antimicrobials effective against both the aerobic and anaerobic components of the infection should be administrated. When such therapy is not given, the infection may persist, and serious complications may occur [5, 6, 107]. A number of factors should be considered when choosing appropriate antimicrobial agents: They should be effective against all target organism(s), induce little or no resistance, achieve sufficient levels in the infected site, cause minimal toxicity, and possess maximum stability and longevity.

When selecting antimicrobials for the therapy of mixed infections, their aerobic and anaerobic antibacterial spectrum and their availability in oral or parenteral form should be considered (Table 2.1). Selection of antimicrobial agents is simplified when a reliable culture result is available. However, this may be particularly difficult in anaerobic infections because of the difficulties in obtaining appropriate specimens. For this reason, many patients are treated empirically based on suspected, rather than established pathogens. Fortunately, the types of anaerobes involved in many infections and their antimicrobial susceptibility patterns tend to be predictable [6, 7]. However, some anaerobes have become resistant to antimicrobials, and many can develop resistance while a patient is receiving treatment [91]. Resistance among some anaerobes has increased significantly over the past three decades. The potential for growing resistance of anaerobes to antimicrobials is especially noted with penicillins, cephalosporins, clindamycin, and fluoroquinolones.

Aside from susceptibility patterns, other factors influencing the choice of antimicrobial therapy include the pharmacologic characteristics of the various drugs, their toxicity, their effect on the normal flora, and bactericidal activity [2, 3]. Although identification of the infecting organisms and their antimicrobial susceptibility may be needed for the selection of optimal therapy, the clinical setting and Gram stain preparation of the specimen may suggest the types of bacteria present in the infection as well as the nature of the infectious process.

Conclusion

Many microbes naturally produce antibiotics and are resistant to the antibiotics they produce. Antibiotic resistant microbes have been present in the environment for millennia. However, the

discovery of antibiotics in the twentieth century has led to increasing antibiotic resistance in clinically important microbes. Antibiotics must be chosen carefully and used wisely to prevent further selection and widespread dissemination of multidrug-resistant pathogens.

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The Role of Biofilms in Upper Respiratory Tract Infections

3

Sara Torretta and Lorenzo Pignataro

Introduction

Bacterial biofilms represent one of the life models of bacteria, and the majority of bacteria may live in biofilms. A large proportion of all human bacterial infections involve biofilms [1]. Although fungi can also live in biofilms, in this chapter we will use the term "biofilm" to refer to bacterial biofilms [2].

Biofilms are dynamic communities of slowly replicating and metabolically quiescent aggregated cells embedded in a three-dimensional extracellular polymeric substance (EPS) rich in exopolysaccharides, proteins, and nucleic acids [3]. The functionally heterogeneous bacterial micro-colonies have different phenotypes in terms of virulence, antibiotic resistance, and molecular signalling [4], and can also communicate with each other at a certain distance by secreting chemical signals that are useful in coordinating their behavioral and phenotypical adaptation to particular environmental conditions [5]. This "quorum sensing" is involved in EPS production, bacterial replication, and the acquisition of adaptive mutations by means of genetic material exchange as a result of horizontal plasmid-related DNA transfer.

The individual bacterial strains within a biofilm are separated from each other by water channels through which nutrients are exchanged and waste is discharged. Biofilms are arranged in discrete layers and the presence of an anoxic and acidic gradient leads to metabolically active strains being positioned in the active outer coatings exposed to oxygen and nutrients, whereas quiescent bacteria are positioned in the deeper anaerobic core [6]. The deeper biofilm layers are relatively protected from the action of antibiotics and antimicrobial compounds because of their reduced metabolism, limited penetration and tolerance, and are sheltered from humoral and cellular immunity [7, 8] (Fig. 3.1).

Biofilms can develop on organic or inorganic surfaces, including dead or living tissue, bone sequestra, and medical devices [9], and can propagate into the surrounding mucous layer as de novo biofilm foci or detached emboli from adjacent sites [10]. It has been reported that host and environmental factors such as impaired upper airway mucociliary clearance, or the secretion of antimicrobial molecules and toll-like receptors may predispose to biofilm formation [11]. However, as biofilm-related infections are due to a dynamic interplay between the host and the pathogens within biofilms, and opportunistic biofilms may also be found in healthy subjects, it has been speculated that biofilm formation may be

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_3

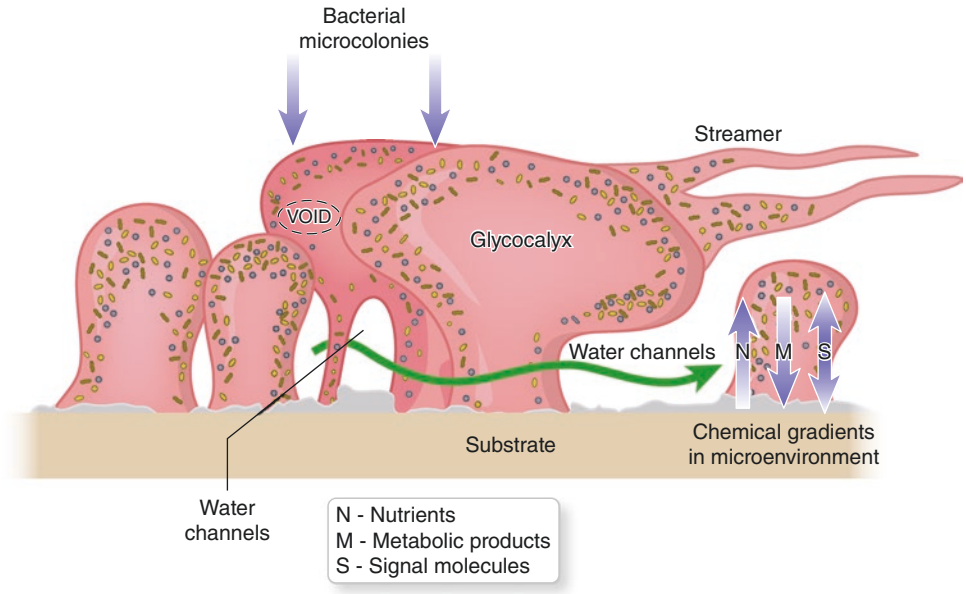

Fig. 3.1 Structure of a mature bacterial biofilm. Based on a figure from Kanaparthy A, Kanaparthy R. Biofilms -- the unforgiving films in dentistry (clinical endodontic biofilms). Dentistry 2012;2:145

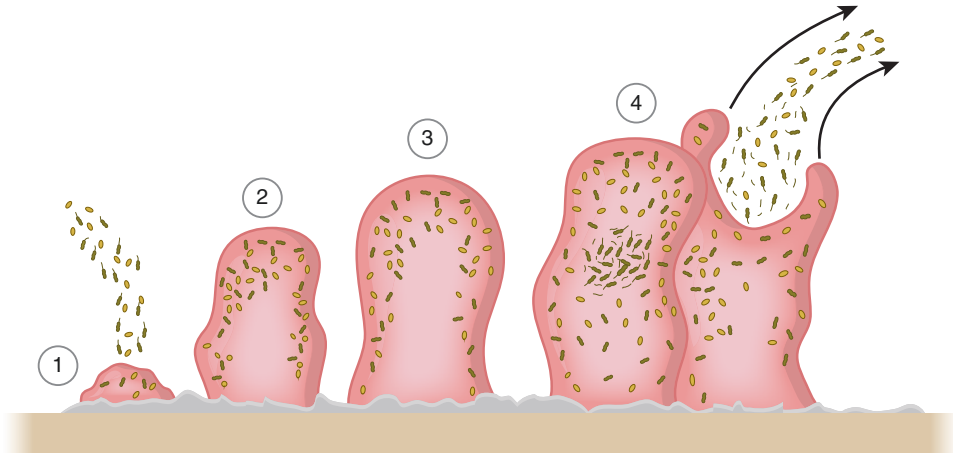

Fig. 3.2 Phases of bacterial biofilm development: (1) early and reversible adhesion of free-floating bacteria; (2) late and irreversible adhesion with production of extracellular polymeric substance; (3) maturation; (4) and periodic spreading of planktonic strains

related to persistent bacterial colonization rather than being an independent virulence factor [10].

The development of biofilms is a multi-step process involving [5] (Fig. 3.2):

1. The early and reversible adhesion of planktonic (free-floating) bacteria to a host surface;
2. Late and irreversible bacterial attachment by means of fimbrial and non-fimbrial adhesins, bacterial aggregation into microcolonies, and EPS production;
3. Biofilm growth and progressive maturation into an organized structure;
4. The periodic spreading of planktonic strains that can rapidly multiply and disperse, thus leading to acute exacerbations, colonization, and the self-renewal of infection in neighboring sites.

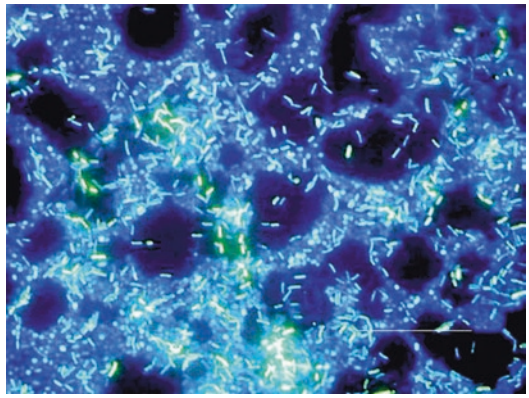

Fig. 3.3 Polymicrobic biofilm on a stainless steel surface examined by epifluorescence microscopy. From Donlan RM. Microbial life on surfaces. Emerging Infectious Diseases 2002; 8:881–890, with permission

These phases are coordinated by the production of *N*-acylated homoserine lactones, which are small diffusible signaling molecules released by biofilm bacteria into their local environment and that activate a quorum-sensing mechanism in a concentration-dependent manner [5].

Given their decreased metabolic rate (especially at the core) and complex 3-dimensional appearance, biofilms are difficult to study by means of traditional staining and culture techniques [12] (Fig. 3.3). More detailed insights into their ultrastructure and environment can be obtained by means of confocal laser scanning microscopy or scanning electron microscopy [13], possibly combined with fluorescent in situ hybridization (FISH) to detect the bacterial strain [14]. Simpler and less expensive spectrophotometry has also been used to quantify biofilm formation by assessing the optical density of stained biofilm-producing bacteria adhering to smooth culture plates [15].

According to Parsek and Singh's criteria [16], biofilm-related infections are conventionally defined by the presence of:

1. An association of pathogens with a surface;
2. Clustered microbial cells (microcolonies) within a matrix;
3. Localized infections;
4. Recalcitrance to antibiotic treatment despite the documented susceptibility of planktonic strains to the same compound.

Bacteria in biofilms may be difficult to culture by the traditional culture technique, which may lead to falsely negative cultures in some chronic infections. Host clearance of biofilms is often sustained but ineffective, as suggested by the presence of bacterial macrocolonies associated with inflammatory host cells.

Bacteria in biofilms show marked resistance to antibiotic treatment and are 10–1000-fold less susceptible than the same bacteria grown in planktonic culture [5]. Because bacterial biofilms display this high degree of antibiotic resistance and can evade the immune system, their role in various upper respiratory tract infections raises important concerns. Biofilms may play a role in recurrent acute tonsillitis, chronic adenoiditis, acute and chronic middle ear diseases, and chronic rhinosinusitis [17], and we will discuss that role and possible therapeutic strategies.

Bacterial Biofilms and Upper Respiratory Tract Infections

Tonsillitis

The idea that biofilms are involved in the pathogenesis of is based on the fact that they have been found in the tonsillar specimens of patients with recurrent acute infections and chronic hypertrophy [18–21]. The reported prevalence of tonsillar biofilms in limited case series of patients ranges from 41% to 85% depending on the microbiological diagnostic procedures used, and seems to be higher in patients with recurrent acute tonsillitis (60–85%) [18–20] than in those with chronic tonsillar hypertrophy without recurrent infections (41%) [20].

Gram-positive organisms seem to predominate [18–20]. Similar to findings by Torretta et al. [21], Al-Mazrou and Al-Khattaf [20] found that *Staphylococcus* species were the most frequently isolated followed by *Streptococcus* species, whereas Galli et al. [19] reported the opposite. Stoodley et al. [22] have suggested that tonsillar calculi (tonsilloliths), which are often associated with chronic tonsillar inflammation [23], are actually living polymicrobial biofilms with a heterogeneous structure revealed by confocal microscopy.

A significant relationship between the presence of tonsillar biofilms and Brodsky's grade of tonsillar hypertrophy has been reported in children with recurrent acute tonsillitis [21]. Torretta et al. evaluated tonsillectomy specimens from 22 children with a history of recurrent acute tonsillitis and found biofilms in 50% [21]. There was no correlation between the presence of biofilms and gender, age, or number of acute tonsillitis episodes in the preceding year, but biofilms were fourfold more likely to be found on tonsils of children with grade 3 or 4 tonsillar hypertrophy versus grade 1 or 2. This relationship may be partly due to the fact that apparently nonpathogenic tonsillar biofilms can also be detected in previously uninfected children with obstructive hyperplastic tonsils [24] and in healthy patients [25]. Therefore, the probability of biofilm is greater in patients with large tonsils and recurrent infectious exacerbations. Bacterial adhesion, the first step in the development of biofilms, is enhanced in the case of mucosal impairment [26], and so it can be presumed that the larger the tonsillar surface, the greater the risk of bacterial adhesion to tonsillar crypts and subsequent biofilm production.

Tonsillar biofilms have been detected in healthy patients but appear to be present in a higher percentage of patients with recurrent tonsillitis. Woo et al. used scanning electron microscopy to compare tonsillar biopsy samples from 20 patients undergoing tonsillectomy for recurrent acute tonsillitis versus 20 control volunteers (patients undergoing laryngeal biopsies), and found biofilms in 80% of the acute tonsillitis group versus 45% of the control group, a significant difference [25]. Biofilms also appeared to involve more of the tonsillar surface in the tonsillitis group than in the control group. This may suggest that, although a small amount of bacteria in a biofilm can colonize the tonsillar epithelium without giving rise to infection, the presence of more developed tonsillar bacterial biofilm can lead to recurrent acute infections.

There may be a significant relationship between the presence of tonsillar biofilms and increased exhaled nitric oxide levels [27]. Nitric oxide is a highly reactive mediator naturally released by human airways that can be a marker of inflammation. Exhaled nitric oxide has been studied as a possible etiological factor in chronic tonsillar disease, with conflicting results [28, 29]. Kasperska-Zajac et al. found increased exhaled nitric oxide levels in adults with recurrent tonsillitis [28], but Torretta et al. found no increased levels comparing children with chronic adenotonsillitis versus adenotonsillar hypertrophy [29]. However, when 24 children scheduled for tonsillectomy were tested for exhaled nitric oxide levels, patients subsequently identified as having tonsillar biofilms had significantly higher mean nitric oxide levels than those without biofilms [27]. The association between biofilms and high exhaled nitric oxide levels is consistent with the hypothesis that nitric oxide-mediated intercellular signaling predisposes to biofilm formation, swarming, and dispersal [30, 31].

On the basis of these observations, some authors have tested the effectiveness of possible medical treatments against tonsillar biofilms [32, 33]. Bulut et al. [32] recently documented a significant reduction in biofilm thickness after the application of *N*-acetyl-cysteine and acetylsalicylic acid to tonsillar samples taken from ten patients undergoing tonsillectomy for recurrent acute infections, with the effect of acetylsalicylic acid being dose-related. Other studies have shown that in vitro hyaluronic acid (a ubiquitous component of many extra-cellular matrices) acts as an anti-adhesive and anti-biofilm molecule on Hep-2 cells exposed to bacterial species isolated from patients with upper respiratory tract infections [33].

However, given the paucity of published studies of biofilm formation on the tonsillar surface of patients with chronic tonsillar disease, there is still a lack of strong evidence concerning the involvement of tonsillar biofilms in the development of recurrent acute tonsillitis, particularly because biofilms have been found in 45% of healthy cases [25]. No definite conclusions can be drawn at the present time, and larger controlled studies are needed to determine the role of biofilms and anti-biofilm therapeutic strategies in chronic tonsillar disease.

Chronic Adenoiditis and Otitis Media

Biofilms are thought to be involved in the pathogenesis of chronic adenoiditis and chronic or recurrent middle ear disease insofar as the adenoids and surrounding nasopharynx seem to act as reservoirs of resistant polymicrobial biofilms (mainly produced by the otopathogens *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) that periodically release planktonic species, which are responsible for local infectious exacerbations and middle ear colonization through the Eustachian tube [34–39]. This hypothesis is supported by electron microscopy findings suggesting the presence of biofilms covering almost all of the mucosal surface of adenoids removed from children with recurrent acute otitis media (RAOM) [34, 35], and the reported detection of otopathogenic biofilms in middle ear samples of patients with recurrent middle ear infections [37]. Taken together, these findings suggest a good correspondence between nasopharyngeal and middle ear colonizing strains.

In particular, Zuliani et al. [40] showed that adenoidal biofilms were significantly more prevalent in children with a history of severe RAOM (four episodes in 6 months or six in 12 months) than in those with obstructive sleep apnea syndrome not associated with middle ear infections, and that an average of 93.5% of the mucosal surface of adenoids removed from patients with RAOM is covered by biofilms, compared with 1.0% of the surface area of adenoids removed from patients with obstructive sleep apnea syndrome.

Biofilms have also been found in patients with persistent otitis media with effusion (OME), which had been typically considered bacteriologically sterile because the pathogens cannot be detected by means of traditional cultural techniques. However, bacterial DNA has been detected by polymerase chain reaction (PCR) testing of the middle ear effusions of patients with OME [41], and the finding of middle ear bacterial mRNA suggests the presence of replicative bacteria [42]. The discovery of biofilms produced by otopathogens in the middle ear mucosa of patients with persistent OME is not surprising: biofilms have been found by means of scanning electron microscopy or confocal laser scanning microscopy in 40–92% of middle ear samples taken from children with OME [42, 43]. However, the association between adenoidal biofilms and persistent OME is questionable: some authors [39, 44] have found that the adenoid tissue of patients with persistent OME has greater biofilm formation than controls, but Hoa et al. [45] found nasopharyngeal surface biofilm involvement in only 28% of patients with persistent OME but in 99% of those with RAOM.

We have investigated whether there is a difference in the prevalence, strains, or biofilm production capacity of biofilm-producing bacteria in children with chronic adenoiditis associated with RAOM and/or persistent OME by taking adenoidal biopsies at the nasopharyngeal dome and near the pharyngeal ostium of the Eustachian tube [34]. Biofilms were significantly more frequent on the adenoidal surface near the ostium of the Eustachian tube than at the nasopharyngeal dome (72.2% vs. 53.3%) but, although *S. aureus* was more prevalent at the nasopharyngeal dome and *S. pneumoniae* and *M. catarrhalis* were more frequently detected near the Eustachian tube, the differences were not statistically significant. These findings indicate that hypertrophic adenoids (particularly when close to the ostium of the Eustachian tube) are reservoirs for the biofilms responsible for the periodic spread of bacterial strains and their colonization of the Eustachian tube and middle ear, thus suggesting that adenoids should be completely removed to ensure the total eradication of adenoidal biofilms.

We have also found that, in comparison with controls, nasopharyngeal biofilm-producing otopathogens are more prevalent in young children with RAOM but without adenoidal hypertrophy, which suggests that nasopharyngeal biofilms play a role per se in the pathogenesis of recurrent middle ear infections [35]. *Haemophilus influenzae* was the main pathogen involved in biofilm formation in the children with RAOM, thus confirming its role in recurrent middle ear infection [35].

Biofilms may also be involved in the development of chronic suppurative otitis media (CSOM) and chronic otitis media associated with cholesteatoma [37, 38, 42, 45–48], particularly biofilms produced by *Staphylococcus aureus* and *Pseudomonas aeruginosa* [37]. In particular, biofilms have been discovered in 43–92% of the samples taken from patients with CSOM [37, 46–48] and in 75–85% of the samples taken from patients with chronic otitis media associated with cholesteatoma [36, 46, 48].

Finally, the finding of biofilm formation by clinically non-typeable *H. influenzae* isolated from children with acute otitis media [49] led to the hypothesis that biofilms may be involved in acute middle ear infections. Bacteria require only a few minutes to start biofilm production when they are in a favorable environment [38], and this may account for a failure of acute otitis media to respond to antibiotics. However, this hypothesis has recently been questioned by Mizrahi et al. [50], who did not find any association between non-typeable *H. influenzae* biofilm formation in acute otitis media and treatment failure or disease recurrence.

These findings suggest that nasopharyngeal and middle ear biofilms produced by otopathogens may play a causative role in chronic adenoiditis, RAOM, and OME, and support a role for middle ear biofilms produced by *S. aureus* and *P. aeruginosa* in the development of CSOM and chronic otitis media associated with cholesteatoma.

Rhinosinusitis

Some authors postulate a relationship between polymicrobial biofilms and recurrent or recalcitrant chronic rhinosinusitis (CRS) with or without nasal polyps, but the results of various studies are conflicting [51–63]. Biofilms have been detected in 25–100% of samples taken from patients with CRS [51–56], although most studies have recorded biofilms in over 70% of CRS patients. Some authors have suggested that biofilms may be more prevalent among patients with nasal polyps (97%) than among those without (82%) [56]. The between-study difference in detection rates has been attributed to differences in the populations considered, the use of biopsy specimens of only a small part of the mucosal surface, and differences in microbiological diagnostic techniques [54].

The role of adenoids as reservoirs for biofilms has been demonstrated in pediatric patients with recalcitrant rhinosinusitis. Coticchia et al. [57, 58] found that about 95% of the mucosal surface of adenoids removed from children with CRS was covered with biofilms, compared with only about 2% of the surface of adenoids removed from children with obstructive sleep apnea syndrome.

On the other hand, the finding that a number of patients undergoing nasal surgery for diseases unrelated to chronic paranasal sinus inflammation have biofilms on the surface of healthy paranasal mucosa [59, 60] suggests the presence of commensal biofilms that can be considered a form of respiratory mucosal blanket [53, 61]. Dlugaszewska et al. [59] recently documented the presence of biofilm in 45% of control samples, and have therefore suggested that the role of biofilms in the etiology of CRS should be reconsidered.

Bacteria detected in cases of biofilm-related CRS have included *S. aureus*, *P. aeruginosa*, coagulase-negative staphylococci, *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*, and fungal species [62, 63]. Sanderson and colleagues used the FISH technique combined with confocal laser scanning microscopy and detected biofilms in 14 of 18 CRS patients but also two of three control patients [62]. Testing for four bacterial species (*H. influenzae*, *S. pneumoniae*, *S. aureus*, *Pseudomonas*) using FISH, they found that *H. influenzae* were the major pathogens present (78%), and that some of these *H. influenzae* biofilms also included other bacteria (*S. pneumoniae* or *S. aureus*). *Pseudomonas* was not detected in any case. Two of the three control biopsies also had *H. influenzae* biofilms. Of interest, routine intraoperative cultures were also obtained in this study and these did not correlate with the findings of the FISH assay, presumably because routine cultures detect planktonic bacteria but often not

those within a biofilm. Routine cultures were negative or grew only coagulase-negative staphylococci, a colonizer, in over three-quarters of biofilm cases: none grew *H. influenzae*. The role of fungal species has been recently assessed in patients with eosinophilic mucin CRS in whom fungal hypersensitivity seems to pave the way for an increased eosinophilic response [64]. Healy et al. used a pan-fungal and bacterial FISH probes and found that most of the patients with chronic sinus disease had a mixture of fungi and bacteria (primarily *H. influenzae*) in their biofilms, but there was a trend to more fungi in the biofilms of patients with eosinophilic mucin CRS and allergic fungal sinusitis than in CRS patients [64]. Boase et al. used an animal model (sheep) to investigate sinonasal fungal biofilms, and inoculated an occluded frontal sinus with fungi (*Aspergillus* or *Alternaria*), along with *S. aureus* in some cases [65]. Interestingly, fungal biofilms formed in 80% of sinuses that had been co-inoculated with *S. aureus*, but only 8% of sinuses inoculated with fungi alone. Moreover, the simultaneous finding of fungal species and *S. aureus* in biofilm-related CRS suggests that they may act synergistically in the development of CRS [65]. It is possible that a biofilm produced by *S. aureus* facilitates the attachment of fungal species within the EPS or that *S. aureus* impairs the sinus mucosa in such a way as to favor fungal adhesion and subsequent biofilm production. However, it is also possible that biofilms are just colonizers of the sinonassal mucosa, and not involved in the pathological process [64].

Interestingly, some authors have suggested that patients with biofilm-related CRS may have more severe disease [54, 66], with poorer symptomatic, clinical, and radiological outcomes [54–56, 67]. In particular, some studies have reported worse Lund-McKay radiological and Kennedy-Lund endoscopic scores in patients with biofilms [54, 66]. Li et al. [55] reported that sinonasal outcome test (SNOT 20) symptom scores and individual nasal symptoms negatively correlated with the presence of biofilms in patients with CRS.

Some studies have indicated a poorer response to traditional treatment in biofilm-related CRS than non-biofilm cases: biofilm-related CRS patients undergoing functional endoscopic sinus surgery had more postoperative recurrences and a greater need for surgical revision [63, 67]. Patients undergoing surgical revisions are more likely to have biofilms than those undergoing primary surgery, and there is a significant correlation between the presence of sinonasal biofilms and the number of previous surgical treatments [63]. This may be due to the persistence of an infectious sinus focus or combined chronic impairment and inflammation of the paranasal mucosa, as some studies have shown that sinus biofilms adhering to a disrupted respiratory epithelium evoke a greater immune response than planktonic bacteria colonizing the sinonasal epithelium [68]. Moreover, biofilms may be associated with an increased number of inflammatory (mainly eosinophil) cells and encourage the host's adaptive immunity to shift toward a Th2-helper state that predisposes to persistent inflammation [69].

Resistance

Biofilms are not only extremely resistant to host immune reaction and antibiotics, but also resistant to non-antibiotic chemical and physical treatments. It has been estimated that in upper respiratory tract infections, bacteria in biofilms are up to 100 times more tolerant of conventional antibiotic treatments than their corresponding planktonic strains [70–72].

Bacteria in biofilms evade antimicrobial challenges in various ways: the low replication rate of the metabolically quiescent bacteria inside the core, and the presence of a strong and continuously remodeled external barrier consisting of the EPS, which limits the penetration of antibiotics and inhibits the effect of immunoglobulins, superoxides, and opsonins [70–72]. Mathematical models have shown that mechanisms other than restricted diffusion (such as a catalytic reaction) are probably responsible for the reduced susceptibility of biofilms to antibiotics [73].

Although the EPS cannot completely prevent antibiotic penetration into biofilm, it may delay penetration sufficiently to allow the expression of

gene mutations determining the acquisition of resistance mechanisms such as efflux pump activation [8]. Furthermore, antibiotic tolerance may be due to its dilution given the many bacteria in a stationary phase [74].

It is well known that biofilms can evade immune action, as suggested by the resistance-to-phagocyte hypothesis [10] according to which leukocytes can penetrate channels but not bacterial cells, and their motility and phagocytic activity is reduced because of the limited oxidative potential within biofilms [75]. Furthermore, the spread of reactive oxygen species into biofilm is hampered by their fast deactivation in the outer layer of the biofilm, and the penetration of IgG is limited to the periphery by the EPS [76].

Therapeutic Strategies

As the resistance of biofilms to conventional doses of systemic antibiotics is increased, topical administration may be preferable as it leads to high drug concentrations at the target site, and reduces the risk of systemic side effects. It has been reported that a 1000-fold concentration of topical antibiotic would significantly reduce the viable bacteria belonging to the *S. aureus* biofilms isolated from patients with CRS undergoing surgery [77], and some studies have shown that mupirocin nasal irrigations (possibly combined with oral doxycycline or trimethoprim-sulfamethoxazole) have positive effects in terms of symptomatic relief in patients with acute CRS exacerbations due to methicillin-resistant *S. aureus* [78]. However, in vivo models have failed to find any significant effect of moxifloxacin, ciprofloxacin, and vancomycin on biofilm eradication [77, 79, 80], although strongly adherent biofilms have been found to be sensitive to locally administered high-dose ciprofloxacin, vancomycin, and imipenem [77].

Treatments aimed at interfering with bacterial adhesion include the use of receptor mimetics or vaccination-delivered immunological blocking [53]. Quorum sensing inhibitors (including sub-inhibitory concentrations of azithromycin, clarithromycin, furanone, and NVC-422) have been studied in in vitro and animal models [81, 82] with conflicting results. Tatar et al. [51] found that 8 weeks of treatment with oral clarithromycin (500 mg twice daily for 2 weeks then 250 mg daily for 6 weeks) reduced the prevalence of in vivo biofilms from 75% to 44% in patients undergoing endoscopic sinus surgery at the end of this treatment course. However, follow-up studies to assess recurrence of biofilms in these patients were not performed.

Proposed treatments have included continuous or pulsed-wave ultrasound [83], diluted baby shampoo [84], washes with citric acid and zwitterionic surfactants [85], airflow blowing and flushing (to eliminate biofilms in a voice prosthesis) [86], and laser-generated shockwaves [87] Many of these proposed treatments have been used only in animals or in vitro models. An in vitro pilot study found that low-frequency ultrasound completely cleared biofilms from polyps removed from patients with CRS and significantly reduced submucosal inflammatory cell counts compared with untreated control polyps [83].

Other therapeutic proposals have included manuka honey (in vitro and in vivo tested) [88, 89], probiotic drinks (fermented milk and buttermilk) (in vitro and in vivo tested) [90, 91], caffeine (in vitro tested) [92], antiseptic mouthwash solutions (chlorhexidine, triclosan; chlorhexidine reduced dental plaque the most) [93], acetylsalycilic acid (in vitro and in vivo tested) [32], furosemide (in vitro tested) [94], gentian violet and ferric ammonium citrate (in vitro tested) [95]. These have all been tried with conflicting results [32, 88–95]. Kilty et al. [88] reported that manuka honey has in vitro activity against biofilm and planktonic species of *P. aeruginosa* and methicillin-resistant *S. aureus*. Recently, Lee et al. [89] reported results of a small trial that randomized patients with chronic rhinosinusitis to use either manuka honey versus saline nasal irrigations for 30 days, along with antibiotics and corticosteroids as needed. There was no difference in outcome as assessed by either symptoms (SNOT-22) or endoscopic sinus score at the end of the trial. Macchi and colleagues used thiamphenicol glycinate acetylcysteinate, a

compound that breaks down on contact with tissue esterases into the antibiotic thiamphenicol (similar to chloramphenicol) and the mucolytic agent *N*-acetylcysteine, to treat 102 patients with recurrent upper respiratory tract infections including some with recurrent sinusitis [96]. The protocol included intramuscular injections on day 1 followed by aerosolized or topical (nasal douch) therapy on days 2–10. A biofilm was detected by scanning electron microscopy in 24 patients, and 21 of these patients had evidence of bacteriologic and clinical resolution on follow-up 5 days after the completion of therapy. However, given that bacterial biofilm was found in only 24 out of 102 patients with recurrent respiratory tract infections (including some with sinusal disease), and considering the short follow-up and the design of the therapeutic protocol, we cannot draw any definitive conclusion about the effectiveness of thiamphenicol and *N*-acetylcysteine in the treatment of recurrent sinusitis related to bacterial biofilm. More recently, the efficacy of topical sinus irrigation with mupirocin was evaluated in a sheep model with experimentally induced frontal sinus staphylococcal biofilms [97]. In particular, regular treatment with mupirocin (12-hourly sinusal flushes for 5 days) significantly reduced the biofilm surface area, and this effect was still apparent 8 days after stopping treatment.

Finally, some researchers have proposed testing the effects of iron-chelating agents [98], dispersing enzymes such as DNase I and dispersin B [99], and metabolites of the nitrous oxide pathways [100].

Conclusions

The potential involvement of biofilms in the pathogenesis of recurrent and chronic upper airway tract infections is an emerging problem. However, despite extensive research, there is still no definitive evidence that biofilms play a causal role in upper respiratory tract infections. There is also a lack of detailed insight into the complex three-dimensional structure of biofilms and the ultra-structural and biochemical mechanisms responsible for their resistance to the immune system as well as to antibiotic and non-antibiotic treatments.

Future scientific efforts should be aimed at overcoming the increasing rate of therapeutic failures by inducing the dispersion of pre-existing biofilms and preventing bacterial adhesion to biotic and abiotic surfaces.

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Acute Otitis Media in Children

4

Eleni M. Rettig and David E. Tunkel

Introduction

Acute otitis media (AOM) is one of the most common illnesses of early childhood. Acute otitis media is generally managed by primary care providers, but occasionally requires referral to an otolaryngologist for management of refractory symptoms, recurrent disease, or concerns about complications. This chapter describes the epidemiology, pathophysiology, diagnosis, treatment, complications, and prevention of AOM in children. We aim to provide treating clinicians with an evidence-based understanding of contemporary diagnostic and management issues for AOM.

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Epidemiology of AOM

Acute otitis media is diagnosed in an estimated 10–12% of children in the United States (U.S.) each year [1, 2]. The treatment of AOM is responsible for more antibiotic prescriptions in the U.S. than any other childhood illness [3, 4]. In 2006, the financial impact of AOM management was an estimated $2.8 billion in the U.S. [2]. Analysis of a 2009 sample of U.S. children estimated that AOM treatment was associated with an increase in healthcare costs of $314 per child per year [1, 2].

Most AOM occurs in children ages 6–24 months, as maternal antibody protection wanes after the newborn period. Acute otitis media incidence peaks between 9 and 15 months, and declines after 5 years of age [5]. Children who develop AOM before age 6 months have an increased risk of subsequent frequent AOM [5].

The epidemiology of AOM has changed in recent decades. In the U.S., a 33% decrease in outpatient visits for otitis media was observed for children younger than 5 years of age from 1995–1996 to 2005–2006 [3]. There was a significant downward trend in otitis media-related healthcare usage, as measured by annual OM visit rates and recurrent OM visit rates, from 2001 to 2011 [6]. These trends have been attributed to several factors including: the introduction of the 7-valent pneumococcal vaccine (PCV7) in 2000 and the 13-valent version (PCV13) in 2010; broader use

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_4

of influenza vaccination since 2004; dissemination of clinical practice guidelines that emphasize favorable natural history of AOM; improved public understanding about the viral etiology and favorable natural history of most upper respiratory tract infections (URTI); and possibly changing access to healthcare and other socioeconomic considerations [6, 7].

Host risk factors for AOM have been well documented. They include group child-care outside the home, exposure to second-hand tobacco smoke, pacifier use, and lack of breastfeeding. The presence of craniofacial anomalies, immune deficiencies, family history of recurrent acute otitis media (RAOM), and gastroesophageal reflux also are associated with AOM [8, 9].

Diagnosis of AOM

Acute otitis media is defined as the rapid onset of signs and symptoms of middle ear inflammation (Table 4.1) [7, 10]. Acute otitis media can also be characterized by the presence of fluid in the middle ear (that is, middle ear effusion) together with signs and symptoms of an acute infection [11]. The 2013 American Academy of Pediatrics (AAP) guideline for the management of AOM emphasizes stringent diagnostic criteria based on otoscopic findings, stating that the diagnosis of AOM should be made in children with "moderate to severe bulging of the tympanic membrane (TM) *or* new onset of otorrhea not due to acute otitis externa," and in those with "mild bulging of the TM *and* recent (<48 h) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM [7]."

Table 4.1 Classification of otitis media[a]

Term	Definition
Acute Otitis Media (AOM)	Rapid onset of signs and symptoms of middle ear inflammation *Specific/sensitive*: new onset otorrhea; bulging, opaque, immobile, and/or markedly erythematous tympanic membrane on otoscopy *Less sensitive/specific*: otalgia, tugging/pulling ear, fever, irritability, decreased appetite, difficulty sleeping
Recurrent Acute Otitis Media (RAOM)	Three or more AOM episodes in previous 6 months, OR 4 or more AOM episodes in previous 12 months with at least one in previous 6 months[b]
Otitis Media with Effusion (OME)	Fluid in the middle ear without signs or symptoms of acute ear infection
Chronic Otitis Media with Effusion (COME)	OME persisting for 3 months or longer from the date of onset (if known) or from the date of diagnosis (if onset unknown)

[a]Definitions adapted from Rosenfeld et al. [59], Casselbrant et al. [68], Bluestone and Klein [69] and Rosenfeld and Bluestone [70]

[b]Episodes should be well documented and separate

Acute otitis media should be distinguished from otitis media with effusion (OME), where a middle ear effusion is present without signs and symptoms of acute infection. Otitis media with effusion should not be routinely treated with antibiotics (Table 4.1) [10]. Acute otitis media should also be distinguished from viral URTI, which usually precedes and often accompanies AOM. Viral URTI shares nonspecific signs and symptoms, such as fever and irritability, with AOM, but generally does not require antibiotics for treatment [12, 13].

Precise diagnosis of AOM can be challenging for a variety of reasons. Accompanying signs and symptoms are often nonspecific, such as the fever, irritability, or insomnia that accompany other childhood illnesses. Otoscopic examination can be difficult in uncooperative children or in those with cerumen impaction. Signs and symptoms evolve and change throughout the course of the disease.

Otoscopic examination, with pneumatic otoscopy to fully evaluate TM mobility, is the cornerstone for diagnosing AOM [14]. The 2013 AAP guideline emphasizes bulging of the TM, or new onset otorrhea not due to otitis externa, as criteria for diagnosing AOM [7]. Tympanic membrane bulging and other signs of TM inflammation have been key diagnostic criteria for AOM in several recent high-quality randomized, controlled clinical trials evaluating treatment of AOM [15–17]. Training and experience in otoscopy is crucial in the proper identification of the bulging tympanic membrane [18]. Shaikh et al. have created an excellent resource for assessing the appearance of the tympanic membrane in AOM, with otoscopic images and videos that are available online [19].

Other signs and symptoms of AOM are less specific than the aforementioned otoscopic findings, and multiple studies have found that symptoms alone are neither sensitive nor specific enough to reliably diagnose AOM [7, 14]. Symptom assessment often centers around caregiver report, which may be unreliable or affected by pre-existing suspicion for the disease; a study of nearly 500 patients ages 6–35 months suspected to have AOM by caregivers found that only 50% met strict diagnostic criteria for AOM [20]. Nevertheless, assessment of symptoms may help refine clinical suspicion for AOM, and may be the only information available to clinicians for children who are difficult to examine. Otalgia is perhaps the most useful symptom with a relatively high specificity of 80–90%, but may only be observed by caregivers in 50–60% of children with AOM [7, 14]. Ear discomfort can also be caused by the presence of middle ear effusion even without acute infection. Fever, cough, rhinitis, excessive crying, and poor appetite are also frequently present in children with AOM [14].

Diagnosis of AOM in infants is particularly challenging. A prospective study of 193 infants followed through their first year of life and examined during each episode of URTI found that symptoms of earache, fever, poor feeding, restless sleep, and irritability could predict accompanying AOM. In a multivariable predictive model that incorporated symptoms, daycare attendance, and age, the most useful symptoms for predicting AOM in the context of URTI were severity of earache and cough. Still, though specificity was high (95%), sensitivity was low in this model (33%) [21]. Although symptoms are useful in shaping clinical concern for AOM, otoscopic examination is critical to confirm the diagnosis.

Pathophysiology and Microbiology of AOM

Aeration of the middle ear is achieved by intermittent opening of the Eustachian tube to the nasopharynx during swallowing, yawning, or valsava, allowing for pressure equalization of the middle ear with the environment. Mucociliary clearance of middle ear secretions through the Eustachian tube into the nasopharynx and mucosal production of antimicrobial proteins also contribute to a healthy middle ear [11]. In the setting of a URTI, viral-induced inflammation and edema impair pressure equilibration and mucociliary function [22]. Negative pressure develops in the middle ear and fluid collects from decreased clearance of secretions, with pressure differential-related movement of microbe-containing secretions from the nasopharynx. Bacterial replication and infection may ensue, with release of inflammatory mediators. Acute otitis media may also be caused by severe viral infection in the absence of bacteria [11]. Young children are at increased risk for AOM because of their underdeveloped Eustachian tubes at baseline, which are smaller and more horizontal than in adults, and subject to impairment by large adenoid pads. Young children may also have immature immunity with increased susceptibility as well as greater exposure to infectious diseases [11, 23, 24].

The microbiology of AOM varies by locale, and can be affected by antibiotic prescribing habits and vaccination practices [5]. The most common bacteria isolated from middle ear aspirates in AOM in the U.S. are *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis* [5, 25]. Viruses are commonly isolated along with bacteria, consistent with the observation that AOM is often associated with viral URTI. A 2006 Finnish study of the middle ear fluid in 79 children with AOM and indwelling tympanostomy tubes using sensitive assays including culture, antigen detection, and polymerase chain reaction found that 66% had bacteria and viruses, 27% had bacteria alone, and 4% had only viruses [26]. The most common viruses in this study were picornaviruses (rhinovirus, enterovirus, nontypeable picornaviruses), present in 41% of all cases, while next most common were respiratory syncytial virus (14%) and parainfluenza virus (6%).

Vaccines and AOM

The 7-valent and then 13-valent pneumococcal vaccines (PCV7 and PCV13) were introduced in the U.S. in 2000 and 2010, respectively, and have led to significant changes in the microbiology of AOM in the U.S. and other countries with high vaccine penetrance. Both vaccines were found to reduce vaccine serotypes of *S. pneumoniae*, assessed in nasopharyngeal aspirates and middle ear fluid of children with AOM. However, serotype replacement with non-vaccine strains occurred after the introduction of both PCV7 and PCV13, and the overall carriage rate of *S. pneumoniae* did not dramatically decrease [25, 27–31]. Despite serotype replacement, pneumococcal vaccines have appeared to coincide with modest decreases in measures of AOM incidence [6, 32, 33]. One study showed a 20% reduction in otitis media-related outpatient visits in U.S. children under 2 years of age after PCV7 [3], and another found a decrease in otitis media-related annual clinic visits by 0.27 per child after PCV13 [6]. Interestingly, the incidence of complex or recurrent AOM has decreased concomitant with widespread pneumococcal vaccination, to a greater degree than would be expected with pneumococcal serotype coverage by current vaccines. This has been attributed to a decrease in AOM from invasive *S. pneumoniae* serotypes in early childhood, preventing the initiation of a pathogenic process that leads to subsequent recurrent and more severe disease with its associated sequelae [34].

Influenza vaccination also has significant potential to decrease AOM, given the frequent comorbidity of viral illness and AOM. Indeed, a Cochrane review found that influenza vaccination is associated with a small 4% reduction in AOM frequency, and a 15% reduction in antibiotic prescriptions, for children aged 6 months to 6 years who received the influenza vaccine [35].

Treatment of AOM

The goals of management in AOM are reduced symptom severity and duration, as well as prevention of sequelae such as infectious complications or hearing loss. Management should be guided by existing evidence-based clinical practice guidelines in the context of shared decision-making with individual patients and caregivers. While the AAP 2013 guideline on AOM will be discussed here, many other developed and developing countries offer AOM guidelines that have similar diagnostic criteria, pain control recommendations, and options for initial observation (in mild or moderate disease) versus antibiotic therapy (for younger children or more severe disease) [36].

Analgesia

Pain is often a prominent symptom of AOM, and should be assessed by caregivers and clinicians [7]. Acetaminophen and/or ibuprofen have been shown to be effective in reducing pain compared to placebo, but there is not enough high-quality evidence to determine which drug is superior, or whether the combination of both is more effective than monotherapy [37]. Ototopical anesthetic drops have also been reported to provide some pain relief, but there is insufficient evidence to recommend routine use [38]. Pain control strategies should be discussed with caregivers, including pain assessment in young children as well as medication options, dosing, and administration schedule [7, 39].

Antibiotics or Initial Observation Without Antibiotics

A key management decision in treating AOM is whether to use antibiotics at the time of diagnosis or to initially observe and use antibiotics for persistent or worsening signs and symptoms. Although AOM has a very favorable natural history without antibiotic treatment for most children, several trials have shown that antibiotic treatment does improve symptom scores and outcomes in select patients [15, 16, 40–42]. The clinical significance of such demonstrated advantages of antibiotics for AOM remains debated. A Cochrane review of randomized controlled trials of antibiotic treatment for AOM evaluating over 3000 children from high-income countries found

that 24 h after diagnosis most (60%) children had improvement in symptoms, and antibiotic treatment had no bearing on whether or not symptoms improved. In the ensuing days to weeks, antibiotics were associated with small reductions in pain, TM perforations, and risk of contralateral AOM, but did not impact late AOM recurrences or hearing loss at 3 months. In general, antibiotics held the greatest benefit for children <2 years old with bilateral AOM, and children with AOM accompanied by otorrhea [42]. Notably, children treated with antibiotics did suffer increased risk of rash and gastrointestinal symptoms such as vomiting and diarrhea. Given the small benefit of antibiotics and the adverse events associated with their use, this review concluded that initial observation without immediate antibiotics was reasonable for most children with AOM [42].

The 2013 AAP guideline, which applies to children 6 months through 12 years of age, recommends a treatment decision algorithm based on the child's age, severity of signs, and symptoms including otalgia and fever, otorrhea, and laterality of disease, combined with joint decision making with the patient and caregiver. According to this guideline, clinicians should prescribe antibiotics for children with AOM with severe symptoms (e.g., fever, severe otalgia, otalgia for >48 h) or AOM with otorrhea, and for children 6–23 months of age with bilateral AOM. Children 6–23 months old with unilateral AOM without severe symptoms, and older children with non-severe AOM (unilateral or bilateral) may be offered either antibiotic therapy or observation with close follow-up (Table 4.2) [7].

The 2013 AAP guideline represents a change from the 2004 AAP guideline, which introduced concepts to guide antibiotic stewardship in the midst of concerns over rising antimicrobial resistance and AOM treatment-related costs as well as antibiotic-related side effects [7, 43, 44]. The 2004 guideline introduced the option for initial observation of non-severe illness, acknowledging the generally favorable natural history of AOM and the potential harms of antibiotic overuse. The 2004 guideline allowed for and incorporated diagnostic uncertainty into treatment decisions [44]. The 2013 guideline also recommends initial observation in select groups, but emphasizes precise diagnosis to guide subsequent treatment decisions. Two randomized trials that used such stringent diagnostic criteria including otoscopic findings and acute onset of symptoms demonstrated a rate of clinical improvement of 26–35% with antibiotics over placebo, which was greater than the 6–12% rates that had previously been reported in studies with less restrictive inclusion criteria [7]. Both the trials used amoxicillin-clavulanate in the treatment arms [15, 16].

The decision for initial observation rather than antibiotic treatment in appropriately selected children should be made together with caregivers, with an agreed-upon plan for initial analgesia and re-evaluation in 48–72 h [7]. A useful strategy is to give caregivers a "wait-and-see prescription ('WASP')" [45] that should only be filled in the event of worsening or persistent symptoms.

Table 4.2 Treatment of acute otitis media: immediate antibiotics or initial observation?[a]

Disease severity[b]	Age	Laterality	Treatment
Severe disease and/or otorrhea	All ages	Unilateral or Bilateral	Prescribe antibiotics
Non-severe disease	<6 months[c]	Unilateral or Bilateral	Prescribe antibiotics
	6–23 months	Bilateral	Prescribe antibiotics
		Unilateral	Prescribe antibiotics *or* offer observation with close follow-up[d]
	≥24 months	Unilateral or Bilateral	Prescribe antibiotics *or* offer observation with close follow-up[d]

[a]Adapted from Lieberthal et al. [7]
[b]Severe disease: moderate or severe otalgia or otalgia for ≥48 h, or temperature 39 °C or higher
[c]Infants <6 months not included in most trials evaluating acute otitis media treatment
[d]Observation consists of initial symptom management only, with a plan in place to start antibiotic therapy if symptoms worsen or do not improve in 48–72 h

This approach resulted in avoidance of antibiotics in up to two-thirds of children managed with initial observation [45, 46]. The initial observation approach can be well received by caregivers with appropriate education and emphasis on shared decision-making [47, 48], and has not resulted in increased rate of suppurative AOM complications such as mastoiditis [49, 50].

Antibiotic Selection for AOM

When the decision is made to administer antibiotics to a child with AOM, the choice of first-line therapy is guided by knowledge of the most common bacteria causing AOM, antibiotic resistance patterns, patient allergies, or intolerances, whether the patient has received antibiotics in the past 30 days, and potential side effects. The most commonly recommended drug for first-line treatment, in a non-penicillin allergic child who has not received amoxicillin in the previous 30 days, is "high-dose" amoxicillin (90 mg/kg/day). Although sensitivity data for uncomplicated AOM are difficult to obtain as it requires tympanocentesis for culture of middle ear fluid, data from the Centers for Disease Control and Prevention antibiotic resistance surveillance program indicate that approximately 95% of *S. pneumoniae* from all the sites were penicillin susceptible in 2014 [51], and another report found 73% of *H. influenzae* isolates from 2008 to 2010 in 71 U.S. medical centers were susceptible to ampicillin [52]. *Moraxella catarrhalis* produces beta-lactamase and is nearly 100% resistant to penicillin [52], but AOM caused by this organism still exhibits high rates of clinical response with few complications when treated with amoxicillin [7]. In cases where a child has received amoxicillin within 30 days, has recurrent AOM that does not respond to amoxicillin, or also has purulent conjunctivitis, the addition of a beta-lactamase stable drug such as amoxicillin-clavulanate is recommended.

Penicillin-allergic patients may be treated with a second or third-generation cephalosporin (cefdinir, cefuroxime, cefpodoxime, or ceftriaxone). While the incidence of "cross-reactivity" of penicillin and cephalosporins has often been quoted as high as 10%, more critical and recent analysis summarized in the 2013 AAP guideline suggests this actual cross-reactivity risk is about 0.1%—and likely lowest for the later generation cephalosporins [7]. While trimethoprim-sulfamethoxazole or erythromycin-sulfisoxazole combinations are reasonable choices for initial treatment of AOM in children with severe penicillin reaction or a history of documented cephalosporin allergy, the considerable rate of pneumococcal resistance to these drugs makes them unsuitable for treating AOM after initial treatment failure. Clindamycin has no activity against *H. influenzae*, and also may lack activity against highly resistant serotypes of *S. pneumoniae*.

If symptoms persist or worsen after 48–72 h of first-line antibiotic therapy, clinicians should consider switching to an alternative second-line agent. This may include amoxicillin-clavulanate, ceftriaxone (intramuscular or intravenous), or a combination of clindamycin and an extended-spectrum cephalosporin. Infections that persist despite second line treatment, or infections in children with multiple drug sensitivities, may require tympanocentesis (or myringotomy and tympanostomy tube placement) for culture and sensitivity testing [7].

The use of ototopical antibiotic drops in place of oral antibiotics for AOM with an associated TM perforation has not been studied. Indirect evidence from a trial demonstrating efficacy of antibiotic ear drops in children with tympanostomy tube otorrhea [53] suggests that drops may be beneficial in the setting of AOM with TM perforation; however, an evidence-based recommendation cannot currently be made for or against their use. If clinicians choose to prescribe topical antibiotics in these cases, ototopical fluoroquinolones should be used rather than potentially ototoxic preparations that contain aminoglycosides [54]. While topical fluoroquinolones are not approved for use in very young children with AOM and tympanostomy tubes (e.g., 6 months of age for ciprofloxacin-dexamethasone otic, or 1 year of age for ofloxacin otic), at least one study of treatment of post-tympanostomy otorrhea with such drops included children as young as age 6 months [55].

Duration of Antibiotic Therapy

The ideal duration of antibiotic therapy for AOM is still debated. For children ages 2–5 years with mild or moderate AOM, a 7-day course has been recommended, and for children 6 years and older a 5–7 day course is considered adequate [7, 56]. A recent randomized controlled trial of 520 children ages 6–23 months compared a 5-day course of amoxicillin-clavulanate with a 10-day course. Those treated for 5 days were more likely to have clinical failure and had significantly worse symptom scores at 12–14 days after treatment, while the longer regimen did not have significantly different adverse event rates or emergence of antibiotic resistance [17].

Complications

Complications of AOM are rare, but prompt diagnosis and treatment are needed to avoid severe morbidity. The most common complication is TM perforation with resultant otorrhea. Although a full discussion of AOM complications is beyond the scope of this chapter, a useful schema for classifying complications of AOM is by anatomic site: (1) *Intracranial*, *extratemporal*; (2) *Extracranial*, *intratemporal*; and (3) *Extracranial*, *extratemporal* (Table 4.3). Complications may be suspected or diagnosed based on history and physical exam findings, but often require imaging such as contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), or possibly a lumbar puncture (if there is suspicion for meningitis), to clarify the diagnosis. Treatment may include parenteral antibiotics, myringotomy with or without tympanostomy tube placement, and/or mastoidectomy. Neurosurgical consultation should be obtained for intracranial complications.

Table 4.3 Complications of acute otitis media

Complication	Presentation
Intracranial, *extratemporal*	
Meningitis	Headache, altered mental status, nausea, vomiting, lethargy, seizures, neck stiffness, photophobia, focal neurologic deficits
Intracranial abscess	
Subdural, epidural, or brain abscess	
Otitic hydrocephalus (elevated intracranial pressure with normal cerebrospinal fluid cytology)	Headache, vomiting, blurred vision, seizures, diplopia, abducens palsy, papilledema
Thrombosis of dural venous sinuses (lateral or sigmoid sinus thrombophlebitis)	Headache, neck stiffness, fever, otalgia, postauricular pain and erythema
Extracranial, *intratemporal*	
Acute mastoiditis	Postauricular erythema, tenderness, edema, protrusion of pinna
Subperiosteal abscess	Postauricular erythema, tenderness, fluctuance
Petrositis ('Gradenigo's syndrome')	Abducens palsy, retrobulbar pain
Facial nerve palsy	Acute onset facial weakness
Labyrinthitis	Acute onset sensorineural hearing loss and vertigo
Tympanic membrane perforation	Otorrhea, possibly following abrupt decrease in pain
Extracranial, *extratemporal*	
Sepsis	Fever, lethargy, tachycardia, hypotension

Sources for this table: Bluestone and Klein [69], Naseri and Sobol [71], Ropposch et al. [72], Rettig and Tunkel [43]

Recurrent Acute Otitis Media (RAOM)

Recurrent acute otitis media is a common reason for referral to an otolaryngologist. Male gender, exposure to tobacco smoke, and winter season all increase the risk of RAOM. While tympanostomy tubes are commonly used to prevent AOM in children with a history of RAOM, few studies have assessed tympanostomy tubes for this indication, particularly in the absence of chronic OME. The 2013 AAP guideline recommended *offering* tympanostomy tubes to children with RAOM on the basis of studies that show a modest reduction in AOM by 1.5 episodes in 6 months [57], and improved disease-specific quality of life after tympanostomy tube placement [7, 58]. The American Academy of Otolaryngology-Head and Neck Surgery, in its 2013 tympanostomy tube guideline, also recommended *offering* tympanostomy tubes for RAOM, but only if a middle ear effusion was present in one or both

ears at the time of evaluation [59]. An important advantage to tympanostomy tube placement is that uncomplicated AOM after such surgery, manifested by post-tympanostomy otorrhea, can be treated with ototopical drops rather than oral antibiotics, reducing potential for systemic side effects [60]. Of note, prophylactic antibiotics for RAOM are not recommended due to demonstrated minimal benefit in preventing AOM, associated side effects of antibiotics, and the potential for encouraging bacterial resistance [7].

Prevention

There are several host-level interventions that can reduce the risk of AOM. Breastfeeding during infancy is associated with significantly lower risk of AOM and RAOM, with greater protection afforded by exclusive and longer duration breastfeeding [61]. The AAP advises exclusive breastfeeding for at least 6 months [7]. Exposure to second-hand tobacco smoke significantly increases the risk of AOM, so that caregiver smoking cessation should be strongly advised [7, 62, 63]. Pneumococcal and influenza vaccinations appear to reduce the frequency of AOM, as described previously [7, 35, 64]. Other potentially modifiable risk factors for AOM are pacifier use and exposure to a group childcare setting [63, 65].

Various other prophylactic strategies have been attempted, including zinc or vitamin D, probiotics, and other dietary supplements and homeopathic remedies [66]. While support for such regimens is seen in lay publications, high-quality evidence does not exist for recommending routine use. Xylitol is a natural sugar substitute that has been shown in meta-analysis to reduce the risk of AOM by 22–30% as compared with control groups among children attending daycare centers. However, it must be taken 3–5 times daily, limiting its practicality [67].

Conclusion

Appropriate management of AOM requires skill in clinical assessment and otoscopic examination, familiarity with the generally favorable natural history of the disease, and shared decision-making with parents and caregivers. Although many children will recover with initial observation without antibiotics, clinicians should be familiar with the indications for immediate antibiotic treatment for AOM. Pain assessment and management is necessary for all children with AOM. Vaccines are changing the epidemiology and microbiology of AOM, and appear to be reducing the burden and severity of disease. Clinical practice guideline updates should be consulted for contemporary evidence-based practice recommendations.

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Chronic Otitis Media

5

Jenna W. Briddell, Jessica R. Levi, and Robert C. O'Reilly

Introduction

Chronic otitis media (COM) is characterized simply as inflammation of the tympanic membrane and middle ear space lasting longer than 3 months [1, 2]. However, COM includes several different conditions that may co-exist, including COM with and without cholesteatoma, chronic suppurative otitis media (CSOM), nonsuppurative chronic otitis media, tube otorrhea, and otitis media with effusion (OME) [2].

Categories

Otitis Media with Effusion

Otitis media with effusion is defined as an intact tympanic membrane with a fluid effusion in the middle ear without signs or symptoms of acute infection [3]. Otitis media with effusion is classified as chronic (COME) when the effusion persists for longer than 3 months. Given the lack of acute inflammatory findings such as purulence or erythema, COME has been previously classified as a non-infectious process, since cultures of aspirated middle ear fluid were often sterile. However, newer technologies, such as polymerase chain reaction (PCR) analysis, have increased the ability to detect the presence of bacteria in these samples [4]. Bacterial presence may also be the result of bacterial biofilms, which will be discussed later in this chapter [5, 6]. Regardless of whether bacteria are present in OME, it is believed to result from poor middle ear ventilation [5]. Middle ear effusions can persist after an episode of acute otitis media (AOM) due to persistent mucosal inflammation resulting in Eustachian tube dysfunction. A transudative effusion may also be the result of more chronic Eustachian tube dysfunction causing negative middle ear pressure (so-called hydrops ex vacuo) [3].

Chronic Nonsuppurative Otitis Media

Nonsuppurative otitis media is defined as a dry tympanic membrane perforation without suppuration or otorrhea (Fig. 5.1) [7]. Although suppuration is not present, the perforation exposes the middle ear mucosa to the surrounding external environment, which may lead to suppuration.

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_5

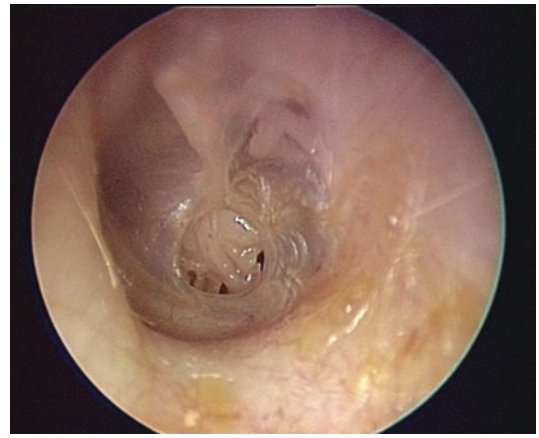

Fig. 5.1 Endoscopic photograph of a tympanic membrane with an inferior central perforation. The tympanic membrane and middle ear are healthy without signs of inflammation or suppuration

Chronic Suppurative Otitis Media

Chronic suppurative otitis media is characterized by chronic inflammation of the middle ear and mastoid air cell system resulting in recurrent or chronic suppuration with otorrhea [8, 9]. This condition can be further subdivided into COM with tympanic membrane perforation and COM with middle ear cholesteatoma [9].

Chronic Otitis Media with Tympanic Membrane Perforation

Chronic otitis media with tympanic membrane perforation is also referred to as COM without cholesteatoma. Causes of tympanic membrane perforation include traumatic injury, residual perforation after tympanostomy tube extrusion, or acute or chronic otitis media. When the perforation is due to traumatic injury to the ear drum or extrusion of a tympanostomy tube, it will often heal spontaneously via circumferential migration of the surrounding tympanic membrane cells. This form of tympanic membrane closure may be at risk of reperforation if the patient has underlying Eustachian tube dysfunction with AOM or COM.

Perforations may also be the result of AOM or COM. The purulent material in AOM may exert sufficient pressure on the tympanic membrane to cause spontaneous rupture. Typically, these post-infectious spontaneous perforations heal quickly after the pus is decompressed from the middle ear and the pressure normalizes. When the infection is cleared, the perforation may remain if it is too large to spontaneously heal or if there is persistent Eustachian tube dysfunction. If the initial AOM does not clear and instead progresses into COM, the persistent infection and drainage can prevent tympanic membrane healing.

In perforations resulting from trauma, tympanostomy tube extrusion, or resolved AOM, there may be periods where the perforation is present but middle ear inflammation is absent, resulting in nonsuppurative COM. The middle ear is not normally a sterile environment since it is in continuity with the nasopharynx via the Eustachian tube. However when a perforation is present, the middle ear is exposed to the external ear and the external environment, which can harbor various species of bacteria. Once bacteria enter the middle ear, they can form biofilms that can be difficult to eradicate, leading to recurrent periods of suppuration and otorrhea [9]. Chronic inflammation of the middle ear mucosa can cause formation of granulation tissue.

Chronic Otitis Media with Cholesteatoma

Cholesteatoma is a proliferative and expansile but non-neoplastic lesion characterized by a sac of stratified squamous epithelium surrounding an accumulation of keratin debris [1, 8]. Cholesteatoma can be either acquired or congenital, but it is the acquired form that pertains to COM. The pathogenesis of acquired cholesteatoma is not fully understood, and there are several suggested pathways of formation. One type results from the invagination of a retraction

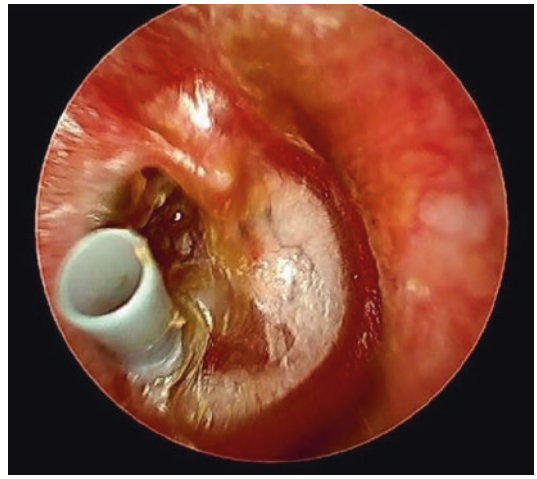

Fig. 5.2 Endoscopic photograph of a tympanic membrane with a pars flaccida retraction pocket in the upper left quadrant. Golden-brown debris is seen within the retraction pocket. Such debris can often be confused for normal cerumen (ear wax). A tympanostomy tube, which was placed to combat the negative pressure from Eustachian tube dysfunction that likely contributed to the development of the retraction pocket, is present in the lower left quadrant

pocket into the middle ear, either through the pars flaccida into the epitympanum or into the meso- or hypotympanum by a collapse of the pars tensa [1, 10] (Fig. 5.2). Other forms of cholesteatoma can result from migration of keratinizing squamous epithelium through iatrogenic or traumatic defects in the eardrum. Some investigators have also theorized that cholesteatoma can result from metaplastic transformation of middle ear mucosa into keratinizing epithelium or basal cell hyperplasia of the middle ear [10]. The common pathologic condition in non-congenital cholesteatoma appears to be the presence of Eustachian tube dysfunction and atelectasis of the tympanic membrane and/or chronic long-term inflammation of the middle ear mucosa [1, 8, 10]. Once a cholesteatoma forms, it typically will continue to proliferate and expand, causing destruction of the ossicles and other related portions of the temporal bone through disruption of blood supply, and suppurative damage if the cholesteatoma becomes infected (Fig. 5.3). Serious complications may include damage to the inner ear (cochlea and vestibular apparatus), facial nerve paresis or paralysis, and intracranial complications (venous sinus thrombosis, epidural abscess, and meningitis) [1, 7, 8, 10].

As the invagination and migration theories would suggest, there typically is a communication with the sac of the cholesteatoma and the external ear. This means that the same bacteria that enter the middle ear when a tympanic membrane perforation is present can also gain access to the middle ear through the cholesteatoma. In addition to harboring infection, the presence of the cholesteatoma causes chronic inflammation of the middle ear, leading to chronic inflammatory changes and the growth of granulation tissue. The presence of the cholesteatoma and the growth of granulation tissue affects the aeration of the middle ear, resulting in further Eustachian tube dysfunction and impairment of mastoid aeration, perpetuating the chronic disease process.

Chronic Tympanostomy Tube Otorrhea

Patients with tympanostomy tubes have an artificially created tympanic membrane perforation. Although tympanostomy tubes are placed to improve the aeration of the middle ear and restore oxygen tensions that may permit the return of functional ciliated epithelium [5], they also create the same exposure to the external environment that is seen with cholesteatoma and tympanic membrane perforation. This permits the same exposure to bacteria that can create biofilms, resulting in chronic middle ear inflammation causing suppuration and chronic otorrhea [5, 11].

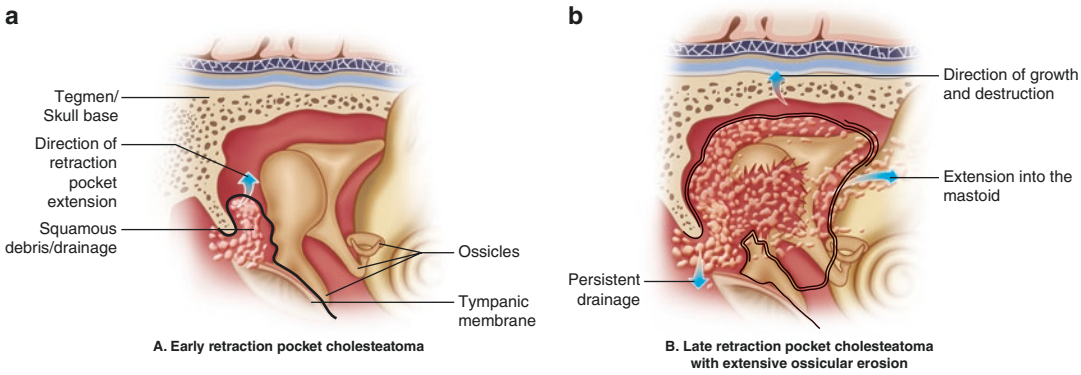

Fig. 5.3 Illustration of the formation of a retraction pocket cholesteatoma, caused by negative pressure in the middle ear space due to Eustachian tube dysfunction. (**a**) In the early phases, the retraction pocket begins to form as the pars flaccida invaginates and wraps around the ossicles. (**b**) As more squamous cells are shed from the surface of the tympanic membrane, they are trapped in the retraction pocket and the cholesteatoma grows, putting pressure on the ossicles and surrounding temporal bone leading to erosion

Epidemiology

Estimates on the prevalence of COM range from affecting 65–330 million people worldwide [2]. The range in prevalence is attributable to the incidence being higher in regions where healthcare resources are limited; thus, its true incidence is underreported. Additionally, the varied definitions may also mean there is underreporting in some areas. In Southeast Asia, Africa, and the Western Pacific, the prevalence is higher than in North America and Europe, where the prevalence is <2% [2]. In regions where healthcare is limited, patients are more likely to develop complications. A 2004 report from the World Health Organization estimated that 28,000 deaths per year are attributable to COM worldwide [2]. Chronic otitis media has additional global impact in being a significant cause of hearing impairment [2].

Risk Factors

Since the middle ear is not protected from the external environment, activities such as bathing or swimming can increase exposure to pathogens. Many of the other risk factors for developing COM coincide with factors that increase one's risk for chronic Eustachian tube dysfunction given its key role in the development of tympanic membrane perforation and cholesteatoma. Eustachian tubes oriented in a more horizontal plane, as in young children and individuals with craniofacial anomalies, are prone to Eustachian tube dysfunction [8]. Patients who have had radiation of the head and neck for treatment of cancer may also develop significant Eustachian tube dysfunction, although this incidence is decreasing with the advent of modern radiotherapy techniques [12].

Other risk factors include those that can contribute to mucosal inflammation of the nasopharynx resulting in Eustachian tube dysfunction as well as inflammation of middle ear mucosa itself. Smoking is a known mucosal irritant that can have this affect. While some studies fail to draw a correlation between allergic rhinitis and COM, others have found direct evidence of eosinophils in the middle ear, suggesting allergy plays a role [13]. Gastroesophageal reflux is also a contributor to chronic nasopharyngeal and middle ear inflammation as evidenced by the detection of pepsin in middle ear fluid [14, 15]. Other studies show that certain patients also may be genetically predisposed to CSOM due to lower expression of certain toll-like receptors in middle ear mucosa biopsies [16, 17].

Physical Examination and Evaluation

Physical examination findings differ significantly depending on the type of COM. In CSOM, otorrhea or ear drainage in the external ear canal is seen. The drainage can vary from a white, yellow, or green purulence to a clear or brown-tinged fluid. When this drainage is removed, one may find a perforation or retraction pocket; however, these findings may be obscured by the presence of granulation tissue [7] (Fig. 5.4). Treatment with ototopical anti-inflammatory and antibiotic drop combinations will dissipate the granulation tissue to reveal the underlying pathology. The cholesteatoma usually appears as a pearly white mass medial to the tympanic membrane in the middle ear. If the cholesteatoma is a retraction pocket cholesteatoma, one may see an invagination of the tympanic membrane filled with squamous debris. This may be disguised by overlying ceruminous debris or granulation tissue. In some cases the invagination is so deep that it tracks into the epitympanum or antrum and the contents are not visible. In COME, the tympanic membrane is intact and of normal color (not red), but there is resistance to insufflation because of fluid in the middle ear.

Initial evaluation of a patient with suspected COM should include assessing hearing, screening for vestibular dysfunction, and assessing for intracranial complications such as meningeal signs, headache, or other neurologic signs [18].

Radiologic Imaging

Computed tomography (CT) has been used for several decades in the diagnosis of many forms of COM [7]. The generalized findings of COM on CT can include middle ear and mastoid opacification with thickening or sclerosis of the mastoid trabeculae [1]. Although these COM findings are easily detected on CT, differentiating between the types and causes of COM can be more challenging. Cholesteatoma, granulation tissue, mucosal edema, and effusions all can appear as opacification and cannot be differentiated on CT [7]. Ossicular chain erosion can also appear in cholesteatoma as well as states of chronic inflammation and infection. However, if there is evidence of bony erosion on the CT, it is generally interpreted as being indicative of cholesteatoma [7] (Fig. 5.5). Bony erosion of the scutum is most commonly seen, since pars flaccida retractions leading to cholesteatoma of Prussak's space are

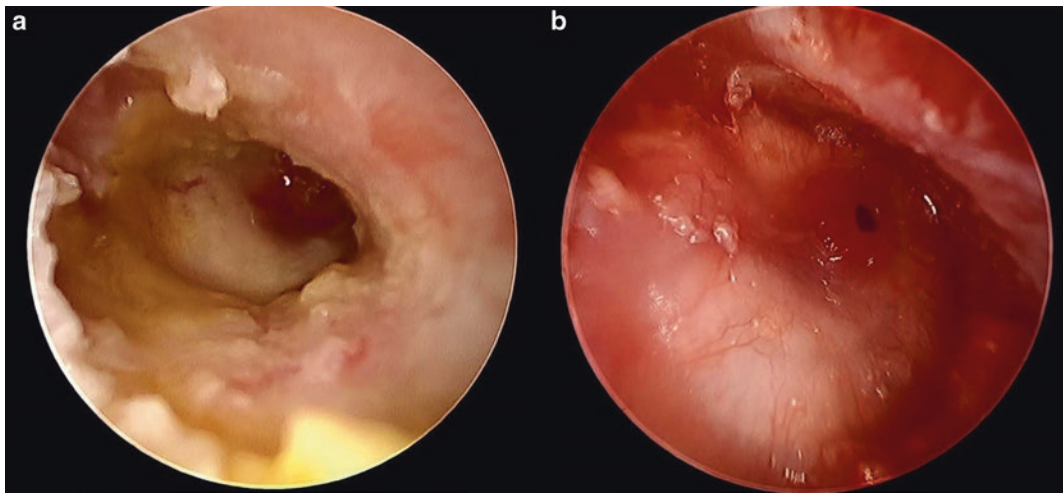

Fig. 5.4 Chronic suppurative otitis media with tympanic membrane perforation. (**a**) Tympanic membrane and external ear canal coated in white/yellow purulence and debris. (**b**) Upon debridement of the canal and tympanic membrane, an anterior perforation is revealed with a rim of granulation tissue visible within the perforation

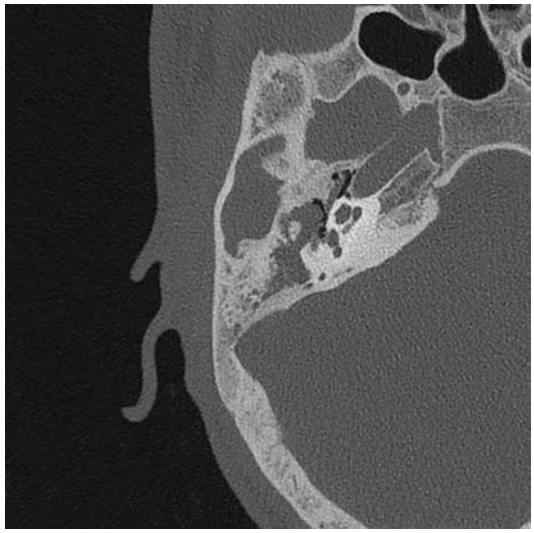

Fig. 5.5 Axial computed tomography scan of the right temporal bone demonstrates a soft-tissue mass of the right middle ear and mastoid cavities that has caused bone and ossicular erosion suggestive of a cholesteatoma

common. Due to concerns for associated complications, erosions of the facial canal, lateral semicircular canals, sigmoid sinus, and tegmen should also be investigated [7].

Magnetic resonance imaging (MRI) shows promise in differentiating the cause of opacification seen on CT. This is particularly true with the advent of diffusion-weighted imaging (DWI) and delayed perfusion imaging (DPI) [1, 19, 20]. Delayed perfusion T1-weighted sequences show enhancement of granulation and inflammatory tissue, while cholesteatoma, which is not perfused, does not enhance [19]. Conversely, cholesteatomas show high intensity on DWI due to diffusion restriction secondary to a high keratin content [1, 19]. With thin-slice non-echo planar DWI MRI, cholesteatomas larger than 4 or 5 mm can be detected reliably, and cholesteatomas as small as 2 mm have also been detected [1, 19, 20]. In addition to DPI and DWI series, traditional contrast-enhanced MRI is useful for the detection of complications, such as intracranial infection, where meningeal enhancement or abscesses can be seen. Magnetic resonance imaging and magnetic resonance venography (MRV) can be used to detect thrombosis of the sigmoid sinus [21]. An MRI should be obtained whenever there is concern for intracranial extension.

Microbiology

Chronic otitis media commonly refers to a state of chronic inflammation with less emphasis on infectious etiologies, but bacteria or fungi typically are present [8, 9]. Their presence can range from fulminant infection, to suppuration, to a less-obvious biofilm. Chronic otitis media is often a polymicrobial disease [22]. Since the middle ear space is connected directly to the external auditory canal in cholesteatoma and tympanic membrane perforation, it is not surprising that the common bacterial offenders are a combination of the microbes that cause otitis media and otitis externa. In addition, cultures of ear drainage fluid are obtained via the ear canal and may be easily contaminated by colonizing bacteria, so cultures may reflect both the COM pathogens and contaminants. Commonly seen microbes include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and coagulase-negative staphylococci (although coagulase-negative staphylococci may be contaminants) [4, 23, 24]. Other organisms that are seen less commonly can include various *Candida* species, *Streptococcus pyogenes*, *Chlamydia trachomatis*, *Klebsiella pneumoniae*, *Escherichia coli*, and atypical mycobacteria [4, 9, 11]. Cultures obtained after patients have been treated with courses of antibiotic ear drops may reflect selection of resistant bacteria as a result of antibiotic pressure.

As previously mentioned, CSOM can be characterized by recurrent periods of suppuration with silent dry periods of various lengths where the infection appears to be temporarily resolved [9]. Current theory now suggests that biofilms are often responsible for this observed pattern [5, 6, 9, 23–25]. Biofilms are structured bacterial communities contained within an extracellular polymeric substance (EPS) composed of lipids, proteins, nucleic acids, uronic acids, humic substances, and exopolysaccharides that attach to a surface [6, 9, 23]. The surface can be mucosa, granulation tissue, cholesteatoma, or a foreign body such as a tympanostomy tube. The EPS protects the bacteria from changes in pH, moisture, and temperature while also shielding against

mechanical shear, phagocytic macrophages, and other clearance mechanisms of the human body [6, 9, 23, 24]. The EPS also allows the bacteria to reside in a dormant state with a reduced metabolic rate, which makes them less susceptible to antibiotics that target the replication cycle of the bacteria [6, 9, 23, 24]. Biofilms may account for the observation that an infection can appear to be resolved after antibiotic treatment only to return soon after discontinuing drug therapy. Once the antibiotic is completed, bacteria that were dormant in the biofilm can exit the stationary phase and resume active growth [6, 23]. Biofilms are discussed in detail in Chap. 3.

The EPS and other protective mechanisms explain pathophysiologically how biofilms are often undetectable or underestimated with standard culture techniques [6]. Newer technologies such as confocal laser scanning microscopy, scanning electron microscopy, PCR analysis, fluorescence in-situ hybridization, and immunostaining have allowed for the identification of these previously undetected biofilms [4, 6, 9]. Biofilms have been found in 60–85% of cholesteatomas, 10–92% of CSOM, 16–43% of non-suppurative otitis media with dry middle ear perforations, and up to 92% of OME [6, 9, 25]. Reported percentages vary by study and by the detection technique.

Treatment

Treatment of COM focuses on clearing infection and creating a safe ear that will not result in recurrence of COM or progression of disease to complications [26]. When a patient presents with active suppuration, the first step in treatment is to eliminate the active infection. This may be accomplished with the use of ototopical antibiotic drops. If granulation tissue is present, the addition of an ototopical steroid is often advantageous as this can speed the resolution of granulation tissue. If ototopical medications are not sufficient to resolve the infection, oral antibiotics may also be used. The choice of antibiotic should be culture directed whenever possible. Future goals in treatment may target the elimination of biofilms prior to surgical intervention [9].

If possible, the active infection should be reduced or eliminated prior to surgical intervention. The objectives of surgery should be to create an aerated, functional, and safe middle ear space whenever possible [27]. In cases of COM with tympanic membrane perforation without cholesteatoma that does not heal over time and does not produce otorrhea, middle ear exploration with tympanoplasty is generally recommended. This allows for the diseased or damaged portions of the tympanic membrane to be repaired and the middle ear space to be explored [17]. During this procedure, the status of the ossicular chain can be assessed for erosion, continuity, and mobility. If there is little inflammation at the time of the surgery, the surgeon may choose to proceed with ossicular reconstruction at the time of tympanoplasty. If the surgeon is concerned that the degree of inflammation present will impair healing, he or she may opt to repair the tympanic membrane only, and return later to surgically inspect the middle ear for resolution of inflammation and perform ossicular reconstruction at that time. Numerous tympanoplasty techniques have been described including medial graft, lateral graft, interlay, and butterfly graft approaches [28–31]. Potential graft materials include autologous grafts such as fascia, perichondrium, and chondroperichondrial grafts. There are also manufactured materials including hyaluronic acid patches and acellular collagen matrices from both human and mammalian species that can be utilized.

In patients with confirmed cholesteatoma, the surgical approach must first focus on elimination of the disease prior to any reconstruction. Depending on the extent of the cholesteatoma, a canal wall down or canal wall intact tympanomastoidectomy can be performed. If the disease extends beyond the confines of the tympanum into the mastoid air cell system and cannot be removed trans-canal, a mastoidectomy is performed, with the extension of dissection into the aditus ad antrum and epitympanum to allow complete removal of the cholesteatoma matrix.

Modern endoscopic techniques have afforded the ability to remove cholesteatoma confined to the middle ear space without the necessity of drilling out the mastoid cavity (trans-canal endoscopic removal of cholesteatoma) [31–33].

The success of endoscopic techniques in eradicating disease depends on both the location of the cholesteatoma and the experience of the surgeon. The surgical goal is *en bloc* removal of the cholesteatoma sac to avoid leaving any fragments of disease behind that might result in recurrence. Once the cholesteatoma is removed, tympanoplasty typically is performed to reconstruct the tympanic membrane, and ossiculoplasty may be performed in select cases if complete removal of the disease has been obtained. If there is any concern that residual cholesteatoma remains in the middle ear or mastoid, the surgeon typically plans a "second look" procedure several months later to re-enter the middle ear and/or mastoid cavity to look for recurrent cholesteatoma. If no recurrence is present, any needed ossicular reconstruction can be performed at that time. In some cases, several surgeries are required until the disease is completely cleared. If a surgeon is confident that all cholesteatoma was removed with the initial surgery, he or she may proceed with ossicular reconstruction at that time and then follow the patient either clinically or with DWI MRI to look for recurrence.

Another surgical option often employed is canal wall down tympanomastoidectomy. In this procedure, the osseous portion of the posterior external auditory canal wall is removed to create a common cavity between the ear canal, mastoid, and middle ear cleft. This approach is considered more definitive, as it externalizes the mastoid and middle ear so that any accumulation of squamous epithelium can be removed from the mastoid bowl in an outpatient clinical setting [34].

The decision to perform a canal wall intact or canal wall down tympanomastoidectomy is guided by extent of disease. In addition to surgeon preference, it is important to consider the patients' age and willingness to undergo either in-office cleanings or returns to the operating room for additional surgeries. A surgeon may decide to also perform a canal wall down surgery if the patient has already undergone several canal wall intact procedures with continued recidivistic cholesteatoma or has experienced a complication from cholesteatoma.

The treatment of COME is a different treatment paradigm. Although this condition can be difficult to treat medically and has detrimental effects on hearing, it is a less aggressive pathology, so the management is more conservative. When treating COME, the main principle is to restore middle ear aeration to bypass Eustachian tube dysfunction. By restoration of aeration, the appropriate oxygen tensions are restored, and the mucosa will regain appropriate ciliary function [6]. To quickly and effectively restore aeration of the middle ear, the treatment is to place tympanostomy tubes, which are sometimes called pressure-equalizing tubes. The American Academy of Otolaryngology and Head and Neck Surgery (AAO-HNS) released clinical practice guidelines on COME in 2016 [3]. The AAO-HNS guidelines recommend offering the placement of tympanostomy tubes if an effusion lasts longer than 3 months. In children with documented associated conductive hearing loss, this is a particularly strong recommendation given the impact on speech and language development. If hearing loss is not present, a patient or family may choose to observe the condition, but the child should still be seen at 3- to 6-month intervals to monitor for resolution or the development of hearing loss. The AAO-HNS guidelines also recommend offering a concomitant adenoidectomy for children over the age of 4 years or in younger children with associated nasal obstruction or chronic adenoiditis. The guidelines strongly advocate for the use of tympanostomy tubes as the primary treatment for COME, and they advocate against the use of antihistamines, decongestants, nasal steroids, systemic steroids, or systemic antibiotics, as none of these medical treatments is reliably effective in resolving COME [3].

Complications

Hearing Loss

Hearing loss can be a sequela of all subsets of COM. The loss may be temporary or permanent. The most common type of hearing loss in COM is conductive hearing loss, which may result from

ossicular discontinuity due to ossicular erosion, impaired ossicular mobility due to the presence of cholesteatoma or granulation tissue, tympanic membrane perforation, effusions, or scar tissue of the tympanic membrane and/or middle ear (tympanosclerosis) [8, 26]. Most of these causes of conductive hearing loss can be improved through surgical reconstruction, although patients are often left with a small degree of conductive hearing loss even after repair.

In addition to conductive hearing loss, there are several hypothesized mechanisms for sensorineural hearing loss in patients with COM. Penetration of bacterial toxins and inflammatory mediators through the round window membrane, or direct penetration of bacteria into the inner ear, can produce end-organ damage and possibly inflammatory labyrinthitis with fibrosis and ossification [18, 26, 35, 36].

Bone Erosion

Cholesteatoma, with or without concomitant infection, produces osseous destruction of the ossicles and temporal bone. Erosion of cholesteatoma in the mastoid cavity can progress in multiple directions. Medial erosion of the cholesteatoma from the middle ear or mastoid can lead to dehiscence of the facial nerve and semicircular canals causing facial nerve paresis or paralysis and semicircular canal fistula [7, 18]. Further medial progression of disease can result in spread of infection to the petrous apex leading to petrositis and thrombosis of petrosal sinuses. This can cause ipsilateral periorbital and facial pain, sixth-nerve palsy, and ear drainage. This collection of symptoms is referred to as Gradenigo's syndrome. If the cholesteatoma progresses anteriorly or laterally, the temporomandibular joint and external auditory canal can be damaged. If the cholesteatoma progresses posteriorly, the sigmoid sinus may be exposed, and in infectious cases of acute mastoiditis, epidural abscess and/or sigmoid sinus thrombosis can occur. If the cholesteatoma progresses superiorly, it can erode the tegmen allowing for direct extension into the middle fossa with possible encephalocele formation and cerebrospinal fluid (CSF) leakage with CSF rhinorrhea [7]. Bacterial superinfection can cause intracranial complications such as meningitis, cerebritis, epidural abscess, subdural abscess, and brain abscess [21].

Conclusion

Chronic otitis media is a complex condition that includes many interrelated sub-classifications. Management and treatment of COM can be complex, requiring an array of medical and surgical interventions. Biofilms may contribute to the destructive nature of cholesteatoma.

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Mastoiditis

6

Kenny Lin, Gul Moonis, and Lawrence R. Lustig

Introduction

Mastoid air cells develop from pneumatization of the mastoid portion of the temporal bone posterior to the auricle and are in continuity with the middle ear space via the aditus and antrum. This relationship allows extension of infection from acute otitis media (AOM) or chronic otitis media (COM) into the mastoid air cells. "Mastoiditis" is a catch-all term for any inflammation or infection of the mastoid air cells and varies widely in severity and clinical significance. Mastoiditis may be diagnosed radiographically whenever opacification of the mastoid air cells is seen, but most otolaryngologists reserve the term "mastoiditis" to indicate bacterial mastoiditis with the destruction of bony trabeculae, a condition that often requires prompt surgical drainage. This chapter will review the spectrum of mastoiditis, its presentation, evaluation, and management, and describe the extracranial and intracranial complications of mastoiditis.

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Epidemiology

As a complication of otitis media, which is a common disease of childhood, mastoiditis is most frequently seen in children. Most cases of AOM occur in children between ages 6 months and 2 years of age, with a decline in incidence after age 5 [1]. Acute otitis media in children is discussed further in Chap. 4. Acute mastoiditis is also most prevalent in very young children. The incidence of mastoiditis in a population, therefore, varies by the range of ages included; studies that include only children younger than 5, for example, will report a higher incidence than studies that include patients of all ages. Van Zuijlen et al. reported that the annual incidence of acute mastoiditis in children younger than 15, based on data from several countries in northern Europe, Australia, Canada, and the United States (U.S.) in the 1990s, varied from 1.2 cases to 4.3 cases per 100,000 children [2]. Countries with the highest rates of prescribing antibiotics for AOM had the lowest pediatric mastoiditis rates. In another review of children between 1997 and 2006, the annual incidence was reported to be 1.62 to 1.88 per 100,000 [3]. Mastoiditis may also occur in adults [4, 5]. One recent study from Italy reported an annual incidence of mastoiditis in adults of 0.99 cases per 100,000 persons [6].

The incidence of mastoiditis decreased significantly following the routine use of antibiotics for AOM beginning in the mid-twentieth century [7,

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_6

8]. In the pre-antibiotic era, nearly 50% of the AOM cases progressed to mastoiditis but this number fell to 0.4% by 1959 and 0.24% by 1993 [9–11]. The introduction of routine childhood vaccinations against *Haemophilus influenzae type b* (Hib vaccine) and *Streptococcus pneumoniae* significantly reduced the incidence of infections due to vaccine strains, but the effect on mastoiditis is less clear. Many cases of AOM and presumably mastoiditis are due to non-vaccine strains of these bacteria. There are over 80 non-typeable *H. influenzae* strains that are not covered by the Hib vaccine and account for the majority of *H. influenzae*-related AOM cases. A study from Japan found that the non-typeable *H. influenzae* strains accounted for over 90% of *H. influenzae*-related AOM episodes both before and after the introduction of the Hib vaccine [12]. The pneumococcal conjugate vaccines PCV7 and PCV13, introduced in the U.S. in 2000 and 2010 respectively, cover 7 and 13 of the most common disease-causing serotypes of *S. pneumoniae*, which has over 90 serotypes. These pneumococcal vaccines have reduced outpatient visits for AOM in children under age 2 and also decreased the incidence of recurrent AOM and chronic OM with effusion in this population [13], but the incidence of acute mastoiditis requiring admission may not have changed. Tawfik et al., using information from a large database of pediatric admissions in 44 U.S. states, reported that admissions for AOM or AOM complications declined following widespread use of pneumococcal vaccines from 4.0 to 2.6 cases per 100,000 persons between 2000 and 2012 [14]. However, acute mastoiditis accounted for 40% of these admissions in 2000 but 65% in 2012. Therefore, the admission rate for acute mastoiditis increased from 1.6 to 1.7 per 100,000 between 2000 and 2012. Choi et al., analyzing admission data from a single children's hospital for acute mastoiditis during pre-PCV7 years 1996 to 2002 and post-PCV7 (but pre-PCV13) years 2003–2009, found a 53% increase in admissions for acute mastoiditis in the post-PCV7 years [13]. *Streptococcus pneumoniae* remained the single most common pathogen in both pre-PCV7 years (34% of cases) and post-PCV7 years (34%) in that study. However, this study did not analyze whether there was a shift to non-vaccine serotypes of pneumococci in the post-PCV7 years. Other studies have found a shift to non-vaccine serotypes of pneumococci in AOM and acute mastoiditis cases, primarily to serotype 19A following the introduction of PCV7, then to other pneumococcal serotypes (e.g., 35B) following the introduction of PCV13 (which covered 19A) [15–18].

Pathogenesis

Pneumatization of the mastoid air cells begins in the first year of life with rapid growth before age 6 and reaching full size during puberty. During nearly all episodes of AOM, an effusion develops in the adjacent mastoid which may be seen on computed tomography (CT). An uncomplicated mastoid effusion is not clinically significant and does not require additional treatment beyond antibiotics for AOM. In severe or untreated ear infections, however, accumulation of pus under pressure in the mastoid may result in the destruction of the bony septae and surrounding bone, leading to a coalescent mastoid cavity or spread of the infection into the surrounding structures. Vulnerable adjacent structures include the intracranial space, sigmoid sinus, facial nerve, labyrinthine structures, and the petrous apex (Fig. 6.1). Mastoiditis may also occur in the setting of COM with chronic inflammation of the middle ear and mastoid. Cholesteatoma is an important cause of both COM and chronic mastoiditis.

Types of Mastoiditis

Acute Mastoiditis

Acute mastoiditis is characterized by local inflammatory findings over the mastoid process in the setting of AOM [19]. Within the mastoid, there is hyperemia of the mucosal lining with fluid and pus filling the air cells. Continued infection may lead to oteitis, and destruction of bony

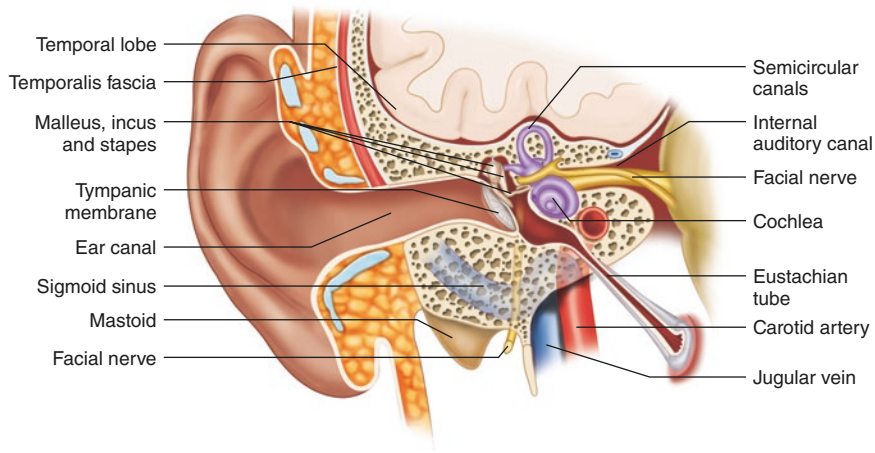

Fig. 6.1 The mastoid and surrounding structures

trabeculae may result in coalescence of the air cells. Symptoms include pain, erythema, tenderness, and swelling with auricular proptosis. Acute mastoiditis may occur when an episode of AOM fails to resolve; indeed, many clinicians require a coexistent AOM to make the diagnosis of acute mastoiditis.

Acute mastoiditis occurs mostly in children. Luntz et al. reviewed 223 admissions (1984–1998) for acute mastoiditis and found that 88% occurred in children under age 8, while only 4% occurred in adults (age 18 or older) [19]. One-third of the patients had a history of AOM (89% of these with recurrent AOM), and 5% had a prior episode of acute mastoiditis [19]. The mean duration of middle ear symptoms prior to admission was 6 days, although one-third of the patients had symptoms for <48 h [19].

The diagnosis of acute mastoiditis is made clinically based on the findings of tenderness, erythema, and/or swelling over the mastoid bone. Proptosis of the ear may result from soft tissue edema overlying the mastoid, and may also be a sign of a subperiosteal abscess. On otoscopy, one quarter of the patients in the Luntz study had a spontaneous perforation of the tympanic membrane and two-thirds had evidence of a bulging or erythematous tympanic membrane [19]. If a subperiosteal abscess or coalescence of the mastoid air cells is suspected, a CT of the temporal bones with contrast may be obtained to evaluate the extent of the disease and identify any extracranial or intracranial complications.

The microbiology of acute mastoiditis has been reported in several studies. From 30% to 40% of cases are culture-negative, and major pathogens include *S. pneumoniae* (10–43% of cases), Group A *Streptococcus* (9–18%), *Staphylococcus aureus* (9–10%), *Pseudomonas aeruginosa* (8–11%), and *H. influenzae* (3–4%) [15, 19]. The serotypes of *S. pneumoniae* causing acute mastoiditis and other invasive pneumococcal infections have varied over the years in response to the introduction of PCV7 and then PCV13 vaccines, as noted above [20–23].

The management of acute mastoiditis requires hospital admission for intravenous antibiotics. If there is evidence of pus in the middle ear with an intact tympanic membrane without coalescence of the mastoid air cells, conservative management with myringotomy or retroauricular puncture is recommended to drain the pus and obtain culture data. In most cases, formal mastoidectomy may be avoided [24]. In the study by Luntz et al., 22% of the patients had complications at the time of admission, with the most common being a subperiosteal abscess followed by intracranial complications such as meningoencephalitis or sigmoid or lateral sinus thrombosis [19]. Despite antibiotics, another 8% of the patients developed complications during their hospitalization. In the presence of coalescence or another

complication, management should include a cortical mastoidectomy to clear the infection from the mastoid cavity. In the Luntz study, 25% of the patients required a cortical mastoidectomy [19].

Coalescent Mastoiditis

Acute mastoiditis may progress to coalescent mastoiditis, which is characterized by breakdown of the bony partitions of the mastoid air cells. This ultimately results in a characteristic coalescent mastoid with a single, confluent air cell seen on imaging. Coalescent mastoiditis typically occurs 2–4 weeks after the initial symptoms of an episode of AOM. Children with well-pneumatized mastoids and no history of prior otologic disease are more likely to develop coalescent mastoiditis compared to children with COM or poorly pneumatized mastoids [25]. It has also been observed that males are more likely to have coalescent mastoiditis [25].

In the setting of coalescent mastoiditis, patients are at increased risk for extracranial and intracranial complications. Infection may spread through the mastoid cortex into the subperiosteal space resulting in a subperiosteal abscess, or may involve the surrounding vasculature causing thrombophlebitis of the sigmoid or lateral venous sinus. Bacteria may also infect the adjacent meninges, cerebellum, or temporal lobe. Bony erosion of the labyrinth or facial nerve canal may also occur. In one series, 23% of the patients with coalescent mastoiditis requiring surgery had a concomitant intracranial complication [26], with sigmoid sinus thrombosis, epidural abscess, and subdural empyema most commonly observed.

Clinically, coalescent mastoiditis is suggested by a chronology of persistent purulent ear drainage for 2 weeks or longer, or recurrence or worsening of drainage 10–14 days after a resolved episode of AOM [25]. Patients typically present with persistent high fevers, severe ear pain, and appear toxic. The diagnosis of coalescent mastoiditis requires cross sectional imaging with CT or MRI (Fig. 6.2). Computed tomography with contrast is the initial study of choice, and an MRI with contrast may be obtained if there is concern for an intracranial complication. On CT, coalescent mastoiditis is characterized by erosion of the mastoid septations and of the inner or outer cortex.

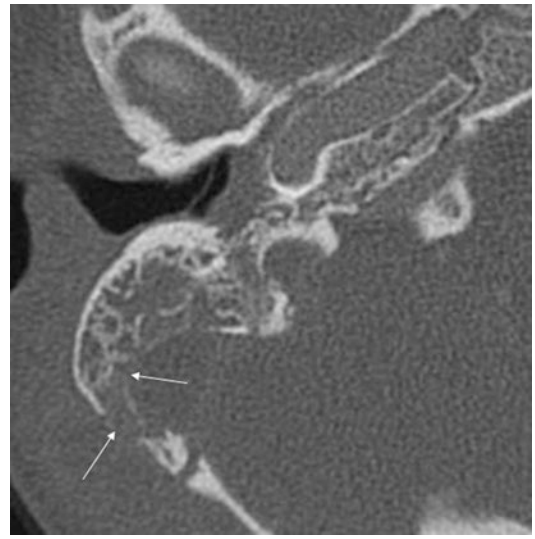

Fig. 6.2 Coalescent Mastoiditis. Computed tomography (CT) of the temporal bones in bone window demonstrates complete opacification of the right middle ear and mastoid. There are multiple regions of bone destruction along the inner and outer cortex of the mastoid (white arrow), indicating coalescent mastoiditis

The management of coalescent mastoiditis requires a course of prolonged intravenous antibiotics and surgical drainage of the infection, including a myringotomy and ventilating tube as well as a cortical mastoidectomy. Follow-up imaging may be helpful in determining resolution of the infection.

Chronic Mastoiditis

While acute mastoiditis and coalescent mastoiditis typically occur in the setting of AOM, chronic mastoiditis usually occurs in patients with COM. These patients often have a chronic perforation of the tympanic membrane with otorrhea, or develop a cholesteatoma within the middle ear and mastoid. Treatment with antibiotics fails to cure the infection and patients ultimately require surgical intervention.

Cholesteatoma is an important cause of COM and chronic mastoiditis. Cholesteatomas are

benign growths of keratinizing squamous epithelium in the middle ear or mastoid. Squamous epithelium is normally found only in the external auditory canal, but may be displaced into the middle ear as the result of chronic infections, deep retraction pockets of the tympanic membrane, or a perforation of the tympanic membrane. Over time, a cholesteatoma expands as a cystic growth with accumulation of keratin debris and mass effect on surrounding structures. While a cholesteatoma may remain uninfected for a long time, it may eventually become superinfected, leading to further bony destruction. A cholesteatoma must be treated surgically with tympanomastoidectomy.

The complications of chronic mastoiditis occur as gradual destruction of surrounding bone creates dehiscences in the tegmen, labyrinth, or Fallopian canal, which contains the mastoid portion of the facial nerve. Complications may occur at any time but typically only after weeks or months of otorrhea indicating the presence of an active infection.

Masked Mastoiditis

A patient treated for mastoiditis with resolution of overt clinical symptoms of pain, fever, and drainage may, in some cases, progress to a subclinical state of chronic inflammation. The terminology of "masked mastoiditis" was first used in the 1960s to describe this phenomenon [27–29]. This is a rare state with a normal tympanic membrane and middle ear on exam but a persistent focus of infection within the mastoid. It may manifest with chronic mild pain, and CT imaging shows a localized area of opacification in an otherwise normal mastoid system. Within this local area of chronic infection, however, there may be granulation tissue and bony erosion with latent potential for significant complications including facial palsy, venous thrombosis, and intracranial abscesses [29]. Diagnosis requires a high degree of suspicion to order imaging when patients report chronic, unexplained ear pain. The treatment of masked mastoiditis involves a tympanomastoidectomy to remove the focal area of infection.

Complications of Mastoiditis

In an infected mastoid, infection may spread laterally to the periosteum and soft tissues over the mastoid process, medially toward the petrous apex and cranium, posteriorly to the sigmoid sinus or posterior fossa, or superiorly into the middle cranial fossa. Infection may lead to bony dehiscence and involve the facial nerve, labyrinth, or tegmen. Potential complications of mastoiditis are categorized as either extracranial or intracranial (Table 6.1).

Extracranial Complications

Subperiosteal abscess. A subperiosteal abscess may result from infection extending laterally across the cortex of the mastoid bone (Fig. 6.3).

Table 6.1 Extracranial and intracranial complications of otitis media

Extracranial complications	Intracranial complications
Subperiosteal abscess	Meningitis
Bezold's abscess	Epidural abscess
Petrous apicitis	Brain abscess
Labyrinthitis	Subdural empyema
Facial nerve paralysis	Venous thrombosis
	Otitic hydrocephalus

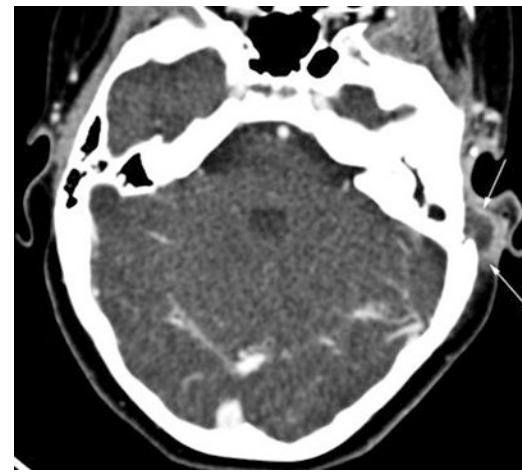

Fig. 6.3 Subperiosteal Abscess. Axial computed tomography (CT) with contrast demonstrates a collection adjacent to the left mastoid compatible with a subperiosteal abscess (arrows)

The most common location is in the postauricular region directly over the mastoid tip superior to the insertion of the sternocleidomastoid muscle. Much less commonly, an abscess may form above and anterior to the ear over the temporal root of the zygoma. A typical subperiosteal abscess presents with swelling, pain, erythema, and fluctuance over the mastoid. The abscess is typically high over the mastoid tip where pneumatization occurs first in children. This results in the characteristic downward proptosis of the affected ear. Infants are particularly susceptible because a developing temporal bone has direct channels between the mastoid cavity and the cortex. Historically, acute mastoiditis was complicated by subperiosteal abscesses in 20% of the cases [30]. Treatment consists of prolonged intravenous antibiotics, drainage of the subperiosteal abscess, and myringotomy to treat the underlying mastoid infection. Mastoidectomy may be added, but may be reserved for the small minority of cases that do not respond to more conservative treatment [24, 31, 32].

Bezold's abscess. A Bezold's abscess is a deep neck abscess secondary to mastoiditis that is usually located beneath the attachment of the sternocleidomastoid muscle (Fig. 6.4). It was first described by Dr. Friedrich Bezold in 1881. Infection in the mastoid may escape medially through the mastoid tip, through the incisura digastrica, and into the deep neck space. In the neck, the infection may then spread along the fascia of the sternocleidomastoid muscle or carotid sheath, with potential extension to the parapharyngeal and retropharyngeal deep neck spaces. True Bezold's abscesses are more common in older children and adults who have pneumatized air cells in the mastoid tip. In the antibiotic era, Bezold's abscess is extremely rare with only 35 cases reported in a review from 2001 [9, 33]. Treatment requires drainage of the abscess, intravenous antibiotics, and management of the mastoid disease with care taken to identify and preserve the facial nerve as the mastoid tip is approached.

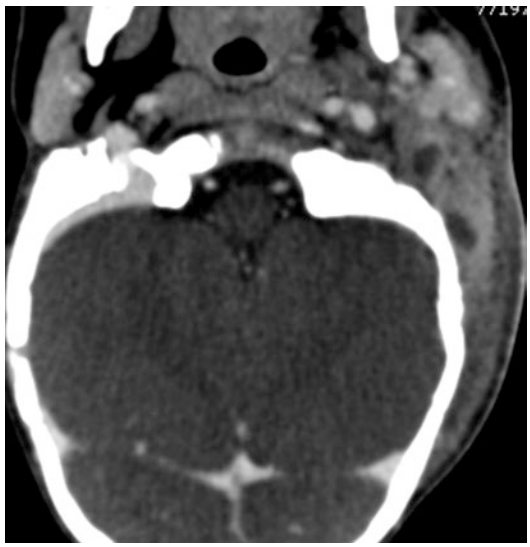

Fig. 6.4 Bezold Abscess. Axial computed tomography (CT) with contrast demonstrates a rim enhancing low density fluid collection lateral and anterior to the mastoid tip on the left representing a bezold abscess

Petrous apicitis. Petrous apicitis, or petrositis, is another rare complication of mastoiditis that results when infection spreads into petrous apex air cells via pneumatized air cell tracts or thrombophlebitis. The petrous apex is the portion of the temporal bone medial to the labyrinth and may be solid bone, marrow-filled, or pneumatized. It has been postulated that petrositis can only occur in a pneumatized bone, which is observed in 9–30% of ears [25]. Patients typically present with fever, otorrhea, and deep mastoid or retro-orbital pain. Further symptoms may be predicted based on the proximity of the petrous apex to the dura, trigeminal ganglion, cavernous sinus, and abducens nerve. In the largest series of petrous apicitis to date, Gadre and Chole reviewed 44 cases treated at a single institution, 1971–2011 [34]. The mean age at the presentation was 39 years, and 89% of the patients were adults. The presenting symptoms included facial pain and otitis in 84% of the cases, while fever was present in only 18%. Retro-orbital pain was present in 55%, otitis media with (36%) and without (25%) otorrhea in 61%, and abducens palsy in 16%. In 1905, Gradenigo described a clinical triad of deep facial pain, otitis media, and ipsilateral abducens nerve palsy, but this "Gradenigo's syndrome" is seen in only a small subset of patients with petrositis [11]. In the report by Gadre and Chole, only 13% of the cases exhibited the complete triad. CT imaging usually dem-

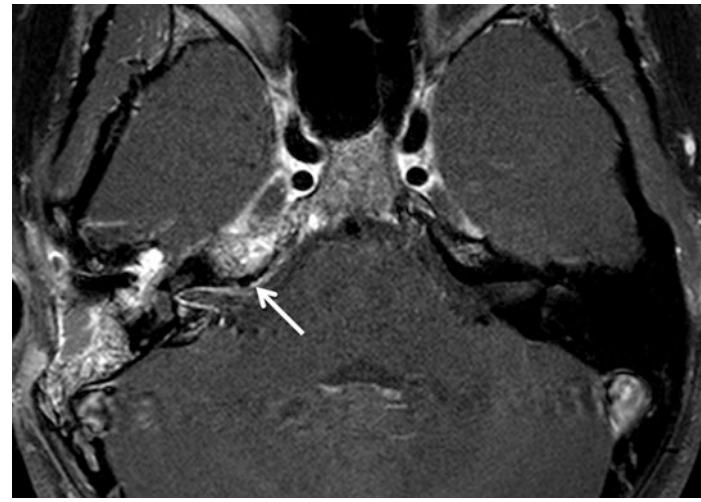

Fig. 6.5 Petrous Apicitis. Post-contrast magnetic resonance imaging (MRI) demonstrates dural enhancement surrounding the right petrous apex and extending into the internal auditory canal (arrow)

onstrates an opacified petrous apex on the involved side with or without bony destruction. However, it is important to note that asymmetric pneumatization may occur as a normal anatomic variant. An MRI scan with contrast will help differentiate petrositis from other petrous apex pathology and MRI findings are characterized by T1 hypointensity, T2 hyperintensity, and enhancement of the petrous apex extending to the adjacent dura [35] (Fig. 6.5).

The primary treatment is antibiotic therapy, but surgery is required in some cases. Gadre and Chole found that the incidence of surgery for petrositis decreased from 50% to 12.6% over the 40-year period studied [34]. *Pseudomonas aeruginosa* is the major pathogen and empiric antibiotics should include coverage for this organism as well as additional potential pathogens such as *S. aureus*. Of 15 patients with positive cultures in Gadre and Chole's series, the pathogens were *Pseudomonas* alone (10 cases), *Pseudomonas* plus *S. aureus* [2], *S. aureus* alone [2], *S. pneumoniae* [1], *Propionibacterium* species [1], and *Prevotella* [1]. Antibiotic treatment is usually continued for 6 weeks or more. For cases that require surgery, surgical access is challenging and must be tailored to the individual based upon the specific anatomy and location of the infection.

Bacterial labyrinthitis. Bacterial labyrinthitis is a rare but devastating complication of otitis media and mastoiditis which results from infection of the perilymphatic fluid, either via the round or oval window, or through a labyrinthine fistula [36]. Irritation and inflammation of the labyrinth causes nystagmus toward the infected ear with associated vertigo, tinnitus, nausea, and vomiting. The incidence of labyrinthitis following mastoiditis is low. In one pediatric series, labyrinthitis complicated 1 (0.4%) of 223 cases of acute mastoiditis [19]. In another series involving 62 adults with acute mastoiditis, labyrinthitis was reported in 13%, but it is unclear if all were cases of bacterial labyrinthitis [6].

Risk factors for bacterial labyrinthitis include congenital anatomic defects such as Mondini's malformation or enlarged vestibular aqueduct, as well as bony erosion from COM or cholesteatoma. In a series of 14 cases of suppurative labyrinthitis seen at a center in Brazil over 26 years, five cases also had mastoiditis, five had meningitis, and six had a labyrinthine fistula [37].

Labyrinthitis may be serous or suppurative. While hearing and vestibular function may recover in serous labyrinthitis after treatment with antibiotics and corticosteroids, patients with acute suppurative labyrinthitis have a much worse outcome. Suppuration irreversibly damages the inner ear resulting in sudden profound sensorineural hearing loss and severe vertigo. Vestibular compensation typically occurs after several weeks, but hearing in the affected ear

does not usually recover. Maranhao et al. reported that 57% of the patients in their series with acute bacterial labyrinthitis became deaf and the remainder developed a mixed hearing loss [37]. A further concern with suppurative labyrinthitis is the development of meningitis because the perilymph is directly continuous with the cerebrospinal fluid via the cochlear aqueduct.

Vertigo in a patient with an infected ear is an ominous finding. Acute treatments include intravenous antibiotics and vestibular suppressants. Patients should be quickly evaluated following bacterial labyrinthitis for candidacy for cochlear implantation since ossification of the labyrinth (termed labyrinthitis ossificans) is a potential sequela of this infection that, once begun, significantly impairs the ability to implant an electrode array into the cochlea.

Facial paresis. Facial paresis may occur in the setting of AOM and acute mastoiditis. Edema and inflammation results in reversible nerve injury but may be irreversible if prolonged. Although there are no conclusive studies, it is believed that the facial nerve is dehiscent in most cases of AOM with facial paresis. Cadaveric studies have found dehiscence in up to 70% of normal ears [38]. Facial paresis is typically incomplete and resolves once the infection is cleared. Less commonly, facial paresis presents as a complication of COM with cholesteatoma, and is due to either direct compression on the nerve, and/or inflammation of the nerve within the Fallopian canal. Temporal bone CT may identify the affected segment and electromyography (EMG) can help predict prognosis. Treatment involves intravenous antibiotics, systemic steroids, and myringotomy. Adequate treatment of the infectious process typically reverses the facial paresis. Surgical decompression of the facial nerve is rarely indicated [39]. Cholesteatoma must be resected through a tympanomastoidectomy.

Intracranial Complications

Intracranial complications of AOM and mastoiditis are rare but potentially devastating. They include meningitis, epidural abscess, brain abscess, subdural empyema, and sigmoid sinus thrombophlebitis. In the pre-antibiotic era, intracranial complications occurred in 2.3% of the cases of AOM with highest risk during childhood and adolescence [30]. Kangsanarak et al. reported that 0.24% of 17,144 cases of "suppurative otitis media" seen between 1983 and 1990 had intracranial complications [9]. Go et al. reported that 8 (6.8%) of 118 children admitted with acute mastoiditis 1986–1998 had intracranial complications [40]. Epidural abscess occurred in four patients (50%), meningitis in one (13%), and sigmoid sinus thrombosis alone in three (38%), although two of the epidural abscess cases and the case of meningitis also had sigmoid sinus thrombosis. Leskinen et al. reported nine intracranial complications in adults and found that four (44%) had meningitis, four (44%) had intracranial abscess, and one (11%) had sinus thrombosis [41]. In another series of 33 patients with intracranial complications, 19 out of 33 patients had multiple intracranial complications with brain abscess and meningitis being the most common [42]. Luntz et al. reported intracranial complications in 19 of 223 patients (8.5%) with acute mastoiditis, with three of these complications developing after admission [19]. Nearly one-third of the intracranial complications in this series were due to meningitis.

Meningitis. Despite advances in therapy, bacterial meningitis continues to have a significant rate of mortality and morbidity (21% mortality in adults) [43]. Otogenic meningitis is rare and may occur more often after COM than AOM [42, 44]. Meningitis is an important intracranial complication of mastoiditis, and infection may spread by several potential routes: direct extension through bone eroded by inflammation, through the cochlear round window and cochlear aqueduct, or by thrombophlebitic spread [45]. Any communication between the middle ear and CSF is a risk factor. Such communications may be due to congenital anatomic defects or iatrogenic disruptions to the tegmen mastoideum. Patients with meningitis typically present with fever, headache, and photophobia; meningeal signs (e.g., nuchal rigidity) may be present. Diagnosis and treatment is a medical emergency, and broad-spectrum intrave-

nous antibiotics with CSF penetration most be started promptly. Adjunctive therapy with dexamethasone is beneficial for pneumococcal meningitis so this agent is started empirically until culture results are known [46]. Pneumococcal meningitis is particularly morbid, and one-third of survivors suffer permanent neurologic sequelae such as deafness, behavioral disorders, and cognitive dysfunction [47]. Introduction of the Hib vaccines reduced the incidence of Hib meningitis by 99% between 1987 and 1999 [48]. The introduction of PCV7 significantly reduced the rate of pneumococcal meningitis in children, particularly those under age 2, although the switch to PCV13 did not reduce this rate further [49].

Epidural abscess. An epidural abscess may form between the temporal bone and dura as a result of coalescent mastoiditis, chronic mastoiditis, or cholesteatoma (Fig. 6.6). Focal neurologic deficits are not seen until an abscess is large, and there is a high risk of developing meningitis, brain abscess, or lateral sinus thrombophlebitis [50]. Patients may present insidiously with several days of fever, altered mental status, and neck pain. Focal neurologic deficits are not usually observed until the abscess grows to a large size. Larger abscesses appear on imaging as a rim-enhancing epidural fluid collection with dural thickening. Magnetic resonance imaging with gadolinium is more sensitive than CT with contrast for small suppurative lesions. A high index of suspicion is required to diagnose epidural granulation tissue and the tegmen should be closely examined when performing mastoidectomy for chronic mastoiditis or cholesteatoma. Treatment is with intravenous antibiotics and surgical drainage of the abscess, typically through a cortical mastoidectomy approach.

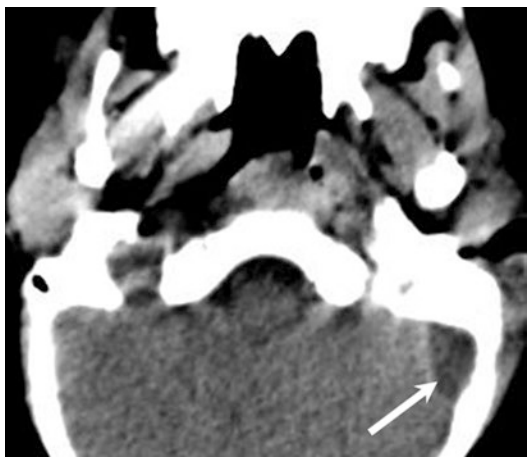

Fig. 6.6 Epidural Abscess. Axial computed tomography (CT) with contrast demonstrates a lenticular low density fluid collection on the left adjacent to opacified left mastoid air cells

Brain abscess. In many series, brain abscesses are the second most common intracranial complication of mastoiditis following meningitis [42, 44]. Cholesteatoma is responsible for 75% of otogenic abscesses [51, 52]. Spread typically occurs via venous thrombophlebitis. Brain abscesses secondary to otitis are most common in the temporal lobe and cerebellum [51, 53, 54]. Symptoms include fever, headache, focal neurologic symptoms, and altered mental status. Involvement of the temporal lobe may cause seizures and hemiparesis. Cerebellar lesions cause vertigo, nystagmus, ataxia, and dysmetria. Two-thirds of patients with otogenic brain abscesses will also have other intracranial complications such as meningitis, sigmoid sinus thrombosis, epidural abscess, or facial nerve paralysis [52]. Magnetic resonance imaging with contrast is diagnostic. Unless the abscess is small, surgical drainage is required in addition to intravenous antibiotics. The timing of surgical drainage of the abscess and otologic surgery to treat mastoiditis is controversial. Some authors recommend delaying otologic surgery days to weeks after intracranial surgery, while others argue that both the sites of infection can be addressed at the same time [9, 53, 55]. Cultures from otogenic brain abscesses typically yield mixed flora that includes some combination of streptococci, Gram-negative bacilli, and anaerobes [51, 53, 54, 56].

Subdural empyema. Subdural empyemas are rare suppurative collections between the dura and pia-arachnoid membrane. Bacteria are seeded by venous channels or infected adjacent tissue. The most common causes are sinusitis, mastoiditis, and meningitis [57]. A subdural empyema is a neurosurgical emergency: thrombophlebitis of cortical veins leads to swelling, necrosis, and infarction of adjacent cortical

brain. In addition to fever, headache, nuchal rigidity, and loss of consciousness, neurologic findings depend on the affected area but may include motor weakness, aphasia, seizures, and papilledema. Imaging shows a crescent-shaped collection with enhancement of adjacent cortex. Lumbar puncture should not be performed because of increased intracranial pressure. Immediate neurosurgical evacuation of the empyema is indicated with survival rates directly related to the level of consciousness at the time of surgery. The underlying pathology should be treated after neurologic stabilization.

Sigmoid sinus thrombophlebitis. The sigmoid sinus may become infected in the setting of mastoiditis as it passes just posterior to the mastoid cavity. Inflammation of the vessel wall leads to thrombophlebitis and a mural thrombus. Occlusion of venous outflow from the brain may then result in increased intracranial pressure. This phenomenon is termed otitic hydrocephalus and the severity depends on the adequacy of collaterals. Moreover, an enlarging thrombus may propagate forward into the jugular vein or retrograde into the transverse and superior sagittal sinuses. Retrograde thrombophlebitis may result in intracranial hypertension, brain abscess, and infarction. Septic pulmonary emboli may occur. Patients typically present with high fevers, headaches, and neurologic symptoms such as cranial neuropathies and signs of elevated intracranial pressure. Ear pain and drainage may be mild [58]. Computed tomography imaging with contrast reveals mastoiditis with peri-sinus enhancement; a filling defect in the sigmoid sinus may be evident (Fig. 6.7). Magnetic resonance angiography is helpful to determine the extent of the thrombus and adequacy of collateral circulation [59]. Treatment includes intravenous antibiotics, myringotomy tube placement, and mastoidectomy [58]. The venous thrombus is generally managed conservatively, though some authors advocate anticoagulation, surgical thrombectomy, or ligation of the jugular vein [60]. However, there is no evidence that any of these interventions reduces recovery time or promotes recanalization [61]. Thrombolytics are not generally recommended.

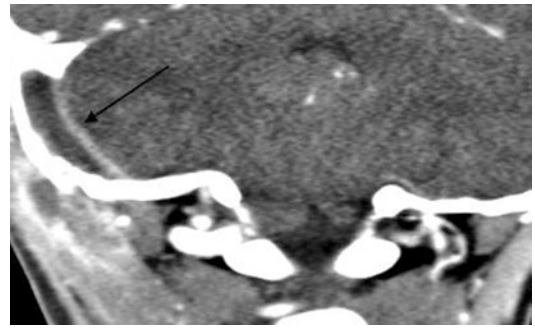

Fig. 6.7 Sigmoid sinus thrombophlebitis. Coronal computed tomography (CT) scan with contrast shows a filling defect in the right sigmoid sinus representing thrombophlebitis. There is also a bezold abscess inferior to the right mastoid

Conclusion

Mastoiditis was common in the pre-antibiotic era but is now rare. Nevertheless, mastoiditis remains an important clinical entity in both children and adults and requires prompt diagnosis and treatment to avoid potentially devastating complications. The extracranial and intracranial complications of mastoiditis may be understood by considering the anatomy of the temporal bone and lateral skull base and considering the potential pathways of spread.

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Inner Ear Infections (Labyrinthitis)

7

Nicholas A. Dewyer, Ruwan Kiringoda, and Michael J. McKenna

Introduction

Infection of the inner ear, or labyrinthitis, can be caused by a variety of pathogens. The diagnosis is clinical and based on the findings of and/or vertigo in the setting of a current or recent infection, particularly otitis media or meningitis. Physical exam findings are largely determined by the underlying cause of the infection; findings that specifically suggest involvement of the inner ear are spontaneous nystagmus and sensorineural hearing loss. It should be determined whether the causative agent is bacterial or viral so that appropriate treatment may be administered. Audiometric testing should be obtained at presentation and resolution of the infection. Laboratory tests such as white blood cell count and differential, C-reactive protein, erythrocyte sedimentation rate, and lumbar puncture with cerebrospinal fluid (CSF) analysis are unreliable as indicators of labyrinthitis, though these may be abnormal in cases of severe infection. Imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is not required to diagnose labyrinthitis, but is often performed to evaluate the extent of the underlying infection. Imaging findings that support a clinical diagnosis of labyrinthitis may be bony erosion through the otic capsule on CT, or enhancement of labyrinthine structures on MRI with contrast.

The treatment of labyrinthitis depends on the etiology. In general, once an infection has reached the inner ear, aggressive treatment is warranted to try to prevent permanent and complete loss of cochleovestibular function and spread to intracranial structures. Treatment consists of anti-infective and anti-inflammatory medications, surgical drainage of abscesses, and supportive care for associated symptoms such as vertigo, nausea, vomiting, dehydration, and pain. Acute suppurative labyrinthitis can progress to intracranial infectious complications and requires prompt treatment. The inner ear is exquisitely sensitive to insults such as infection, and in many cases the patient is left with permanent hearing loss and vestibular dysfunction following an inner ear infection.

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_7

Anatomy

The inner ear, or labyrinth, is contained within the dense otic capsule of the temporal bone, and consists mainly of the cochlear and vestibular systems with their corresponding sensory organs for detecting sound and movement, respectively. The cochlea, vestibule, semicircular canals, and intracranial subarachnoid space are in continuity, with CSF flowing from the subarachnoid space through the cochlear aqueduct to the labyrinth. The oval and round windows are interfaces between the inner and middle ears, and allow for sound pressure to be transduced to electrical signals in the cochlea. The oval window contains the stapes footplate, a thin bone surrounded by ligament, and the round window is membranous. Normal labyrinthine anatomy and histology is shown in Fig. 7.1.

Pathophysiology of Labyrinthitis

The structure of the inner ear, lying deep within the temporal bone and surrounded by dense otic capsule bone, renders it relatively well protected from infection. When infection does occur, routes of entry for the infectious agents are typically direct spread from the middle ear, via the oval or round window, or through CSF. Less frequently, infection may enter through erosion of the otic capsule bone from chronic otitis media with cholesteatoma.

The auditory and vestibular sensory organs contained in the inner ear are exquisitely sensitive to insults such as infection and trauma. Inflammation of the inner ear, or labyrinthitis, typically manifests with symptoms of hearing loss and dizziness. The severity of these symptoms is

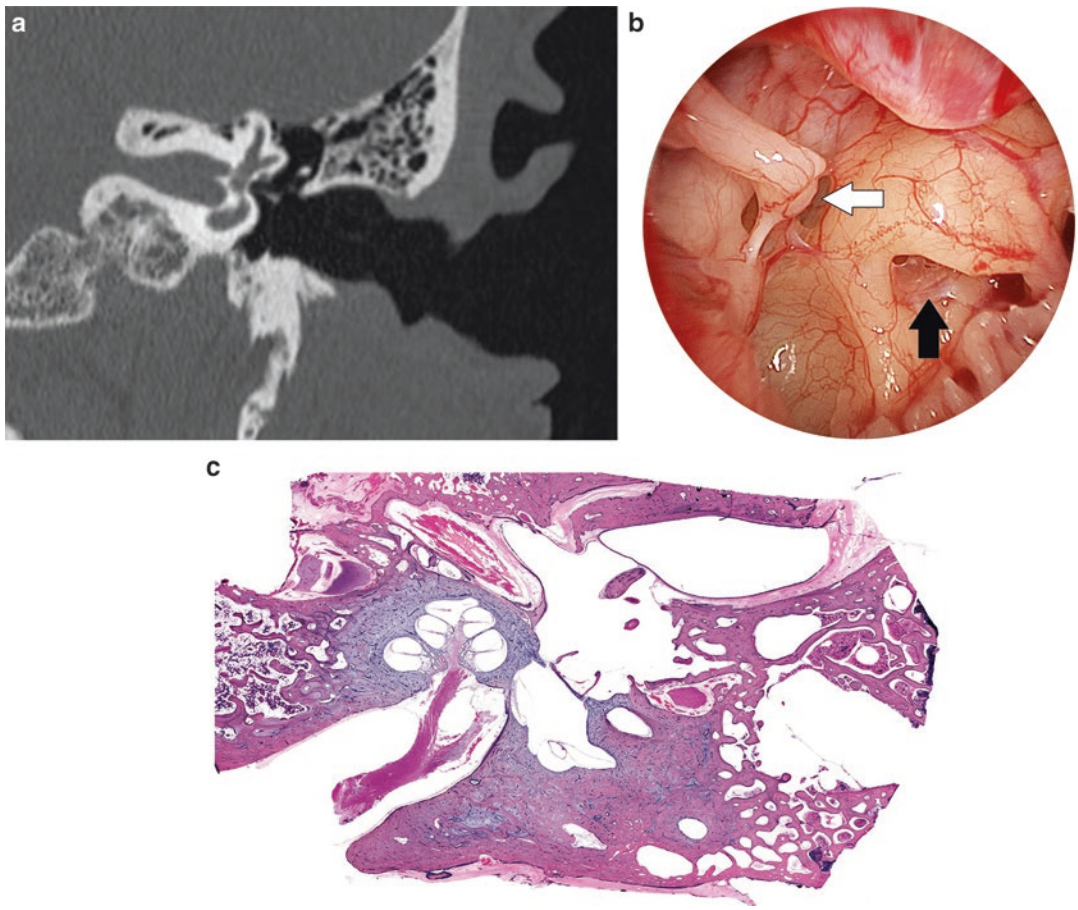

Fig. 7.1 (**a**) CT image in the coronal plane of a normal temporal bone. (**b**) Endoscopic image of the middle ear showing the oval (white arrow) and round (black arrow) windows (Image courtesy of Daniel J. Lee, MD. Unpublished) (**c**) Histopathologic section of a normal cochlea. (Image courtesy of Massachusetts Eye and Ear Temporal Bone Laboratory. Unpublished)

variable, but they often are severe and leave the patient with permanent cochleovestibular dysfunction. Otogenic labyrinthitis may spread to the intracranial space and cause meningoencephalitis, septic thrombophlebitis, and abscesses.

We will discuss specific presentations of infectious labyrinthitis using a classification scheme based on the pathogenesis and clinical presentations of disease.

Bacterial Infections

Serous Labyrinthitis

Serous labyrinthitis is a sterile inflammation within the labyrinth. It is presumed to occur when bacterial toxins or host inflammatory mediators enter the labyrinth, without direct spread of bacteria into the inner ear. This process is not well characterized, but animal studies have demonstrated that pneumococcal proteins applied to the middle ear space result in inflammation and hair cell damage in the inner ear [1–4]. Serous labyrinthitis typically occurs in the context of acute or chronic otitis media (see Chap. 6). In this situation, it is thought that otitis media generates toxins and inflammatory mediators, which then cross the round and oval windows or, rarely, a labyrinthine fistula to reach the inner ear [5]. Although acute otitis media is very common, serous labyrinthitis is rare, reported as complicating <1% of cases of acute otitis media [6, 7]. Serous labyrinthitis can also occur in the setting of meningitis, in which case it may not be noticed due to the more severe symptoms of meningitis.

In serous labyrinthitis, patients suffer SNHL and vestibular symptoms of variable severity. Mild cases may return to normal function following treatment. Severe cases may be lethal to the sensory cells and cause permanent hearing loss and vestibular dysfunction (Fig. 7.2). In the acute period, serous and suppurative bacterial labyrinthitis cannot be differentiated. A diagnosis of serous labyrinthitis is presumed retrospectively if there is some recovery of auditory and vestibular function.

Treatment requires drainage of the middle ear effusion by myringotomy if a tympanic membrane perforation has not already occurred. A tympanostomy tube may be placed, which ensures that a drainage and ventilation route remains patent. This tube also facilitates delivery of antibiotic and corticosteroid ear drops to the middle ear space. Systemic broad spectrum antibiotics with CSF penetration should be used initially, and then narrowed based on culture and sensitivity results. This is because even though serous labyrinthitis is sterile, the condition cannot be differentiated from suppurative (bacterial) labyrinthitis. Systemic corticosteroids should be used in an attempt to decrease damage to the audiovestibular sense organs and reduce subsequent labyrinthitis ossificans [8, 9]. Vestibular symptoms are treated symptomatically.

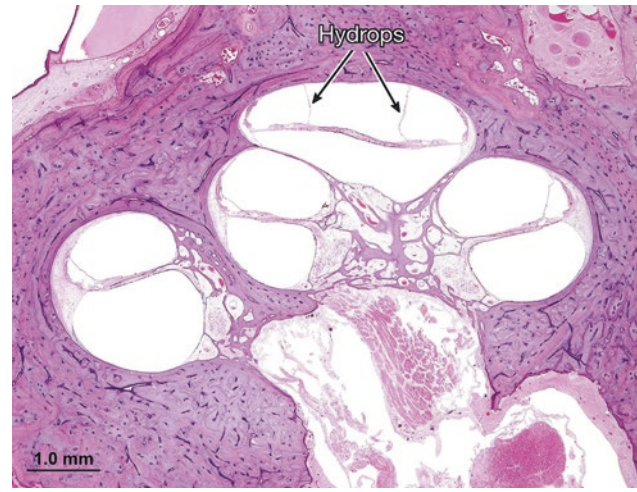

Fig. 7.2 Histopathology of a patient with serous labyrinthitis. (Image courtesy of Massachusetts Eye and Ear Temporal Bone Laboratory. Unpublished)

Otogenic Suppurative Labyrinthitis

Otogenic suppurative labyrinthitis is caused by contiguous spread of bacterial infection into the inner ear from surrounding spaces in the temporal bone, most frequently the middle ear. The most common situation is for cholesteatoma in the middle ear to erode through the otic capsule bone overlying the horizontal semicircular canal, producing a pathway for direct bacterial spread into the labyrinth (Fig. 7.3). Suppurative labyrinthitis tends to cause severe hearing loss and vertigo with permanent auditory and vestibular function loss. After the infection resolves, the labyrinth fills with fibrous and bony tissue, a process called labyrinthitis ossificans (Fig. 7.4). If left untreated, otogenic suppurative labyrinthitis frequently leads to intracranial complications.

Diagnosis and treatment are similar for suppurative and serous labyrinthitis, with the exception of surgical approaches. Empiric broad-spectrum antibiotics should be started as soon as the diagnosis of acute suppurative labyrinthitis is suspected. Most otogenic suppurative labyrinthitis results from cholesteatoma, and surgical removal of the cholesteatoma is critical for definitively treating the inner and middle ear infections. Myringotomy with or without tympanostomy tube should still be performed promptly to drain the middle ear effusion and allow antibiotic and corticosteroid ear drops to reach the middle ear space. Tympanomastoidectomy with the removal of cholesteatoma should occur urgently to prevent intracranial spread of the infection. If cochlear implantation is a possibility, early implantation, before labyrinthitis ossificans begins to ablate the cochlear lumen, should be considered [10].

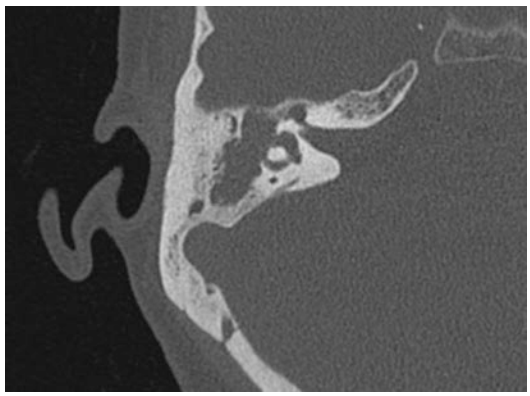

Fig. 7.3 CT image in the axial plane showing chronic otitis media with cholesteatoma that has eroded into the horizontal semicircular canal. The labyrinthine fistula is a route of bacterial spread from the middle ear to the inner ear

Meningogenic Suppurative Labyrinthitis

Sensorineural hearing loss is a common sequela of bacterial meningitis. There is a higher incidence of SNHL following pneumococcal than meningococcal meningitis (14–69% versus 3–40%, respectively) [11]. The route of spread seems to be through the cochlear aqueduct and internal auditory canal, based on post-mortem temporal bone histopathology [12]. Meningitis can result in partial or complete fibro-ossification of the bilateral cochleae and vestibular systems. Aside from pneumococcal meningitis, the protective effects of administering adjuvant corticosteroids in acute bacterial meningitis are unknown. A Cochrane Review reviewed 25 studies (4 high quality, 14 intermediate quality, 7 low quality) and concluded that the high quality studies found no benefit of corticosteroids in reducing the incidence of severe hearing loss [8]. A small retrospective study (ten pediatric patients) undergoing cochlear implantation for SNHL occurring after meningitis (pneumococcal in 9) concluded that corticosteroids may prevent the development of labyrinthitis ossificans [9]. Early bilateral cochlear implantation should be considered in cases with bilateral profound sensorineural hearing loss [10].

Viral Labyrinthitis

A broad group of viruses are known to affect the inner ear. Viral infections of the inner ear may affect the labyrinthine organs or their peripheral nerves. In addition to the clinical presentations listed below, there are clearly many acute disorders of the inner ear that are characterized by sudden hearing loss and/or vertigo, such as sudden idiopathic sensorineural hearing loss, laby-

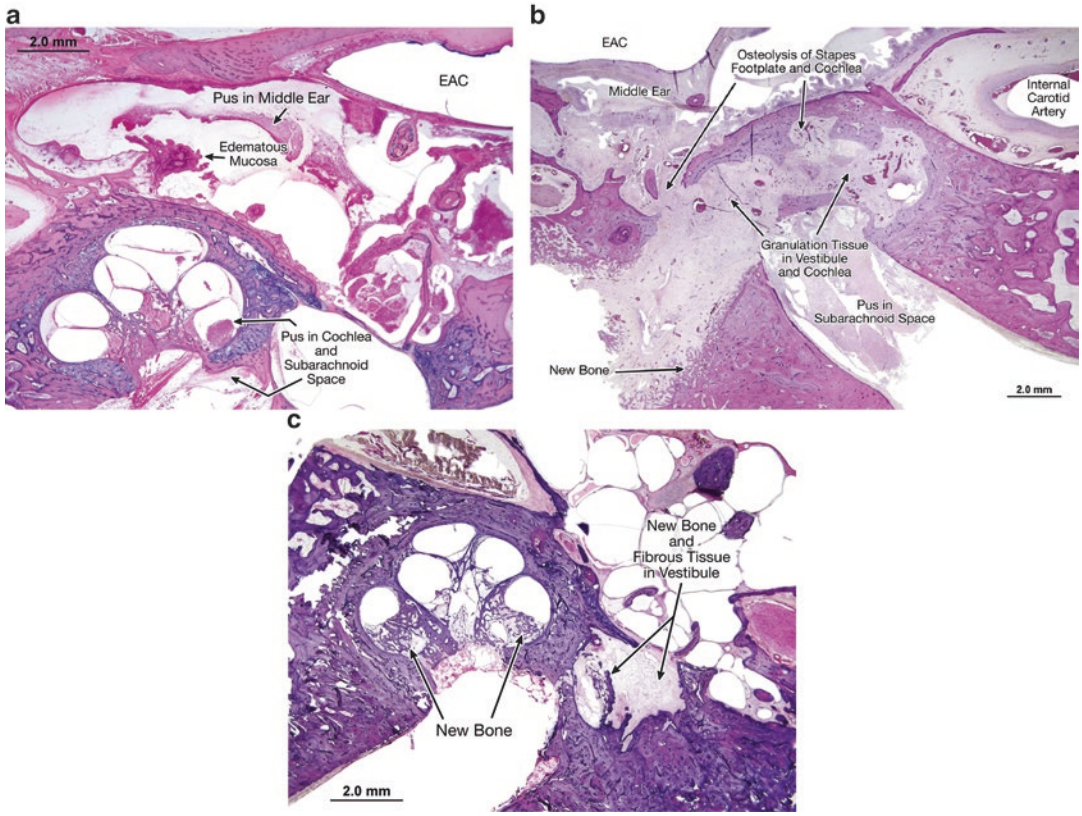

Fig. 7.4 Histopathology of patients with suppurative labyrinthitis and the resulting labyrinthitis ossificans (All images courtesy of Massachusetts Eye and Ear Temporal Bone Laboratory. Unpublished). (**a**) Image shows active otogenic suppurative labyrinthitis. (**b**) Section from a patient with chronic suppurative otitis media and mastoiditis. He died of spread to an epidural abscess and purulent meningitis. (**c**) Image shows labyrinthitis ossificans many years after a patient suffered hearing loss from a febrile illness

rinthitis, or vestibular neuritis, that are attributed to viral causes but lack definitive pathologic or clinical evidence.

Herpes Zoster Oticus (Ramsay Hunt Syndrome)

Herpes zoster is caused by the varicella zoster virus (VZV) that also causes chickenpox and shingles. The virus remains latent in the central nervous system and possibly the geniculate ganglia. Reactivation often occurs years later in settings of biologic stress or immunosuppression. When reactivation occurs in nerves that innervate the ear, this is termed herpes zoster oticus (also called Ramsay Hunt syndrome).

Frequently, the first symptom is burning pain in the region of the ear. This is followed by a vesicular eruption of the external auditory canal and concha, and sometimes surrounding dermatomes. Facial paralysis, hearing loss, and vertigo may occur after the onset of pain, and before or after vesicular eruption. Other cranial neuropathies may also develop. Diagnosis is made clinically and may be confirmed by testing scrapings of the base of the vesicular lesions for the presence of VZV.

About half of the patients with herpes zoster oticus retain some permanent facial motor disturbance and a few have permanent complete paralysis [13]. Prognosis is poorer for patients with complete paralysis, age over 50, or incomplete eye closure with a dry eye [14–16]. For hearing loss, some recovery is expected with resolution of the infection; however, with severe losses the

recovery is rarely complete [17]. Studies suggest that early treatment with an antiviral medication (e.g., acyclovir or valacyclovir) and corticosteroids improves the outcome of facial paralysis, though high-quality evidence is lacking [18]. Consultation with an ophthalmologist should be pursued if there is any concern about ocular involvement. Surgical decompression of the facial nerve for facial paralysis in this setting is not indicated.

Congenital Cytomegalovirus (CMV)

Cytomegalovirus is a DNA virus that belongs to the Herpesviridae family. Congenital CMV produces symptomatic infection at birth (e.g., petechiae, hepatomegaly, splenomegaly, hepatitis, chorioretinitis, central nervous system abnormalities) in a minority of infected infants. Asymptomatic congenital CMV presents without any of the above findings, but may include undetected SNHL. Some children may have normal hearing at birth but suffer progressive hearing loss. Importantly, the risk of SNHL from congenital CMV is decreased with early antiviral therapy, so high awareness and vigilance by clinicians is critical.

Congenital CMV infection is the most common cause of non-syndromic SNHL in children. Cytomegalovirus affects approximately 0.6% of live births in developed countries, and 85–90% of congenital CMV infections are asymptomatic at birth [19]. However, approximately one-third of infants born with symptomatic CMV and 6–25% of infants with asymptomatic CMV will develop SNHL [19, 20]. The onset of hearing loss may be delayed. A recent meta-analysis estimates the prevalence of hearing loss due to CMV as approximately 20% in children with hearing loss of unknown origin [19].

There is no pathognomonic pattern of SNHL from CMV. It may be unilateral or bilateral, with variable frequency, severity, and progression characteristics. Sixty percent of children with CMV-related hearing loss will have passed their newborn hearing screening, and hearing loss may present at any time from birth up to 9 years of age [20, 21]. The exact mechanism of CMV-induced hearing loss is not known, but inflammation of the labyrinth in response to the infection appears to play some role [22].

Congenital CMV is diagnosed by testing urine or saliva for CMV in the very early neonatal period. Polymerase chain reaction (PCR) and viral cultures are the test methods used. After 2–3 weeks, postnatal and congenital CMV cannot be distinguished based on saliva or urine samples, so diagnosis is based on retrospective testing of a dried blood spot sample drawn within the first week of life. Sensitivity and specificity of urine or saliva PCR is reported at >97% [23]. Dried blood spot testing has poor sensitivity (34%) but excellent specificity (99.9%) [24].

A randomized, controlled trial published in 2003 evaluated the effect of 6 weeks of ganciclovir, an intravenous antiviral agent, on change in audiometric thresholds in neonates with symptomatic CMV involving the central nervous system [25]. This trial demonstrated that treatment with ganciclovir significantly improved or stabilized hearing at 6 months compared with controls. However, almost two-thirds of the infants treated with ganciclovir developed significant neutropenia (all reversible on cessation of the drug). A more recent randomized prospective trial (published 2015) compared audiometric and neurodevelopmental outcomes in neonates with symptomatic congenital CMV who received 6 weeks versus 6 months of oral valganciclovir [26]. Valganciclovir is a prodrug of ganciclovir. The longer administration led to modestly better hearing and neurodevelopmental test scores at 24 months [26]. At 24 months, hearing remained normal or was improved in 77% of the 6-month group versus 64% of the 6-week group. Approximately 20% of the infants developed grade 3 or 4 neutropenia during the first 6 weeks of the trial (when both the groups received valganciclovir), but only 3% required a temporary cessation of the drug. The incidence of neutropenia during the remaining 4.5 months of the trial was similar between the two groups, and no child required temporary cessation of the drug. Treatment of congenital

CMV with valganciclovir is currently limited to infants born with symptomatic congenital CMV as no prospective trial has evaluated the efficacy or safety of this medication in infants whose only manifestation is SNHL.

Measles (Rubeola)

Measles is caused by a paramyxovirus and is highly contagious. A live virus vaccine against measles was licensed in the U.S. in 1963, and since then the disease has become very rare in the U.S. However, measles still occurs in unvaccinated populations worldwide (36 cases per million population annually). Of infected patients, 0.1% develop acute encephalitis and 0.2% die from respiratory or neurologic complications [27]. Measles has been implicated as a cause of bilateral moderate to profound loss of auditory and vestibular function [17, 28]. Persistent measles virus within the otic capsule has been proposed as a cause of otosclerosis, supported by findings of viral-like particles and measles virus gene products in active otosclerotic lesions [29–37].

Mumps

Mumps is a highly contagious viral illness that is discussed in depth in Chap. 23. Mumps may cause meningoencephalitis and/or SNHL. The hearing loss tends to be unilateral and of variable severity. Vestibular symptoms are also frequently present.

Maternal Rubella

Rubella infection during pregnancy can result in significant teratogenic effects to the fetus, with SNHL being the most common manifestation [38–40]. The pattern of hearing loss tends to be flat (i.e., pure tone thresholds are elevated to a similar degree at all frequencies) and considerably different between the two ears [41]. The mechanism of hearing loss seems to be from both direct cytopathogenic effects from virus-induced apoptosis and inhibition of cell division [40]. The characteristic otopathologic finding is cochleosaccular dysplasia [17]. Treatment is similar to other forms of sensorineural hearing loss, with listening strategies, amplification, and cochlear implantation as indicated.

Infectious Causes of Facial Paralysis

Although the facial nerve is not properly part of the inner ear, it does pass through the temporal bone in close proximity to the cochlea and labyrinth. Infectious causes of facial paralysis without suppuration are discussed here. For a discussion of facial paralysis with otitis media or mastoiditis, see Chap. 6.

Herpes Simplex Type 1

The cause of idiopathic facial palsy, or Bell's palsy, is unknown, but a theory is that it may be caused by *Herpes simplex* virus type 1 [42–44]. The diagnosis of Bell's palsy is made clinically. Treatment is with oral corticosteroids, with or without oral antivirals. The current American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) guideline on Bell's palsy recommends treatment of adults (age ≥16) with oral corticosteroids, starting within 72 h of symptom onset [45]. Early corticosteroid treatment results in recovery of normal facial function by 9 months in approximately 12% more patients than those given placebo (94% versus 82%) [46]. No benefit has been demonstrated for treating Bell's palsy with antiviral therapy versus placebo, however, and the AAO-HNS guideline strongly recommends against antiviral treatment alone [45]. The guideline also notes that large randomized trials have found no benefit of corticosteroids plus antivirals over corticosteroids alone, but suggests combination therapy as an "option" because the published trials could not exclude a small, non-significant benefit [45]. A survey of neurotologists showed that most prescribe both corticosteroids and antivirals, and conclusions from a 2015 Cochrane Review support this practice [47, 48].

The prognosis for complete recovery of facial function in Bell's is excellent if paralysis is incomplete. For complete paralysis with axonal degeneration of >90%, measured by electroneuronography (ENoG) and absence of muscle activity on volitional electromyography (EMG), middle fossa craniotomy and surgical decom-

pression of the facial nerve may be considered within a 14-day window of symptom onset [48–50], although this is controversial because of the poor quality of available evidence (graded as "D" by the AAO-HNS) [45]. Randomized controlled trials are not available. A case series by Gantz et al. retrospectively combined the experience of three U.S. centers (Iowa, Michigan, Texas) over many years (≤15 years) in treating a total of 31 patients with surgical decompression [49]. The study was initially designed in 1982 as a prospective trial involving 22 centers, but only three enrolled more than one patient. The study allowed patients who met criteria (complete paralysis with axonal degeneration of >90% plus absence of muscle activity) to "self-select" for surgery versus corticosteroids. The early years of the study allowed surgery for up to 21 days after symptom onset but this was later revised to 14 days. The results favored surgery within 14 days versus corticosteroids, and noted that patients who underwent surgery 14–21 days after symptom onset had the same outcomes as the corticosteroid group. A retrospective case series by Cannon et al. evaluated outcomes in 14 patients who met the Gantz criteria and who were treated with surgery at a single center over a 12-year period [50]. The study had no control group. The majority (73%) regained normal (27% with House-Brackmann 1) or near-normal (47% with House-Brackmann 2) return of facial nerve function.

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, transmitted by tick bite. The clinical presentation and progression varies significantly. A subset of patients with Lyme disease may develop meningoradiculitis and neuropathies of multiple cranial nerves. Of patients who develop meningoradiculitis, it is estimated that 60% will have facial palsy, with 30% of these being bilateral [51]. Patients who live in or visit Lyme-endemic areas and who present with unilateral facial palsy or other symptoms of Lyme disease, including multiple cranial neuropathies or bilateral facial paralysis, should be tested for Lyme disease. Treatment is with doxycycline.

Otosyphilis

Syphilis is caused by the spirochete *Treponema pallidum*, and may be congenital or acquired. Otosyphilis, or syphilitic involvement of the labyrinth and temporal bone, is a common feature in both congenital and acquired syphilis. In both forms, hearing loss may be sudden or progressive, is usually bilateral, and may or may not include vestibular symptoms. Frequently, the symptoms of otosyphilis mimic those of Meniere's disease. Pathologically, otosyphilis is characterized by progressive endolymphatic hydrops, degeneration in the sensory and neural structures, and inflammation and resorption of the bony labyrinth (Fig. 7.5). Otosyphilis is treated with high-dose intravenous penicillin. Corticosteroids are often given as well, although no randomized controlled trials have been performed to evaluate the value of this adjunctive therapy. Treatment often halts progression of hearing loss, and in some cases hearing may improve [52].

Conclusion

Labyrinthitis is characterized by sensorineural hearing loss and/or vestibular dysfunction. It can be caused by viruses or bacteria, and determination of the pathologic agent is important for directing treatment. Treatment is often with a combination of antibiotics and empiric corticosteroids. If suppuration is present, it should be drained to expedite resolution of the infection and prevent intracranial spread. Labyrinthitis often leaves patients with permanent hearing loss and vestibular dysfunction. Labyrinthitis ossificans complicates later cochlear implant placement, and early cochlear implantation should be considered in patients with profound sensorineural hearing loss from labyrinthitis.

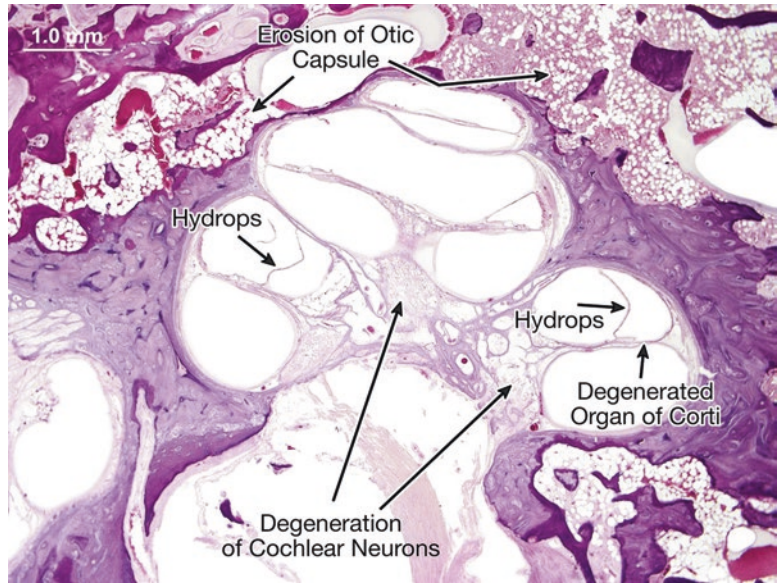

Fig. 7.5 Histopathology of a patient with otosyphilis. (Image courtesy of Massachusetts Eye and Ear Temporal Bone Laboratory. Unpublished)

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Cochlear Implant Infections

8

Jessica Ky-Lee Choong and Stephen John O'Leary

Introduction

Infections associated with cochlear implantation surgery are uncommon but can have devastating effects. Persistent infection may require removal, with or without device replacement, causing significant patient morbidity and expense. This chapter will review the epidemiology, microbiology, diagnosis, treatment, and prevention of cochlear implant infections.

Cochlear Implant Surgery

A cochlear implant is a prosthesis that provides direct electrical stimulation to the auditory nerve in order to evoke the perception of sound. It is the gold-standard treatment for deafness in the severe-to-profoundly hearing impaired where a hearing aid does not provide adequate speech recognition for daily communication. The surgery involves a mastoidectomy approach that allows access to the middle ear, and the implantation of a long, thin electrode array into the scala tympani of the cochlea (Fig. 8.1). This electrode is attached to an implant body, known as the "receiver stimulator," that is placed beneath the temporalis muscle (in the subperiosteal plane), posterosuperior to the pinna. These components are fully implanted, with no direct physical communication through the skin. This receiver-stimulator communicates through a radiofrequency coil to the externally worn "speech processor." The processor has a microphone(s) to detect sound and extracts components of the acoustic signal pertinent to the understanding of speech. These signals are encoded as a series of electrical pulses. This code is transmitted to the receiver-stimulator across the skin by the radio-frequency link, then via the electrode into the cochlea where electrical stimulation of the inner ear is relayed via the auditory nerve to the brain.

Infections in cochlear implantation relate to the surgical incision, the implant body or electrode, including the intracochlear electrode, and meningitis. The risk of meningitis is increased partly because of the potential connection between the cochlea and the meninges. The cochlea is filled with perilymph and communicates with the cerebrospinal fluid (CSF) via the

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_8

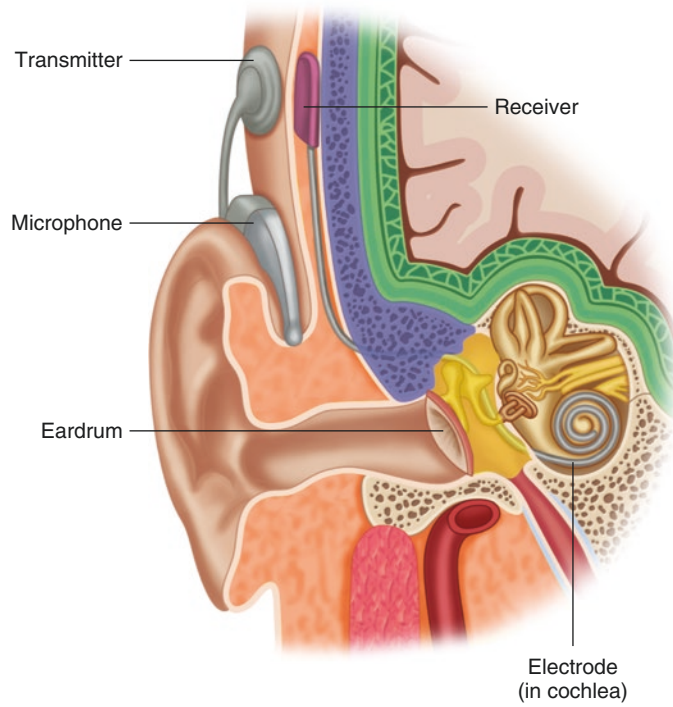

Fig. 8.1 Anatomy of the ear with a cochlear implant. Yellow = middle ear; blue = temporal bone and mastoid; green = meninges

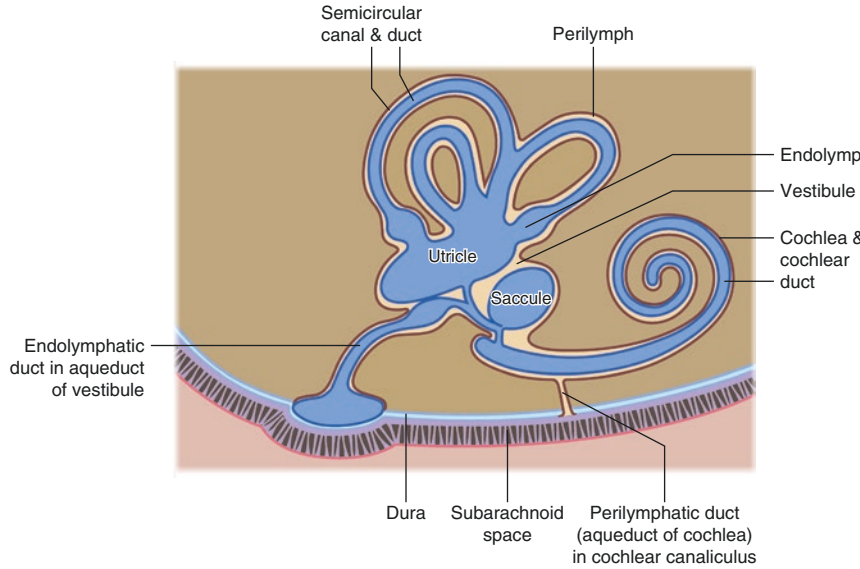

Fig. 8.2 Relationship of the cochlear aqueduct to the central nervous system. Adapted from O'Rahilly R, Müller F, Carpenter S, Swenson R. *Basic Human Anatomy*: *A Regional Study of Human Structure* (online textbook developed at Dartmouth Medical School), www.dartmouth.edu/~humananatomy. With permission

cochlear aqueduct. The cochlear aqueduct, which is located in the scala tympani near the round window, is very narrow and of variable patency in humans [1] (Fig. 8.2). The cochlea can also communicate with the CSF in a dysmorphic cochlea [2], or if the surgery causes significant trauma to the medial (modiolar) wall of scala tympani.

Epidemiology

Infections associated with cochlear implantation occur in 1.7–4.1% of cases and include wound infection, otitis media and mastoiditis, implant body infection, cochlear infection, and meningitis [3–5]. Infections may occur at any point after surgery, but the majority of infections occur >30 days postoperatively, often months to years after surgery. Table 8.1 notes the overall incidence and mean time of onset for various infections. A history of chronic otitis media may increase the risk of post-implantation infection. Similarly, patients with a history of meningitis, bacterial labyrinthitis, or cochlear dysmorphism (which may have caused the hearing loss necessitating the cochlear implant) are more at risk of developing meningitis post-operatively compared with patients who have no history of meningitis [6].

Microbiology

Cochlear implant surgery is typically classified as a "clean" operation and most of the microorganisms responsible for infection in cochlear implant surgery are skin flora, *Staphylococcus aureus* in particular. Upper respiratory tract microorganisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* may be the cause of cochlear implant infections associated with otitis media or meningitis [7]. Table 8.2 lists pathogens commonly cultured in various types of cochlear implant infections.

Cunningham et al. evaluated reported wound cultures from 15 of 30 patients with infections and found that most (73%) were due to *S. aureus* (11 cases); other pathogens included Group A streptococci (1) and Gram-negative bacilli (3, *Escherichia coli*, *Klebsiella*, *Pseudomonas*) [5]. Hopfenspirger et al. reported 26 organisms grew in cultures from 22 wound infections, and the major pathogens included *S. aureus* (12 cases), *Pseudomonas* (5), coagulase-negative staphylococci (4), *Alcaligenes* (2), and *Candida albicans* [8]. Neither Cunningham nor Hopfenspirger evaluated cultures by time of onset of infection. Gawecki et al. reviewed 19 late-onset skin flap and implant-related infections, and of 16 with positive cultures, 69% were due to *S. aureus*, either alone (50%) or in combination (19%) with Gram-negative bacilli such as *Pseudomonas*, *Klebsiella*, *Enterobacter* [9]. Zawawi et al. reviewed the literature and found 43 cases of postoperative mastoiditis, with mean onset 17.2 months; results of cultures are listed in Table 8.2 [10]. Reefhuis reviewed 26 cases of meningitis following cochlear implantation in 4262 children and found that 65% of meningitis cases developed >30 days postoperatively and all of these late onset cases were due to *S. pneu-*

Table 8.1 Incidence and time of onset of cochlear implant infections

Study	Total # patients (% pediatric)	Study years	Incidence of infection (major)	% early onset (≤30 days)	Mean onset (months)
Cunningham [5]	734 (37%)	1993–2002	4.1%	27%	11.2
Hopfenspirger [8]	268 (100%)	1990–2007	8.2%	27%	7.3 for late-onset cases
Zawawi [10]	N/A (100%)	2000–2013	N/A (all mastoiditis)	N/A	17.2
Reefhuis [7]	4262 (100%)	1997–2002	0.6% (all meningitis)	35%	11.8 for late-onset cases
Yu [4]	241 (N/A)	1990–2000	1.7%	25%	24 for late-onset cases
Gawecki [9]	1076 (59%)	1994–2013	1.8%	none	33.2

Cunningham [5], Hopfenspirger [8], Yu [4], Gawecki [9] reviewed wound and implant-related infections; Zawawi [10] reported mastoiditis cases, Reefhuis [7] reported meningitis cases.

Table 8.2 The microbiology of cochlear implant infections

Surgical site infections	Otitis media/mastoiditis	Meningitis
Staphylococcus aureus	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*[a]
Coagulase-negative staphylococci (indent)	*Streptococcus pyogenes*	*Haemophilus influenzae*[a]
Streptococci	*Staphylococcus aureus*	*Acinetobacter baumannii*
Pseudomonas aeruginosa	*Pseudomonas* species	*Escherichia coli*
Escherichia coli	*Haemophilus influenzae*	*Enterococcus* species
Klebsiella pneumoniae		
Alcaligenes xylosoxidans		
Candida albicans		

Data from several series of cochlear implant infections [5, 7, 8, 10]
[a]Data from Reefhuis, et al. [7] Late onset meningitis cases (>30 days post-implant) were all due to *Streptococcus pneumoniae* and *Haemophilus influenzae*, while early onset cases were caused by one of the five organisms listed

moniae or *H. influenzae* [7]. Early onset cases (<30 days postoperatively) also included enterococci and Gram-negative bacilli.

Clinical Manifestations and Management

Operative Management and Wound Infection

Surgical site infections are the most common infectious complications after cochlear implant surgery. However, as the surgical technique has improved, the rate of wound infections has decreased. Early cochlear implant incisions had an inverted "C" shape that commenced behind the ear, curved upward and backward and then inferiorly [11]. The concept was to expose the region where the implant body would sit. This approach was associated with a high incidence of wound infection, likely due to interference with the occipital blood supply [12]. More recently, incisions have become more linear, or curvilinear, running essentially vertically, in order to avoid disruption to the scalp circulation [12, 13]. Disruption of the scalp blood supply has been reduced further by the introduction of shorter ("minimally invasive") incisions. Another important concept in designing an incision is that it should not cross the implant body, and to facilitate this, incisions should be close to the postauricular sulcus. The development of surgical access that reduces the risk of infection has been helped considerably by improvements in the design of the implant body, which is now thinner, smaller and requires less bone-drilling to seat the device in the cortical bone of the cranium. These revised surgical requirements have subsequently reduced the size of the surgical incision. Figure 8.3 illustrates historical and current types of surgical incisions.

Patients with any active infections, such as otitis externa or otitis media, should be treated and cleared of these infections prior to cochlear implant surgery. At the time of surgery, prophylactic intravenous antibiotics should be started within 1 h prior to the surgical incision (within 2 h for antibiotics with long half-lives such as intravenous vancomycin). The major risk is of wound contamination with *S. aureus* [5, 8], so the antibiotic chosen should cover staphylococci. There is no consensus on the optimal prophylactic antibiotic for cochlear implant surgery, nor whether the type of prophylaxis should differ for children and adults. A 2010 policy statement from the American Academy of Pediatrics discussed prophylaxis but did not make a specific recommendation [14]. The guidelines published in 2013 by a group of U.S. national organizations regarding antibiotic prophylaxis for various types of surgeries did not specifically mention cochlear implant surgery, but recommended a single preoperative dose of either cefazolin or cefuroxime for clean procedures in the head and neck involving an implant [15]. These guidelines noted that a single preoperative dose of vancomycin may be added to the chosen prophylactic regimen for patients known to be colonized with methicillin-resistant *S. aureus* (MRSA). A first generation

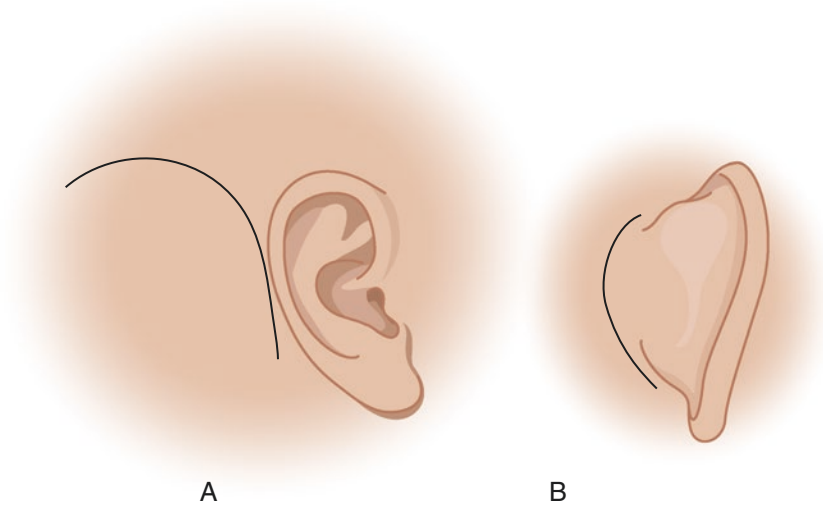

Fig. 8.3 Incisions used in cochlear implant surgery, past and present. (**a**) This is a historical incision, while (**b**) represents the current type of cochlear incision, which is smaller, straighter, and closer to the postauricular sulcus than (**a**)

cephalosporin, such as cefazolin, is effective against methicillin-sensitive staphylococci. This was the antibiotic given as prophylaxis in 83% of 98 cochlear implant surgeries (1991–2005) in a series by Hirsch et al.; 15% of the patients were children [16]. No patient developed a major early (≤30 days) postoperative infection and only one patient developed a minor infection (incisional cellulitis). For pediatric patients in particular, some surgeons prefer to use cefuroxime, since this agent covers common otitis pathogens such as *S. pneumoniae* and *H. influenzae* in addition to *S. aureus*. For patients colonized with MRSA, an antibiotic such as intravenous vancomycin with activity against MRSA should be included in the prophylactic regimen (e.g., vancomycin plus cefuroxime, each given as a single dose preoperatively and started in the appropriate window of time as discussed above). Patients with dermatological conditions such as seborrheic dermatitis or psoriasis, where excessive scaling of the skin prevails, should be treated aggressively for their skin conditions prior to surgery.

During surgery, the cutaneous and the muscle/periosteal incisions are off-set, so that a wound infection will be less likely to track down to the implanted device [17]. Similarly, each of these layers is closed separately at the end of the procedure. This provides a layer of vascularized tissue (i.e., fascia, muscle) between the skin and the implant body. Subperiosteal dissection (for the placement of the implant body) should be no more extensive than required, to reduce the risk of a subperiosteal hematoma developing as this will increase the risk of a wound infection. Similarly, a compression bandage ("mastoid dressing") must be applied to reduce the risk of a subperiosteal collection developing and becoming infected. In this regard, it is important to appreciate the posterior and superior extent of the implant body. To provide compression over the implant, the mastoid dressing needs to be more extensive than that applied in conventional mastoid surgery.

Surgical site infections may present as a stitch abscess, localized cellulitis, or infection of the implant body. Provided that the precautions outlined above have been undertaken, a stitch abscess or localized cellulitis is unlikely to lead to a spread of infection to the receiver-stimulator. A stitch abscess is treated along conventional lines, with the removal of an infected stitch and oral antibiotic therapy to cover staphylococci as needed. A localized area of cellulitis may also respond to oral antibiotics, but more extensive cellulitis or systemic symptoms will require admission to hospital and intravenous antibiotics.

Fluctuance over the implant heralds an infection of the receiver-stimulator, and this may not present until several weeks after surgery. The patient may not complain of discomfort or pain and is usually systemically well. If the ear is discharging, a sample should be sent for microbiology to facilitate targeted therapy. One needs to exclude mastoiditis, and although this does not usually co-exist with an infection of the implant body, it should be considered. Computerized tomography (CT) imaging in the first 2–3 weeks after surgery may be of limited value because the mastoid will be filled with blood. Therefore, clinical assessment is of greater importance in diagnosis. Mastoiditis may be anticipated if the patient is systemically unwell, or the focus of the fluctuance and/or post-auricular discharge is not in the vicinity of the implant body. The presence of pus in the middle ear (rather than blood) would confirm the diagnosis of mastoiditis, as would a mucopurulent discharge from a middle ear ventilation tube. The management of implant body infection and mastoiditis is considered in greater detail in the following sections.

Implant Body Infection

Infections of the implant body occur most frequently in the perioperative period, but may occur at any time in the life of the implant. Refractory infections are likely to involve biofilms on the surface of the implant: biofilms have been demonstrated on several devices removed because of persistent infection [18, 19]. The likely cause of the infection will depend on the circumstance. Perioperative infections are thought to arise from contamination of the implant body at the time of surgery by cutaneous pathogens, and *S. aureus* is the most common cause of surgical site infections. Anything that causes a hematoma in the vicinity of the implant body postoperatively, such as poor compression over the implant or perioperative anticoagulation, will increase the risk of a postoperative infection. Late-onset infections may occur following head trauma involving the implant. The hematoma may be initially sterile and later become superinfected. An extensive hematoma must be drained, but compression may be sufficient to treat a small, uninfected hematoma and thus, compression is the preferred option early after surgery. Drainage may involve either aspiration (in a sterile field), or surgical incision and drainage. The aspirate or surgical drainage sample should always be sent for microscopy and culture. If a new incision is to be made, then this should not overlie the implant body. If an infection is found, the wound will always need to be opened and explored.

Implant body infection may present as a relatively painless swelling over the implant, with or without a purulent discharge from the surgical incision in the vicinity of the prosthesis [20]. In some cases, the patient's main complaint is that their transmitter does not fit correctly, or that it is constantly falling off. When wounds in these types of infections are surgically explored, granulation tissue is typically found surrounding the device.

An infected implant is notoriously difficult to treat. Patients will often have little to no improvement with antibiotic treatment. Surgical exploration is required, and if, as anticipated, there is granulation tissue on the implant device, the implant body should be removed. This is because direct washing of an infected device is ineffective at removing biofilms and therefore at eliminating infection [19]. The electrodes are left within the cochlea until re-implantation, which may be undertaken several months later. At this time both the implant body and the intracochlear electrode can be replaced.

Studies on explanted prostheses have shown evidence of biofilms (particularly *S. aureus*) within the depressed areas on the receiver/stimulator that most likely to act as a reservoir [19]. These observations have led to revisions of implant design, minimizing the risk of further infections.

Extrusion of a cochlear implant is a special case. This presents as a gradual breakdown of the skin, revealing the implant beneath (Figs. 8.4 and 8.5). This condition is associated with excessively thin or poorly vascularized skin, and will often break down along an incision line when the

device has been placed immediately beneath this. It may also occur when there has been excessive pressure across the skin between the antenna on the receiver-stimulator and the coil of the speech processor. There is typically no granulation tissue. The implant might be salvaged by rotating a skin flap over the implant and treating with a course of antibiotics, but this approach is not always effective in salvaging the implant. Geraghty et al. reported three adults with cochlear implants who developed device exposure; one had postoperative wound dehiscence that was successfully treated with flap rotation, but two others failed flap coverage and antibiotic treatment and the implant was removed [21]. Gawecki et al. evaluated the experience of 632 children and 444 adults with cochlear implants placed between 1994 and 2013 and found that a major skin flap complication, including some with device extrusion, occurred in 2% of children and 1.4% of adults [9]. Attempts to treat with antibiotics and primary wound closure failed; rotational skin flaps succeeded in 50% of the cases. Parkins et al. reported seven cases of threatened device extrusion out of 74 cochlear implants (9.4%) performed in their center over a 13-year period. Four of these seven were in patients who had undergone a "magnet upgrade" procedure. They reported successful rotational flaps in two of the three single surgery device extrusions, and one of the four "magnet upgrade" patients [22]. Hoffman et al. described a case of partial migration of the electrode array from the cochlea resulting in loss of speech perception with no overlying skin changes. This was able to be managed with re-opening of the cochleostomy and replacement of the existing electrode array with a resultant return to preoperative function [23].

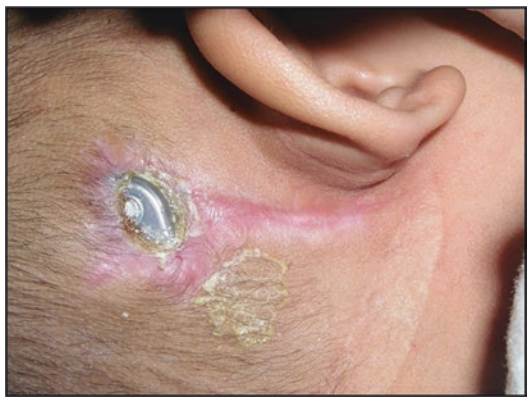

Fig. 8.4 Cochlear implant receiver exposure with minimal evidence of active infection. Photograph courtesy of Dr. Robert Briggs, University of Melbourne, Royal Victorian Eye & Ear Hospital, Melbourne, Australia

Otitis Media

Otitis media is associated with a potential risk of meningitis when it occurs in an implanted ear. However, acute otitis media is common in

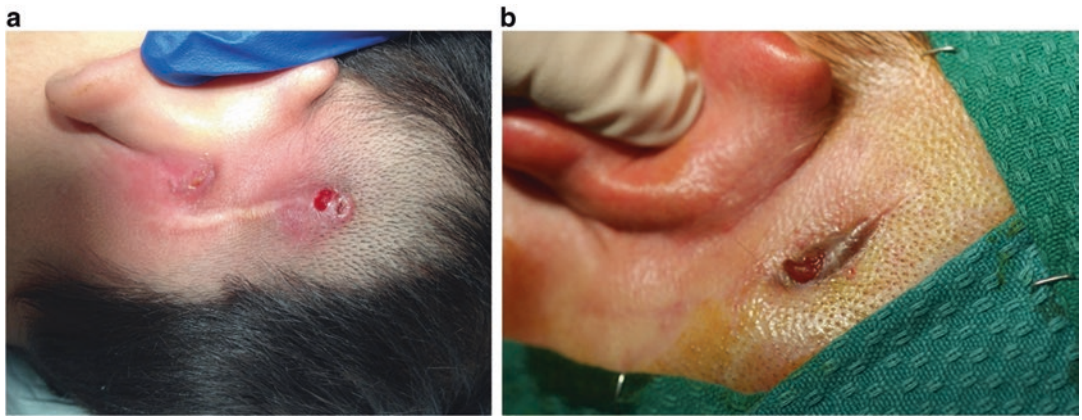

Fig. 8.5 Device exposure with chronic active infection in two different patients. Photographs courtesy of Dr. Robert Briggs, University of Melbourne, Royal Victorian Eye & Ear Hospital, Melbourne, Australia

younger children and seldom causes complications in children with cochlear implants. Uncomplicated otitis media in children with a cochlear implant is not an emergency. There is a lower threshold for prescribing oral antibiotics than usual; we caution against the "wait and watch" approach advocated for otitis media seen in the wider community [24]. Once the infection has settled the associated middle ear effusion is not a risk to the implant, and is treated conventionally, with a ventilation tube if it persists for 3 months or more. The effusion may however change the electrical field potential between the stimulating electrode to the auditory nerves, and (for reasons that are poorly understood) reduce the current required to elicit a perceptual threshold [25]. This means that sounds are too loud, and a child's reluctance to use the implant may be the first clinical sign of a middle ear effusion in a child with an implant. Patients with recurrent otitis media should have a tympanostomy tube inserted, and this is particularly recommended prior to implantation in patients with a history of recurrent acute otitis media.

Mastoiditis

Mastoiditis occurs in approximately 1% of pediatric cochlear implant recipients [26]. This is most prevalent in the first few weeks after implantation. Complicated wound infections with signs of a fluid collection or a discharging wound are indicative of mastoiditis and require hospitalization for treatment with intravenous antibiotics, and may require surgical drainage/washout with or without device explantation. As described above, the location of the wound discharge and the presence or absence of fluctuance over the implant can help to differentiate mastoiditis from an implant body infection. Infected fluid or tissue should be taken for microbiology and then empirical antibiotics should be commenced. Intracranial involvement (such as lateral sinus thrombosis or an intracranial collection) should be excluded. Surgical intervention is recommended in the following circumstances: if it has been established that there are complications, when there is severe infection, or a failure to respond to antibiotic therapy. A tympanostomy tube together with intravenous antibiotics may be all that is required (to drain the purulent discharge), or it may be necessary to perform a formal mastoid exploration for the removal of the inflammatory tissue. Where possible, the implant should be left in place, however failure to improve with the above measures may indicate implant body infection. A prolonged course of antibiotics is indicated when mastoiditis occurs early after cochlear implantation; input from an infectious diseases physician is recommended.

Meningitis

Meningitis following cochlear implantation surgery is a rare but devastating complication. This may present as early as within 24 h post-implantation or as late as several years after, with the highest risk within the first 2 months.

An increased risk of meningitis has been found to be associated with structural anomalies of the inner ear, especially when there is an abnormal communication between the perilymph and the internal auditory meatus. Other risk factors include immune deficiency, the presence of neurological prostheses, cerebrospinal fluid (CSF) leak, and a history of basilar skull fracture or meningitis [27]. One cochlear implant design was associated with a significant increase in the incidence of meningitis in the early 2000s [6, 7]. This device required the use of a positioner—a plastic spacer that was inserted lateral to the cochlear electrode to push it medially. The rationale was that this should bring the electrode contacts closer to the modiolus. The device was voluntarily recalled by the manufacturer in 2002. It is still debated whether the meningitis was caused by the degree of cochlear trauma seen with this electrode design, which far exceeded that of other implants, or the presence of two prosthetic materials in close proximity within the cochlea. The latter may have caused a dead space within which bacteria could grow while evading immune surveillance [28].

Streptococcus pneumoniae accounts for the majority of cases of meningitis. Similarly, *S. pneumoniae* is associated with meningitis under other conditions where the dura has been breached, such as a skull base fracture or CSF leak [27]. Meningitis may be caused by several mechanisms following cochlear implantation. The most obvious is spread of infection along the electrode within the cochlea and from there, to the CSF via the route(s) described above. This is the major concern, especially in the first few weeks after surgery. To mitigate this risk, patients should be vaccinated against *S. pneumoniae* prior to surgery. In addition, a prophylactic antibiotic should be started within the appropriate window of time prior to incision as discussed above, and after the insertion of the electrodes into the cochlea via a cochleostomy, fascial tissue may be packed around the cochleostomy to seal off the cochlea from the middle ear. In animal studies, adding this fascial tissue has been shown to reduce the subsequent risk of infectious spread from otitis media [29]. In the event that a CSF "gusher" is encountered at surgery, the seal is reinforced with muscle, the patient is rested head-up, and on rare occasions consideration may need to be given to the insertion of a lumbar drain [30]. All the patients undergoing cochlear implantation should be advised that potential symptoms of meningitis (e.g., fever and/or headache) at any point postoperatively should prompt urgent medical assessment because of the increased risk of meningitis in cochlear implant patients.

Meningitis can occur months or years after surgery. If a patient with a cochlear implant presents with suspected meningitis, their initial management follows conventional lines: urgent antibiotics are administered, a lumbar puncture is performed and the CSF should be sent for cell counts, Gram staining, and culture. The major clinical decision for the cochlear implant team is to ascertain whether the infection has arisen from the implanted ear. This can be confirmed by the observation of a purulent middle ear effusion in the implanted ear, or the presence of mastoid and middle ear opacification on CT scanning. Magnetic resonance imaging (MRI) will likely be required, but because of the magnet in the receiver-stimulator's coil, the image quality may be too poor in the vicinity of the middle ear to discern the presence of an effusion. MRI may be used in some cochlear implant recipients with additional stabilization measures in place to minimize the risk of displacing the implant or causing significant pain due to force pressures. The risk of displacement differs with different types of cochlear implants due to varying torque measurements between models, and this should be managed on an individual basis in consultation with the device manufacturer [31]. In the event that otitis media is confirmed in the implanted ear, the surgeon may need to consider whether surgical drainage of the fluid or removal of the device is warranted. These are complex matters that will depend on the specific circumstances. It is worth keeping in mind that the origin of the meningitis may not be related to the cochlear implant, and if that is the case, the only impact of the implant on management will be the complexity of performing safe MRI imaging and the image distortion that results from the cochlear implant magnet [32]. If need be, the implant magnet can be removed through a minor surgical procedure prior to the MRI, and then replaced later on.

Meningitis also has an influence on the possibility of *future* cochlear implantation. Hearing loss is frequently a complication of meningitis. When caused by *H. influenzae* there is a chance that the hearing may recover spontaneously in the months after infection, but this seldom occurs when the causative organism is *S. pneumoniae*. The main concern regarding cochlear implantation is that the scala tympani may fibrose and then ossify. This may occur as early as a month after meningitis or may not become clinically apparent until several months later [33]. The fibrosis and ossification have been attributed to injury to the cochlear endosteum [34]. This pathological change can make cochlear implantation impossible, as the lumen to receive the device is obliterated. In light of this, sequential MRI scanning is required after meningitis when there has been severe hearing loss, with urgent cochlear implantation if the cochlea begins to ossify. Once implanted, the

device will function quite well, even if the scalar ossification continues.

To decrease the risk of meningitis, all children should be immunized with vaccination against *H. influenzae* and *S. pneumoniae* prior to implantation. Guidelines for specific vaccinations have been published [14].

Special Considerations

Acute Otitis Media

Acute otitis media (AOM) is the most common bacterial infection in children and many pediatric cochlear implant candidates have a history of otitis media. Given the benefit of early cochlear implantation for speech and language development, delaying implantation until the child is older to reduce the likely incidence of AOM is not recommended. Control of AOM is required very early on in the assessment, as it is difficult to ascertain whether the patient is an audiological candidate for implantation if their evaluation is complicated by the conductive loss associated with a middle ear effusion. Furthermore, it is not possible to proceed safely to implant surgery if there is a middle ear effusion, especially when purulent. Tympanostomy tube placement is recommended for these patients and we have a low threshold for also recommending an adenoidectomy, to reduce the risk of subsequent otitis media. Patients with a dry and clean tympanostomy tube can safely proceed to cochlear implantation. Studies have demonstrated that good control of AOM before implantation reduces the risk of AOM post-implantation [35].

Acute otitis media at the time of surgery increases the risk of device contamination and has the potential to increase the risk of meningitis [27]. If a patient has otitis media at the time of implantation, we advocate that surgery be delayed 6 weeks until the infection has resolved and the inflammation has settled. Some surgeons are of the opinion that implantation may proceed without complication in the presence of otitis media with effusion, but we view this as taking an unnecessary risk. Placement of a tympanostomy tube provides much greater certainty concerning the safe timeline for implantation after a delay for treating otitis media. This approach is of particular value in young children (under 3 years of age) who are in the critical stage of speech and language acquisition.

Chronic Otitis Media

Cochlear implantation is contraindicated in patients with untreated chronic otitis media, due to the potential for device infection or chronic middle ear inflammation spreading into the cochlea. With the latter, granulation tissue spreads into the inner ear and cochlear implant function deteriorates and/or fluctuates [36]. The implant electrode must be removed and the inner ear, which will then undergo fibrotic change, cannot be implanted again. Interestingly, in these patients the disease extends no further than the cochlea, and does not present as otitic meningitis.

Management is determined by the activity of the chronic otitis media. Cochlear implant candidates with inactive disease (i.e., a dry ear) may present with either a tympanic membrane perforation or a dry mastoid cavity. Tympanic membrane perforations are closed prior to implantation to reduce the risk of device and middle ear infection through contamination via the external ear canal. Autologous cartilage is the preferred graft tissue in these cases as the risk of retraction of the graft onto the implant electrode is lower than with fascia. However, myringoplasty failures are not uncommon and it is recommended that cochlear implantation be delayed until the tympanic membrane is both intact and stable, which is a minimum of 3 months post-myringoplasty. Tiny tympanic membrane perforations may not require a myringoplasty as the risk of exposure to the external environment is considerably less than with a large perforation; in this regard a small perforation is similar to a tympanostomy tube. The over-riding consideration with a small perforation is whether the ear ever discharges—if so it should be closed. Dry mastoid cavities may be implanted by rotating a vascularized fascial flap in over the implant electrode [37]. Alternatively, the mastoid can be obliterated with blind closure of the exter-

nal ear canal [38]. Cochlear implantation follows 3–6 months later or when deemed appropriate; implantation can be performed at the first operation as a single-stage procedure.

Chronic active otitis media (also known as chronic suppurative otitis media) implies that there is aural discharge. Treatment of these ears is always staged. The first stage aims to dry up the ear, and eliminate middle ear/mastoid infection and/or granulation or cholesteatoma. A canal wall up mastoidectomy may be appropriate, provided that the surgeon is confident that the ear will remain stable, and in particular that the tympanic membrane will not retract around the implant. If a mastoid cavity needs to be created, then the mastoid should be obliterated together with a blind sac closure of the external ear canal.

Conclusion

Cochlear implantation is a common and safe procedure with a relatively low incidence of infectious complications. Surgical site infections are the most common postoperative infectious complication; most are minor and can be treated with oral antibiotics in an outpatient setting. Children with cochlear implants may have episodes of AOM and these should be managed with conventional antibiotics; tympanostomy tube placement should be considered in children with recurrent episodes of AOM. Less common but more severe complications including mastoiditis, implant body infection, and meningitis require hospital admission for intravenous antibiotics and surgical management. Device removal is rarely necessary but if required, efforts should be made to preserve cochlear architecture to allow for possible re-implantation in the future.

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External Otologic Infections

9

Kathryn Y. Noonan and James E. Saunders

Introduction

Otitis externa is common. The most common form, acute otitis externa (AOE), accounted for approximately 2.4 million clinic and emergency department visits in 2007 in the United States (8.1 visits per 1000 population) and cost approximately 0.5 billion dollars [1]. The annual incidence has been reported between 4 and 14 episodes per 1000 population and each episode generally results in decreased quality of life and missed work or school for about 3 days [2, 3]. Otitis externa can affect people of all ages and is more prevalent in warmer climates [4].

Otitis externa can be defined as an infection involving the external auditory canal, tympanic membrane (TM), and/or pinna. Common symptoms and signs include otorrhea, canal inflammation, otalgia, pruritus, tinnitus, and usually mild hearing loss. Most otitis externa infections present acutely and are caused by bacteria, but otitis externa can also be due to chronic bacterial inflammation, fungal infections, chronic myringitis, or viral infections. Treatment may involve topical antimicrobial medications, antiseptics, steroids, aural toilet, and even surgical debridement. It is important to recognize the underlying diagnosis and common pathogens to appropriately treat the disease. In addition, the integrity of the tympanic membrane must be considered as many ototopical medications are potentially ototoxic. This chapter reviews the diagnosis, microbiology, and management of noninvasive external otologic infections. Invasive ("malignant") otitis externa is discussed in Chap. 10.

Embryology

Embryological development of the external auditory canal (EAC) arises from the first pharyngeal groove and is a complex process starting early during fetal life and continuing throughout childhood. Around 10 weeks of fetal development a meatal plug develops which elongates, splits (13–15 weeks), and then partially resorbs (16 weeks) to form a fully patent canal by 18 weeks of fetal life [5]. The external canal is nearly linear at birth with a more horizontally oriented tympanic membrane. The canal matures into an elongated "S" shape by age 9 and the tympanic membrane rotates to form a 45-degree angle with the canal by adulthood [6]. At birth the tympanic ring has a non-ossified lamina fibrosa which forms a gap known as the foramen of Huschke. There is usually osseous fusion by the third to fourth year of

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_9

life. However, incomplete fusion results in a potential route of spread for infections and neoplasms in the medial canal [6].

Anatomy

The EAC is a skin lined sac approximately 2.5 cm in length and separated from the middle ear by the tympanic membrane medially. The outer one-third has a cartilaginous framework while the inner two-thirds has a bony framework that mostly arises from the tympanic portion of the temporal bone (Fig. 9.1). The bony canal is covered by very thin skin (approximately 0.2 mm thick) with virtually no subcutaneous tissue or skin appendages. This close approximation to bone accounts for the osteomyelitis seen with severe infections in immunocompromised patients. By contrast, the skin of the cartilaginous canal is much thicker (0.5–1.0 mm) and contains hair, sebaceous glands, and ceruminous glands (Fig. 9.2). There are small slits in the anterolateral outer cartilaginous canal known as Fissures of Santorini which allow for increased flexibility of the canal. These fissures, along with a patent Foramen of Huschke, provide a potential route for infections and neoplasms to extend into the parotid or soft tissues of the face and neck [6, 7].

Several arteries supply the EAC. Laterally, the canal receives blood from the posterior auricular and superficial temporal arteries. Medially the blood supply arises from the deep auricular artery which is a branch of the internal maxillary artery. It enters the canal in the region of the bony-cartilaginous junction and sends branches superiorly to supply the vascular strip [6]. Venous drainage is typically to the superficial temporal and posterior auricular veins which drain to the external jugular vein. However, the posterior auricular vein may drain via emissary veins to the sigmoid sinus which creates a portal for intracranial spread of infections.

Natural Defenses

There are several protective functions of the EAC that are felt to promote ear health. Ceruminous glands are modified apocrine sweat glands that are surrounded by myoepithelial cells which allows for compression of the glandular duct to expel secretions. Cerumen is formed by this secretory product mixing with sebum from sebaceous glands [6]. These hydrophobic secretions provide a natural water barrier to protect the skin. The presence of cerumen also creates a slightly acidic pH in the canal making it a more hostile environment for bacterial growth. Finally, the ceruminous secretions contain lysozymes, immunoglobulins, and polyunsaturated fatty acids which additionally may provide direct antimicro-

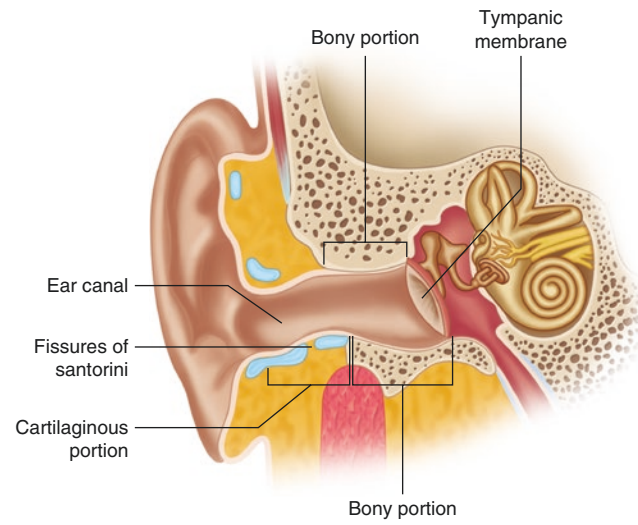

Fig. 9.1 Diagram of the ear canal, illustrating the orientation of the tympanic membrane as well as the underlying bony and cartilaginous portions of the canal. Note that the skin lining the canal is thinner over the bony portion than the cartilaginous portion

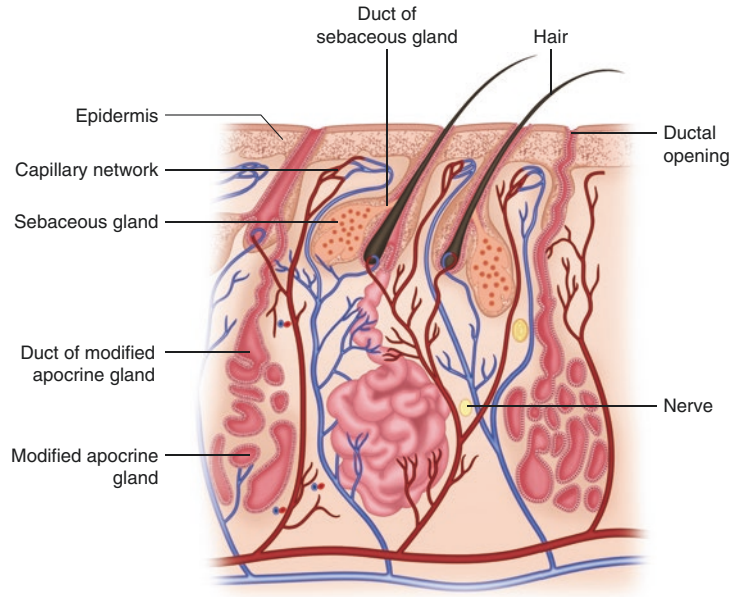

Fig. 9.2 Diagram of the cutaneous glands and hair follicles of the ear canal

bial protection [8]. The EAC also possesses a self-cleaning mechanism via the migration of the external canal skin. The cerumen and hairs in the lateral EAC trap debris and foreign material from entering deeply into the canal. The skin of the EAC slowly migrates to expel debris away from the tympanic membrane. Alberti et al. report a migration rate of 0.07 mm/day in a radial pattern away from the umbo and toward the lateral end of the canal. This promotes natural clearing of secretions and debris [9].

Normal Flora

Several studies have examined the flora of the external auditory canal in healthy subjects in an attempt to differentiate routine colonization from true pathogens. Gram-positive organisms are the most commonly found microbes and in particular *Staphylococcus* species [10–13]. *Corynebacterium* species ("diphtheroids") are also highly prevalent in healthy-appearing ears [10, 11]. Gram-negative species are relatively rare by comparison. In one study, Gram-negative bacteria were found in <5% of ears [11]. Interestingly, *Pseudomonas* species and fungal isolates, which are known otitis externa pathogens, can occasionally be found in healthy-appearing ears [11–13]. Brook cultured *Pseudomonas* from 11% of 72 healthy ear canals in 72 children [12], while Stroman et al. found *Pseudomonas* in only 1.3% of 310 healthy canals of adults and children. Stroman et al. cultured fungi (*Candida*, *Curvularia*, *Penicillium*) in 2.5% of healthy canals but in a higher percentage (7%) of cerumen samples (7%) [11]. Therefore, the diagnosis of otitis externa must be based on clinical findings and not on the presence of pathogens alone.

Infections of the External Canal

Acute Otitis Externa

Acute otitis externa (AOE) is defined as diffuse inflammation of the external ear canal skin lasting <3 weeks. It is characterized by symptoms of ear canal inflammation such as otalgia, fullness, or pruritus and may be associated with hearing loss or jaw pain. The onset of symptoms is usually <48 h and the vast majority of infections arise from bacterial causes [4]. Physical findings must include ear canal inflammation and edema (Fig. 9.3), but examination may also demonstrate otorrhea, lymphadenitis, erythema of the tym-

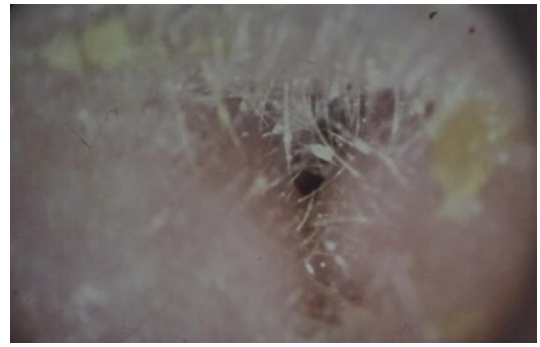

Fig. 9.3 Acute otitis externa. Severe edema with near complete closure of the external auditory canal

panic membrane, and cellulitis of the pinna and surrounding skin [14]. The clinical presentation in some cases may be similar to acute otitis media and these conditions should be differentiated with pneumatic otoscopy.

Risk factors for AOE include warmer climates, water exposure, younger age, and high humidity [4, 14]. In a study of over 2000 patients in North America, the summer months accounted for 80% of all AOE cases [4]. The association of AOE with water exposure and warm weather has led to the commonly used term "swimmers ear," but it is important to recognize that water exposure is not a prerequisite for developing AOE. Additional insults or canal obstructions such as canal trauma from aggressive cleaning, hearing aids, stenosis or cerumen impaction, or dermatologic conditions can often trigger an infection [7]. The presence of diabetes, HIV/AIDS, chemotherapy, radiation, or otherwise immunocompromised states predisposes patients to developing more significant infections, often requiring systemic antibiotics [14].

The microbiology of AOE has been well studied. The two most common organisms involved in acute infections are *Pseudomonas aeruginosa* (10–60% prevalence) and *Staphylococcus aureus* (10–70% prevalence) [14]. *Corynebacterium* species may play an important role in chronic otologic infections, but it is relatively uncommon in AOE [15]. Methicillin-resistant *S. aureus* (MRSA) is found in 6–12% of cultures [15–19]. Polymicrobial infections are reported in 41–50% of AOE cases [4, 14, 16].

The mainstay of AOE treatment includes topical antibiotic therapy and aural toilet. Topical antibiotics are preferred as they can reach higher concentrations in the ear canal and have been shown to be a safe and effective method of treatment [3]. The high local concentrations provided by topical antibiotics may treat some bacteria reported to be resistant based on the minimal inhibitory concentration (MIC), a value that refers to levels achieved in the serum by systemic administration of antibiotics [20, 21]. However, some bacterial resistance mechanisms are independent of antimicrobial concentration. The use of ototopical medications does not, therefore, eliminate the need for cultures, especially in refractory cases. The most recent practice guideline for AOE from the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) (2014) makes a strong recommendation against the use of systemic antibiotics in uncomplicated AOE unless there are certain modifying factors [14]. Quinolone agents, with or without corticosteroids, are the most commonly used topical medications. Several formulations are approved by the Food and Drug Administration (FDA) for otic use and have been shown superior to other combination topical agents [22]. If there is no improvement in symptoms within 48–72 h of topical treatment for AOE, thorough cleaning and reevaluation are indicated [14]. In cases with severe edema, otologic wicks may be placed in the EAC to facilitate the instillation of ototopical medications (Fig. 9.4). Analgesics should also be used as needed due to considerable associated otalgia. The AAO-HNS 2014 guideline recommends using only non-ototoxic topical antibiotics to treat AOE in patients with an opening to the middle ear [14].

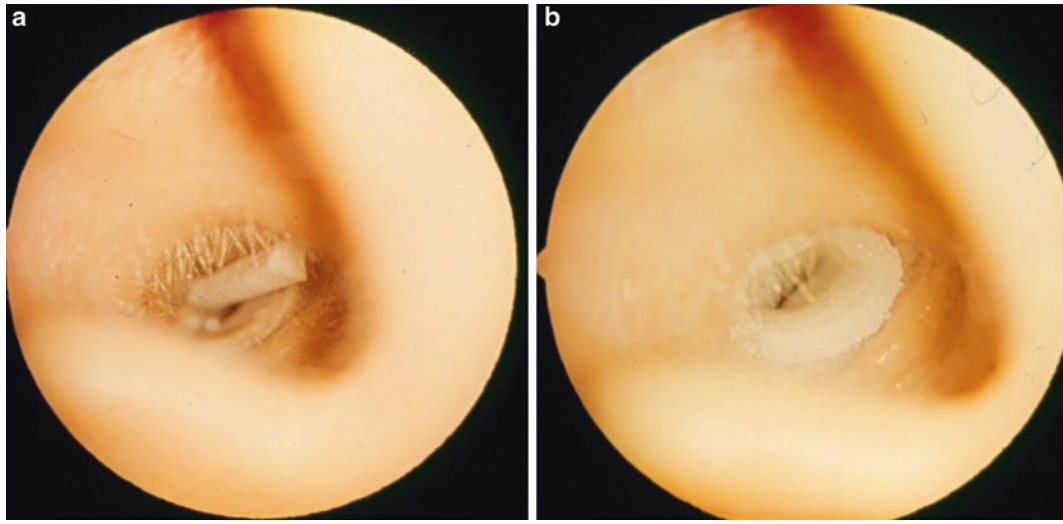

Fig. 9.4 Otic wick. (**a**) Placement of (unexpanded) otic wick in a moderately edematous ear canal (**b**) Expanded otic wick after instillation of ototopical drops

Chronic Otitis Externa

Chronic otitis externa (COE) is characterized by diffuse inflammation of the external canal and often exhibits a smoldering or relapsing course over months to years. Patients present with otorrhea, pruritus, and aural fullness. In contrast to AOE there is typically less otalgia [23]. Chronic otitis externa may be idiopathic but is often related to an underlying dermatologic, autoimmune, or allergic disease that predisposes the canal to recurrent infections. Chronic otitis externa is also found more commonly in patients with hearing aids, cholesteatomas, and foreign bodies (e.g., tympanostomy tubes) and biofilms may play a role [16, 24]. Chronic otitis externa may lead to medial external auditory canal stenosis, a relatively uncommon, idiopathic condition that eventually results in scarring of the EAC (Fig. 9.5). This condition typically begins with chronically inflamed tissue in the medial EAC and recurrent infections. Later in the course of the disease, the inflammation subsides and mature scar tissue fills the medial end of the canal.

The microbiology of COE is less well characterized than AOE. Cultures in COE may grow bacteria or fungi; in some cases a pathogen is not identified [25]. Cultures in patients with COE most commonly grow *S. aureus* and *P. aeruginosa* but other organisms include *Enterobacter*, *Escherichia coli*, *Proteus mirabilis*, and fungi [26]. More recent studies have proposed that *Corynebacterium* and other bacteria associated with biofilm formation may be major contributors to COE [16, 27]. One study identified biofilms in 92% (23 of 25 patients) of chronically draining ears [24].

Treatment frequently proves challenging due to the chronic relapsing course of the disease. It is necessary to treat any underlying conditions that may be contributing, such as autoimmune diseases or dermatologic conditions (e.g., psoriasis, eczema), and the otologist should work in conjunction with the patient's rheumatologist or dermatologist in these cases. Other treatment approaches involve topical antibiotic and corticosteroid medications, including CSF-HC (chloramphenicol, sulfanilamide, amphotericin B, hydrocortisone) powder, acidification of the ear canal (e.g., with 2.0% acetic acid), and topical emollients. Surgical treatments such as meatoplasty or canalplasty may be employed in rare cases with associated anatomical abnormalities that are predisposing to infection [23–25, 28]. Fusconi et al. described a treatment of EAC bio-

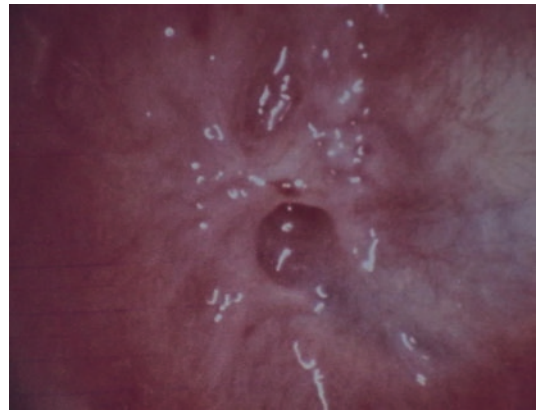

Fig. 9.5 Medial external auditory canal stenosis. Diffuse inflammation and scar formation obscuring landmarks of the tympanic membrane

films in COE patients with recurrent acute exacerbations by applying ciprofloxacin//hydrocortisone drops followed by topical acetic acid daily for 7 days to perform a "chemical peel" [29]. While end-of-treatment success in the 28 COE patients studied was 93%, relapses occurred in 57% of patients during long-term follow-up. Additionally, this study reported that chemical peels resulted in a longer time interval between relapses.

Cultures are recommended to direct antibiotic therapy and especially for persistent drainage after initial treatment [15]. Resistant organisms are more prevalent in chronic infections as compared to AOE [16]. It is also important to evaluate for TM perforations and open mastoid cavities because they may alter therapy if using ototoxic medications. The role of prior treatment with ototopical medications is controversial. Weber et al. did not find that use of ototopical medications increased resistance patterns [30], while Saunders et al. did find a higher rate of resistant bacteria in chronic or recurrent otitis externa cases with a history of prior antibiotic treatment, including ototopical medications [31]. Of particular concern is the relatively high rate of quinolone resistance in chronic ear infections [15, 31]. Studies report varying degrees of success with different management strategies for COE, so it is important to carefully evaluate contributing factors (microbial, anatomical, and systemic) for each patient and individualize treatment accordingly.

Cultures of drainage should be obtained in patients with persistent or recurrent otorrhea, especially if systemic antibiotics or ototoxic medications are being considered [32]. Quinolone drops are non-ototoxic and FDA approved for use in the middle ear, but many ototopical medications are potentially ototoxic (Table 9.1). Ototoxic medications should be avoided if possible in patients with a non-intact TM (e.g., TM perforation, tympanostomy tube, or mastoid opening) because ototoxic medications may cause vertigo and permanent sensorineural hearing loss (SNHL).

In 2004, the AAO-HNS published a consensus statement regarding the use of potentially ototoxic medications in the middle ear which stated that (a) non-ototoxic medications should be the first-line therapy; (b) if used, ototoxic medications should only be used in infected ears, and use discontinued shortly after the infection resolves; and (c) patients should be warned about the potential effects of ototoxic medications and instructed to call or follow up if hearing loss, dizziness, vertigo, or tinnitus develop [33]. The consensus panel did not believe at that time that routine auditory or vestibular testing was indicated if treatment duration was short (5–10 days) [33]. It is important to remember that vestibular symptoms may present without hearing loss and can therefore be missed when monitoring ototoxicity strictly based on hearing evaluations [34]. No specific guidelines for the treatment of COE have been published, but the AAO-HNS Clinical Practice Guidelines for AOE published in 2014 states that ototoxic medications should not be used in patients with a non-intact TM.

Table 9.1 Ototoxicity of topical medications in patients with non-intact tympanic membranes

Class	Medication	Ototoxicity	Comments
Antibiotics	Ofloxacin	No	FDA approved
	Ciprofloxacin	No	FDA approved
	Sulfacetamide	Unknown	Ophthalmological (e.g., Vasocidin)
	Tobramycin	Yes	Ophthalmological
	Gentamicin	Yes	Ophthalmological
	Neomycin	Yes	Component in Cortisporin
	Chloramphenicol	Yes	Otic component of "CSF" powder
Antifungals	Clotrimazole	Probably not	See discussion in the text
	Fluconazole	Unknown	
	Ketoconazole	Unknown	
	Miconazole	Unknown	
	Amphotericin B	Yes	Component of "CSF" powder
	Nystatin	Unknown	
Antiseptic	Gentian Violet	Yes	
	Boric Acid	Yes	
	Acetic Acid	Unknown	Ototoxic in chinchillas
	Cresyl acetate	Yes	Ototoxic in chinchillas
	Povidone iodine	Yes	Ototoxic in chinchillas
	Chlorhexidine	Yes	Ototoxic in rats

FDA = Food and Drug Administration; CSF = chloramphenicol, sulfamethoxazole, and amphotericin powder (the "F" in "CSF" was Fungizone, which was a trade name for amphotericin by E. R. Squibb & Sons, LLC), "Cortisporin otic" is the trade name for neomycin, polymyxin B, and hydrocortisone solution by Pfizer, "Vasocidin" was the trade name for sulfacetamide/prednisolone ophthalmic suspension by Novartis [21, 33, 46, 65]

Cases of AOE or COE refractory to treatment with a non-intact TM and culture-proven bacteria that are resistant to quinolone antibiotics present a challenging clinical situation. Treatment options for such patients include using a culture-directed systemic (non-ototoxic) antibiotic or a short-term application of a potentially ototoxic antibiotic. Systemic antibiotics are marginally effective in AOE and their benefit in patients with COE is unknown. In addition, the options for culture-directed systemic antibiotics in some cases may be limited to intravenous medications. Many otologists believe that ototoxic medications may be used for short durations in select cases that have culture-proven quinolone resistance as long as patients are well informed of the risks and alternatives.

There have been no randomized prospective trials to evaluate the safety of potentially ototoxic topical medications in patients with non-intact TMs, but there is clear evidence that prolonged or recurrent use of such medications can increase the risk of (SNHL) [35–38]. Winterstein et al. reported that, based on a large Medicaid claims database, there was no increased risk of SNHL for children with non-intact TMs using a single (brief) prescription of topical neomycin versus topical quinolone sometime during the study period (1 year following tympanostomy tube or TM perforation) [35]. However, children in that study who had received two or more prescriptions of topical neomycin during the study year had a 45% increased risk of developing SNHL versus the quinolone group. A study from Israel found no short-term hearing loss in 358 children with normal preoperative hearing who received 2 weeks of postoperative topical neomycin-polymyxin-hydrocortisone "prophylaxis" immediately following tympanostomy tube placement, based on audiometry tests performed 1–3 months postoperatively [36]. However, even if all children in the study had 3 months of follow-up, that would still be only 90 patient-years of follow-up, probably too low a number to detect medication-related SNHL. In the Winterstein study, the estimated rate of developing SNHL in the year following tympanostomy tube or TM perforation was 7.4 cases per 1000 person-years in the topi-

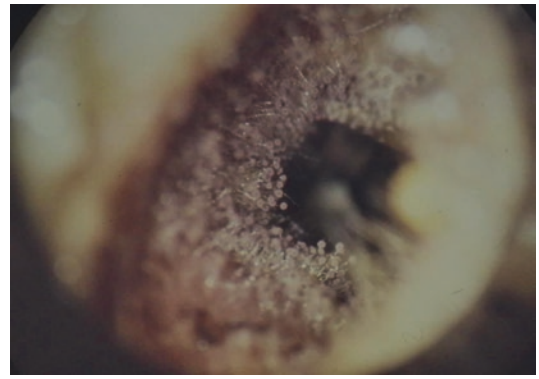

Fig. 9.6 Fungal otitis externa due to mold. Black hyphae consistent with *Aspergillis species*

cal quinolone group versus 10.7 cases per 1000 person-years in the group that received more than one topical neomycin prescription, a difference of 3.3 excess cases per 1000 patient-years that was significant [35].

Case reports confirm the toxicity of repeated or prolonged use of ototoxic medications. Linder et al. reported two cases of irreversible severe SNHL in adults with chronic TM perforations whose deafness developed soon after prolonged (1–2 months) use of topical aminoglycoside-containing medications (neomycin in one, polymyxin-neomycin-hydrocortisone in the other) [37]. Matz et al. performed a literature review of all publications (including case reports) 1966–2004 that included a discussion of hearing loss or vestibular dysfunction resulting from ototopical medications, and found 54 well-documented cases of ototoxicity from topical gentamicin and 13 from topical neomycin [38]. Vestibular toxicity was reported more often than cochlear toxicity in the studies included in this review.

If used in the presence of a non-intact TM, the authors believe that potentially ototoxic medications should be given for only short durations (1 week), discontinued once the infection has resolved, and patients should be closely monitored for the duration of their therapy. More difficult COE cases may require both systemic and topical therapy, as well as management of any underlying predisposing factors (dermatological, anatomical, or systemic) as above.

Otomycosis

Fungal infections are relatively less common when compared to bacterial infections in otitis externa, with rates reported between 7% and 24% for all types of chronically draining ears [16, 39–43]. Risk factors include prior treatment with ototopical medications, history of a chronic infection, tropical climates, and prior otologic surgeries, especially canal wall down mastoidectomies [44, 45]. Unlike AOE that peaks in summer months in temperate climates, otomycosis may have a higher incidence in the autumn [40, 46]. Otorrhea, otalgia, pruritus, aural fullness, and hearing loss are the most common presenting symptoms making it difficult to differentiate from other otitis externa infections [41, 42, 45]. Physical examination may show black hyphae in the ear canal, which is nearly pathognomonic for *Aspergillus* species (Fig. 9.6). Alternatively, there may be a thick, creamy, semi-solid discharge (Fig. 9.7), often referred to as fungal mats, and these are more common in *Candida* infections. Both hyphae and fungal mats may be present, but physical findings may also be nonspecific depending on the state of fungal growth. Other common otomycosis physical exam findings include the absence of significant edema of the canal skin and well-circumscribed areas of granulation tissue on the tympanic membrane or in the external canal [41, 45]. In a study of over 1000 fungal infections, 61% were originally misdiagnosed as bacterial otitis externa and only

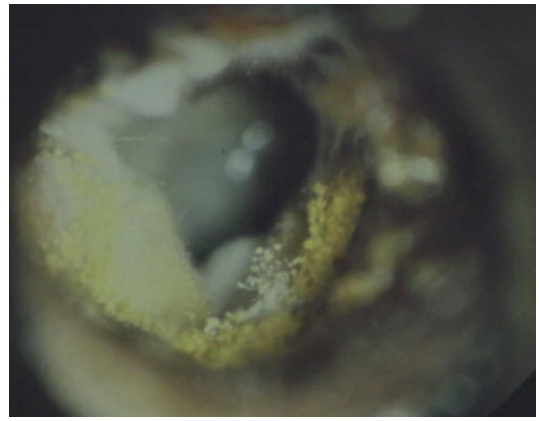

Fig. 9.7 Fungal otitis externa due to yeast (*Candida*). Thick yellow discharge and white hyphae consistent with *Candida species*

11.6% were diagnosed correctly on initial presentation [40]. In a more recent study of chronically draining ears, only 38% of otomycosis cases had physical examination findings typical of fungal infection [16]. Because of this inaccuracy of clinical diagnosis, cultures are essential to obtaining the correct diagnosis in suspected cases of otomycosis.

Otomycosis is most commonly caused by *Candida* species or *Aspergillus* species with relative frequencies varying by region [16, 40, 44, 47, 48]. *Candida albicans* has been reported as the most common *Candida* species in otomycosis followed by *C. parapsilosis* [16, 40, 44]. *Candida* species tend to cause superficial infections of the ear canal whereas *Aspergillus* species have a tendency to cause more aggressive infection involving the deeper subcutaneous tissues [7]. Commonly cultured *Aspergillus* species include *Aspergillus niger* and *Aspergillus fumigatus*. Although less common, *Mucor* species or *Penicillium* species may also cause otomycosis [49].

Treatment approaches vary widely and may include topical antifungal therapy, topical "painting" of the ear canal with antiseptics such as the dye gentian violet (methylrosanilin), topical steroids, oral antifungals, acetic acid, and aluminum acetate otic [41, 42, 45]. There are no FDA-approved topical antifungal agents for otomycosis. Serial debridement of the ear canal of fungal debris, performed with microscopic direct visualization so not to introduce additional trauma to the canal, is important in some cases for control of the infection. Typically topical antifungals are the most common first-line therapy, although practice patterns vary widely [42].

Azoles, which include the older imidazoles (e.g., clotrimazole, ketoconazole, miconazole) and newer triazoles (e.g., fluconazole, itraconazole, voriconazole), have coverage of yeasts, molds, or both. In general, molds are more difficult to treat and agents such as fluconazole, when used systemically, are only effective against yeasts. Although there is no consensus on the optimal treatment of otomycosis, topical cotrimazole is often considered the first-line treatment in the U.S. It can be used topically as ear drops or cream applied to the EAC in the office. It is thought to be non-ototoxic even in ears with non-intact TMs, although this has not been studied in prospective trials. A small study in animals found no ototoxicity from either topical clotrimazole 1% solution or topical miconazole cream 5% applied to the middle ears of guinea pigs [50]. Herasym et al. reviewed all the literature pertaining to topical clotrimazole use in humans with otomycosis and found only two studies that specifically mentioned ototoxicity (there was none) [51]. Fluconazole is often administered orally but has reports of topical use in otomycosis [47]. Azoles have been shown effective in up to 95% of patients [45]. The polyene antifungals nystatin (not tested for ototoxicity) and amphotericin B (ototoxic) can also be applied topically as either a

powder or cream [47]. Many otomycosis cases due to *Aspergillus* or resistant *Candida* species may require oral azoles such as itraconazole or voriconazole. Cresyl acetate otic (86% cure rate but ototoxic) and aluminum acetate otic (86% cure rate but ototoxic in chinchillas with TM perforations [52]) also have relatively high cure rates [45, 47]. In a survey of over 100 otolaryngologists, Arndal et al. found 80% of physicians used topical antifungal therapy as initial therapy and 27% used some kind of antiseptic therapy [42]. However, many antiseptic therapies (e.g., gentian violet, acetic acid, povidone iodine) have been shown to be ototoxic in animal models and therefore should be avoided if possible in patients with tympanic membrane perforations [42, 47].

Chronic Myringitis

Myringitis, or "chronic myringitis," is an external ear infection characterized by loss of the epithelium of the TM leading to the formation of granulation tissue on the TM and in the external canal. It occurs in the absence of middle ear involvement. Various degrees of myringitis may exist ranging from a mild form with a denuded TM to a diffuse carpet of granulation tissue on the tympanic membrane (Fig. 9.8) and external canal [53]. It is important to distinguish myringitis from acute bullous myringitis, an idiopathic condition of the tympanic membrane without a known infectious etiology. Bilateral involvement has been reported in nearly 20% of cases of myringitis [53]. Myringitis typically presents with malodorous otorrhea, pruritus, and aural fullness and patients may have less associated otalgia than in acute infections [54]. It should be distinguished from tympanic membrane infections secondary to otitis media by the absence of significant hearing loss, a mobile tympanic membrane with pneumatic otoscopy and a normal tympanogram. It displays a relapsing and remitting course and can be extremely difficult to manage [55]. In a prospective study Wolf et al. found it recurred in over a quarter of patients despite appropriate therapy [53].

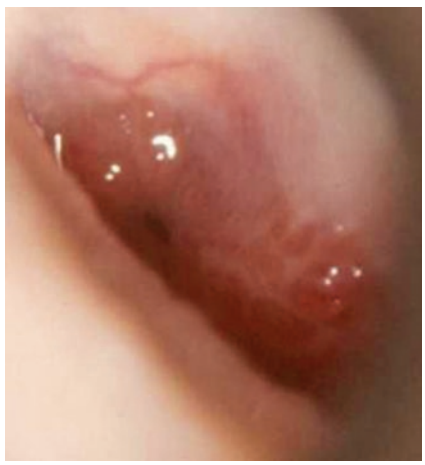

Fig. 9.8 Diffuse granular myringitis. Granulation tissue covers the lateral surface of the tympanic membrane

The microbiology of myringitis is similar to other otologic infections although resistant bacteria are more commonly cultured. Approximately 40% of myringitis cases are due to resistant bacteria, including MRSA in 14–17.5% of infections [16, 56]. These results reflect the chronic nature of this condition. *Corynebacterium* is frequently associated with chronic myringitis and should always be included in culture data when present [15].

Treatment options may include a wide range of topical medications and may require cauterization or debridement [54]. Jung found a 96% reduction in the recurrence rate using dilute vinegar solution in patients who failed treatment with antibiotics and steroids [54]. Other topical treatments include gentian violet and 5-fluorouracil [57]. When granulation tissue is present, CO_2 laser ablation and surgical excision has also been shown superior to topical combinations of antibiotics and/or steroids [56, 58, 59].

Acute Localized Otitis Externa

Acute localized otitis externa (ALOE) or furunculosis is defined as localized swelling of the lateral cartilaginous EAC, often associated with an infected hair follicle. It most commonly involves the posterior lateral canal and may present with pain, localized swelling, otorrhea, pustular lesions, and/or fluctuance [20]. *Staphylococcus*

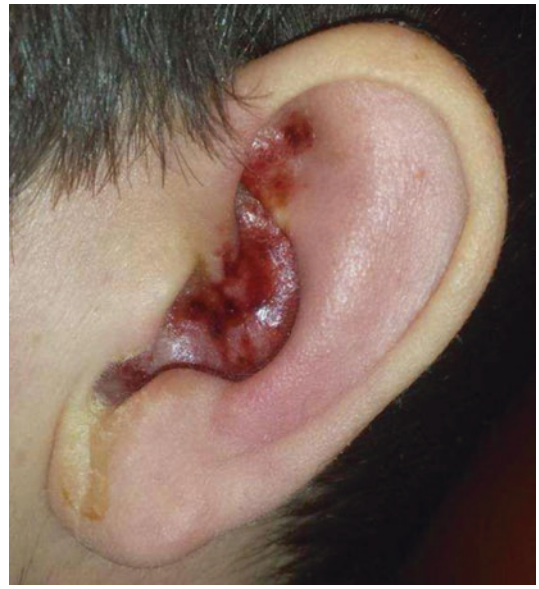

Fig. 9.9 Ramsey-Hunt Syndrome (Herpes Zoster Oticus). Vesicular lesion in the conchal bowl of the pinna

aureus has been identified as the most common pathogen [60]. Treatment options include heat, incision and drainage, and oral antibiotics with anti-staphylococcal coverage [25].

Ramsay-Hunt Syndrome

Ramsay-Hunt syndrome (herpes zoster oticus) is the reactivation of latent varicella zoster virus in the geniculate, spiral, and/or vestibular ganglions. It is relatively uncommon with an estimated incidence of five cases per 100,000 population [61]. It typically presents with facial paralysis and a painful vesicular rash in the concha (Fig. 9.9) or EAC, but may also include, hearing loss, polycranial neuropathies, dysgeusia, tinnitus, and cochlear vestibular symptoms [61–65]. In some patients Ramsay-Hunt syndrome may additionally present with tongue, buccal, laryngeal or palatal vesicles, and vocal fold paralysis [64]. When compared to Bell's palsy, facial nerve symptoms are typically more severe in Ramsay-Hunt (House-Brackmann Grade of facial palsy of III-VI/VI) and less likely to recover [61, 62, 66].

Treatment typically involves oral antivirals (e.g., acyclovir, valacyclovir, famciclovir), plus corticosteroids [62, 67]. The majority of patients will have improvement in facial function to a House-Brackmann I or II, but the more severe cases may not recover [66]. On average, patients recover three grades on the House-Brackmann scale [61]. Higher recovery rates have been demonstrated in patients with therapy starting within the first 3 days when compared to those treated after 1 week [68].

Other Considerations for Differential Diagnosis

Several conditions can mimic external ear infections and should be considered in the differential diagnosis (Table 9.2). Middle ear disease may present with otorrhea, otalgia, and hearing loss but can be differentiated on physical exam using pneumatic otoscopy. Patients who are diabetic or immunosuppressed have an increased risk of developing malignant otitis externa (see Chap. 10) [14]. Cholesteatoma, keratosis obturans, or malignancy may harbor infectious bacteria mimicking an infection but will not resolve until the underlying cause is addressed. Autoimmune diseases, such as Sjögren's syndrome, systemic lupus erythematosus, or granulomatosis with polyangiitis, cause an underlying skin reaction which makes tissues more prone to superinfection [23]. Management of patients with these diseases includes treatment of

Table 9.2 Differential diagnosis for external ear infections

System	Differential diagnosis
Autoimmune	Sjögren's Syndrome Granulomatosis with polyangiitis Systemic lupus erythematosis
Dermatologic	Eczema Psoriasis Seborrheic dermatitis
Neoplastic (benign)	Cholesteatoma Keratosis obturans
Neoplastic (malignant)	Basal cell carcinoma Squamous cell carcinoma
Musculoskeletal	Temporomandibular joint syndrome
Infectious	Malignant otitis externa
Inflammatory	Medial third stenosis
Allergic	Contact dermatitis Drug reaction

the underlying causes as well as treatment of any superinfection. Dermatologic conditions such as eczema, psoriasis, seborrheic dermatitis, or contact dermatitis may present similarly or may perpetuate infection and thus need to be treated appropriately [14, 23]. Temporomandibular joint syndrome presents as otalgia in a non-inflamed ear and is usually associated with bruxism and pain radiating to the preauricular area. Crepitus and tenderness to palpation over the area can often be found on exam and is helpful in differentiating from external ear infections. Medial third stenosis, an uncommon idiopathic condition that results from extensive scarring of the EAC, may also be considered in the differential diagnosis. This condition generally develops spontaneously, but may follow a trauma, infection, or surgery. It typically present with chronic otorrhea with granulation tissue in the medial end of the EAC. Secondary acute infections may occur, but the underlying etiology is not believed to be infectious and cultures are often negative.

Conclusion

Otitis externa is a common complaint in otolaryngology offices and may be caused by bacterial, fungal, or viral infections. History and physical examination findings provide clues to the type of infection but persistently draining ears should be cultured to evaluate for resistant bacteria or fungal causes of infection. Treatments typically involve topical antimicrobials and may also require topical antiseptics, topical corticosteroids, oral antibiotics in some cases, and debridement.

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Malignant Otitis Externa

10

Marlene L. Durand

Introduction

Malignant otitis externa (MOE), also called invasive or necrotizing otitis externa, is a subacute to chronic invasive infection of the external auditory canal (EAC) and temporal bone. The disease primarily affects older diabetics, and the major pathogen is *Pseudomonas aeruginosa*. The typical finding is granulation tissue in the ear canal at the cartilage-bony junction. Nearly all patients present with persistent, unilateral ear pain and most have ear drainage. Common features of MOE are listed in Table 10.1.

Patients with MOE are often misdiagnosed for weeks to months. They are frequently given multiple courses of antibiotic ear drops, or even short courses of oral antibiotics, but their ear pain progressively worsens. Misdiagnosis is common because MOE is very rare and patients do not present with features typical of infection. They are usually afebrile and have a normal white blood count. An erythrocyte sedimentation rate might provide a clue if ordered, as this is typically very high. In approximately 25% of patients, a facial palsy develops before the correct diagnosis is considered.

The infection was first described by Melzer and Kelemen in 1959 [1], but Chandler was the first to name it "malignant external otitis" because 6 of the 13 cases he described died [2]. Chandler gave the infection its "malignant" designation in 1968, however, and since then the mortality has fallen dramatically. In many series, the mortality due to MOE is 0–5%. This lower mortality is partly due to the availability of better anti-*Pseudomonas* antibiotics. The antibiotics commonly used to treat MOE today, such as ciprofloxacin and ceftazidime, became available in the U.S. in 1985 or later. The lower mortality today is also due to earlier recognition and treatment of the disease. However, late diagnoses still occur and delay in diagnosis can affect both morbidity and mortality.

Definition. A formal definition for MOE has not been universally adopted and there is some variability in the literature as to what constitutes a case. Thirty years ago, Cohen and Friedman reviewed the 107 cases of MOE published 1959–1985 and based on the frequency of various characteristics of those cases, proposed that MOE criteria should include all of the following: (1) ear pain, (2) exudate, (3) edema, (4) granulations, (5) either failure of at least 1 week of local treatment or a positive technetium 99m (Tc99m) bone scan, and (6) evidence of microabscesses

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_10

Table 10.1 Malignant otitis externa: common clinical, laboratory, and radiologic features[a]

Diabetes (or less often, immunocompromised)
Older age (usually >60 years)
Pain in the involved ear. Persistent ear pain, often gradually worsening over weeks to months, is present in almost all patients with malignant otitis externa (MOE).
Ear canal edema, exudate, and granulation tissue
Culture positive for *Pseudomonas aeruginosa*
Elevated erythrocyte sedimentation rate (ESR), often >50
Cranial nerve (CN) palsies are usually late findings. CN 7 is most common (~25% of patients). Other CN palsies include 9–11, 12, or less often 6.
Abnormal computed tomography (CT), magnetic resonance imaging (MRI), or technetium 99m scan. Note that bone erosion is not always present.
Rapid decrease in ear pain on appropriate systemic antibiotic therapy. Pain usually starts to decrease by 1 week, resolves by several weeks. Decrease in pain is usually the first indication of response to therapy.
Gradual decrease (e.g., weeks) in ESR with appropriate antibiotic therapy.
Gradual improvement (e.g., weeks to months) in soft tissue changes on CT or MRI. Changes of bony demineralization on CT usually persist, sometimes for years.
Failure to respond to empiric anti-*Pseudomonas* therapy should suggest an alternative diagnosis such as fungal MOE (usually due to *Aspergillus*), a malignancy, or MOE due to a bacterial species (or *Pseudomonas* strain) resistant to the antibiotics chosen.

[a]Not present in all patients. Some patients are immunocompetent, some are young, some do not have ear canal edema or exudate, etc.

if surgery is done [3]. Diabetes (90% of cases) and a culture (usually ear drainage) positive for *Pseudomonas* (98% of cases) were not required for diagnosis but were supportive. Recent studies include some cases that meet most but not all of the Cohen and Friedman criteria, as studies of MOE are retrospective and some symptoms or signs (e.g., canal edema) may not be recorded in the medical record. Technetium 99m scanning, although sensitive for osteomyelitis, can be nonspecific and falsely positive in acute otitis externa. Computed tomography (CT) scanning is the radiologic imaging of choice for MOE at most centers but CT underestimates the presence of bony involvement. For example, 30% of MOE patients in one study had no CT evidence of bony erosion, including two patients with facial nerve palsy [4]. The diagnosis of MOE is based on a combination of clinical, radiologic, and laboratory findings as discussed later.

Pathophysiology

Pseudomonas aeruginosa, the major cause of MOE, is not a normal colonizer of the ear canal but may be introduced by exposure to water. *Pseudomonas* colonizes <2% of healthy ear canals [5], and the incidence in diabetics appears to be similar [6]. *Pseudomonas* is a water-loving Gram-negative bacillus and can be found in lakes and rivers in concentrations of 10–>1000 organisms per 100 mL [7]. Although only about 2% of drinking water samples test positive, *Pseudomonas* can form biofilms in plumbing fixtures and can be isolated from showerheads, faucets, and sink drains. Hospital water supplies have been the source of several outbreaks of serious *Pseudomonas* infections in susceptible populations, such as neonates in an intensive care unit [8]. Several studies have reported a significant association between MOE and a history of irrigation of the ear canal to remove wax, with the irrigation usually occurring a few days before symptom onset [9–11]. It is possible that the microtrauma of the irrigation and contamination of irrigation water by *Pseudomonas* contribute to the development of MOE in some susceptible hosts.

Diabetes is the major risk factor for MOE but the reason for this is unknown. In many MOE patients, diabetes is mild and in good control, and hyperglycemia is probably not a risk factor in itself [12]. It has been postulated that the microangiopathy characteristic of diabetes results in increased susceptibility to infection once pathogens have been introduced into the ear canal [12].

In MOE, pathogens such as *Pseudomonas* invade through the ear canal into the adjacent bony and soft tissue structures. The initial site of invasion probably occurs at the osseous-cartilaginous junction of the external ear canal, since this junction is where granulation tissue is usually found in MOE cases. As infection progresses, there may be involvement of cranial nerves. Cranial nerve (CN) 7 is the CN involved

most commonly and signifies spread within the temporal bone toward the stylomastoid foramen (CN 7). Infection can also spread toward the jugular foramen (CN 9, 10, 11), hypoglossal canal (CN 12), or petrous apex of the temporal bone (CN 6, less often CN 5). Extension anteriorly into the temporomandibular joint (TMJ) can cause joint destruction, with resulting pain and trismus. Spread of infection across the skull base may reach the clivus and then progress to the opposite side. Spread of infection is typically slow, and involvement of the clivus usually occurs only after several months of symptoms. Figure 10.1 illustrates locations of important bony structures and CNs involved in MOE.

Epidemiology

Malignant otitis externa occurs worldwide. Table 10.2 lists 15 studies published since 2007 from centers in Taiwan, Australia, Singapore, India, Saudi Arabia, Israel, Turkey, Tunisia, France, the United Kingdom, and the U.S. [4, 13–26]. These 15 studies include a total of 397 patients with MOE and have features similar to earlier studies: diabetes is the major risk factor (79% of cases, range 51–100%), three-quarters of patients are male (range 63–89%), and the mean age is over 70 years old. Diabetes may be mild in MOE and controlled only by oral hypoglycemic medications. Many series include a few patients who are younger than 40 years [4, 13, 15, 17–19], and most of these younger patients are immunocompromised or have Type 1 diabetes. Immunocompromising conditions have included HIV [27], end stage renal disease on hemodialysis, solid organ transplant, acute leukemia, chemotherapy, and corticosteroid therapy. A few cases occur in patients without an apparent risk factor other than advanced age. Cases in children are very rare [28].

The incidence of MOE is very low. A study from Spain found that there were 355 hospital admissions in Spain for MOE during 2008–2013, yielding an incidence of 1.3 cases per million population per year [29]. The incidence was higher in men than women (relative risk 2.4), and the predominant age group was over 84 years old (incidence of 19.3 cases per million population per year). A study from the U.S. used the Nationwide Inpatient Sample database, a database reported to represent approximately 20% of all U.S. admissions, and found there were 8300 admissions for MOE during a 12-year period (2002–2013) [30]. Using this information, and assuming an average U.S. population of 300 million people, one can calculate an approximate incidence of MOE of 11 cases per million population. The U.S. database study found no increase in admissions for MOE from 2002 to 2013, but a similar study in the U.K. found a 2.5-fold increase during a time period when total hospital admissions increased only 1.4-fold [31].

Clinical Manifestations

Clinical manifestations will vary depending on duration of symptoms prior to diagnosis. Diagnosis is often delayed by weeks to months. Loh et al. reported that the time from symptom onset to diagnosis was a mean of 7 weeks (range 1–12 weeks) [25], while Pulcini et al. reported a mean delay of 3 months [22].

Nearly all patients with MOE have unilateral ear pain, and most have otorrhea. Patients may also have a headache on presentation with MOE, usually temporal or parietal, on the affected side. The ear pain may be mild initially but gradually worsens to a deep, aching, persistent pain. It is often worse at night and awakens the patient from sleep. The pain may worsen with chewing, especially if there is involvement of the TMJ. Temporomandibular joint pain may be present in 20% of patients [24], and TMJ involvement may cause tender preauricular swelling and trismus. One series found severe TMJ involvement in 15% of MOE patients, with diagnosis occurring an average of 3.5 months after onset of otitis symptoms [32]. Another study found CT evidence of significant TMJ involvement (abscess or osteomyelitis) in 26% of patients [15].

Facial nerve palsy is present in approximately 25% of patients at the time of MOE diagnosis (Table 10.1). Rarely, cranial nerve 7

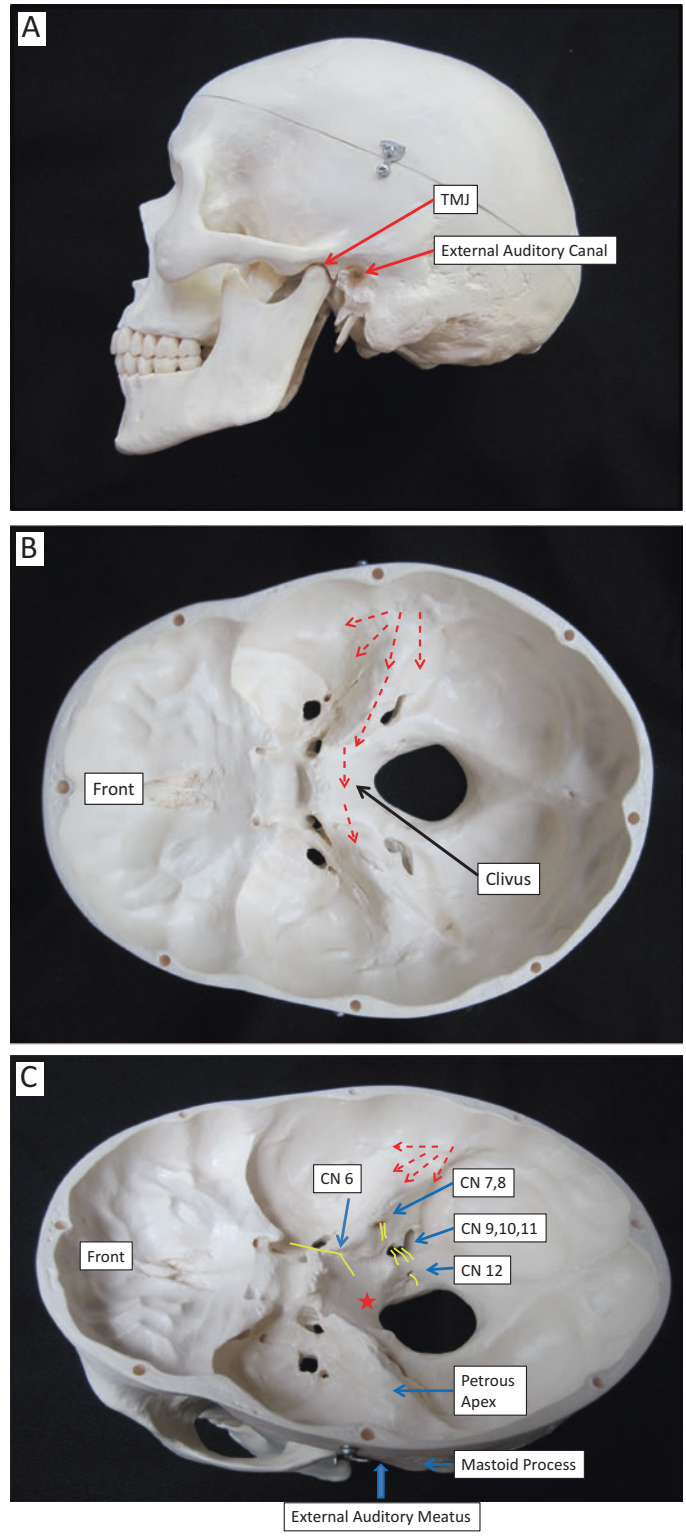

Fig. 10.1 Anatomy of malignant otitis externa (MOE). (**a**) Note the proximity of the external auditory meatus to the temporomandibular joint (TMJ), a structure often involved in MOE. (**b**) Infection may spread (dotted red lines) across the skull base to the clivus and to the opposite side. (**c**) Approximate location of various cranial nerves (CN) that can be involved in MOE. The clivus is indicated by a star, and dotted red arrows indicate potential directions of spread of infection in MOE from the external auditory canal (photographs by Dr. Marlene L. Durand)

Table 10.2 Malignant otitis externa (MOE): recent series of cases from centers around the world

Author (Country)	Study years	*N*	Male	Mean age (years)	Diabetes (%)	Any CN palsy (CN 7 alone)	Pseudomonas[a]	Mortality from MOE[b]
Hamzany [13] (Israel)	1990–2008	60	65%	73	83	20% (20%)	74%	10%
Al-Noury [14] (Saudi Arabia)	NR	18	89%	65	100	39% (28%)	NR	6%
Sudhoff [4] (UK)	"10 years"	23	83%	71	91	43% (26%)	86%	0
Chen [15] (Taiwan)	1995–2010	19	63%	67	82	31% (26%)	29%	0
Hobson [16] (USA)	1995–2012	20	NR	65	75	25% (25%)	53%	0
Franco-Vidal [17] (France)	1995–2005	46	70%	74	65	20% (20%)	75%	4%
Hariga [18] (Tunisia)	1997–2006	19	NR	72	95	32% (32%)	71%	0
Chin [19] (Australia)	1998–2007	24[c]	NR	64	54	NR	68%	4%
Meade [20] (UK)	2000–2009	37	81%	81	51	65% (41%)	29%	0
Stevens [21] (USA)	2004–2014	28	86%	62	93	29% (29%)	NR	18%
Pulcini [22] (France)	2004–2011	32	80%	74	63	25% (25%)	88%	0
Lambor [23] (India)	2006–2012	27	81%	64	96	33% (26%)	56%	15%
Bhat [24] (India)	2006–2013	15	80%	N/A	93	7% (7%)	92%	0
Loh [25] (Singapore)	2006–2011	19	84%	69	95	21% (21%)	90%	16%
Karaman [26] (Turkey)	2007–2012	10	70%	74	90	40% (40%)	90%	0
TOTAL or Mean	–	397	76%	73	79	30% (25%)	–	5%

CN = cranial nerve; MOE = malignant otitis externa; UK = United Kingdom; USA = United States of America; NR = not reported

[a]Of cultures that grew pathogens (excluded skin flora)

[b]An additional 0.5% (two patients) died from complications of antibiotic therapy: catheter-related infection [16] and intracranial hemorrhage from ceftazidime-related thrombocytopenia [25]

[c]Chin et al. included a case with squamous cell cancer, which would have been excluded in other series

palsy develops as early as 1 week after onset of otitis symptoms, but it is usually a late finding. The facial nerve is the cranial nerve most commonly involved because of the proximity of the stylomastoid foramen to the external ear canal and susceptibility to involvement with temporal bone erosion. Other cranial nerve palsies are present in approximately 5% of patients, most commonly involving the lower cranial nerves (CNs 9–12) [20, 23, 33].

At the time of MOE diagnosis, physical examination reveals granulation tissue in the ear canal in most cases (75–100%) [3, 23, 34]. Canal edema and drainage are also usually seen, and occasionally exposed bone is visible in the canal (5% of cases in one series) [34]. The tympanic membrane, when visible, is usually intact. Movement of the pinna may elicit ear pain. The space between the mandible and mastoid tip may be tender on digital palpation. Facial palsy or other cranial neuropathies may be present, as noted above. A conductive hearing loss is often present in the affected ear due to soft tissue blocking the external canal [20]. The remainder of the physical examination is usually normal.

Fever is uncommon in MOE and reported in approximately 5% of patients (range 0–13%) [20, 22, 24]. Fever usually occurs late in the course of untreated infection. Any patient with fever should be evaluated for other fever sources such as pneumonia, urinary tract infection, bacteremia, as well as possible complications of MOE. Bacteremia is very rare in MOE except in pediatric cases. Since many patients admitted with MOE have had trials of oral antibiotics and antibiotic use can lead to *Clostridium difficile* infection, patients complaining of diarrhea should be evaluated for *C. difficile* infection. This infection can lead to toxic megacolon and bowel perforation if not diagnosed and treated early. Patients with MOE who have fever and headache may have extension of infection to the central nervous system, and evaluation for this should be considered.

Laboratory Findings

Laboratory studies are usually normal except for elevated glucose levels in diabetic patients, and an elevated ESR or C-reactive protein (CRP). Diabetic patients with any infection develop some glucose intolerance even if they were previously in good control. Diabetic patients may have noticed a gradual increase in their blood glucose levels on home monitoring, prior to the diagnosis of MOE. The glucose level is often elevated on admission with MOE but ketoacidosis is very rare. Because some patients with MOE may have previously unrecognized diabetes, all the patients should be evaluated with a fasting glucose and hemoglobin A1C level.

The ESR is often very high, from 50 to over 100 mm/h. There are few non-rheumatologic chronic conditions that give such high ESR values. A study from Egypt found an elevated ESR, ranging from 70 to 150 mm/h (mean 103), in all the patients tested [35]. This is a higher mean than seen in other studies, and some patients with MOE may have a normal ESR or CRP. A study from Singapore reported a mean ESR of 67 mm/h, with 16% of patients having a normal ESR [25]. The CRP was elevated in 72% of the patients in this study (mean 43 mg/L) but normal in 28% [25]. A normal ESR or CRP, although unusual, does not exclude MOE.

The ESR should be obtained in all the patients as soon as MOE is suspected, and again at the start of antibiotic therapy. This will serve as a baseline value, and repeating ESR levels every few weeks is helpful in monitoring antibiotic therapy. Successful therapy is nearly always accompanied by a gradual decline in ESR. Relapse of infection is often accompanied by an increase in ESR levels.

The white blood count is usually normal or mildly elevated. The mean white blood count in one study was 10,000 cells/μL [25]. In a patient with MOE who has marked leukocytosis, an evaluation for other sources of infection (e.g., pneumonia, bacteremia) or complications of MOE (e.g., *C. difficile* infection, drainable abscess) should be considered even if the patient has no fever.

Bacteriology

A swab culture of the ear canal should be obtained in all the cases of suspected MOE. A small biopsy for culture of granulation tissue in the ear canal may be helpful, and is often necessary if the patient has no ear drainage. A deeper biopsy or surgery (e.g., mastoidectomy) for culture is usually not necessary except in atypical cases or cases that have progressed despite empiric anti-*Pseudomonas* therapy. In such patients, a surgical specimen for culture can be life-saving as it may reveal an unsuspected pathogen such as *Aspergillus*. Biopsy is also critical in ruling out a potential malignancy which might have a similar clinical presentation.

Pseudomonas aeruginosa. This Gram-negative bacillus, an obligate aerobe, is the most common cause of MOE. In older studies, especially before the availability of fluoroquinolone ear drops, *Pseudomonas* was the pathogen in 98% of MOE cases [3]. More recent studies have shown a higher rate of negative cultures (approximately 20%, including those with skin flora contaminants) and a lower rate of *Pseudomonas*

(Table 10.1). Some studies report recovery of *Pseudomonas* in only 30% of culture-positive cases [15, 20]. Fluoroquinolone ear drops in particular may have contributed to this lower rate of recovery of *Pseudomonas*, as these ear drops can suppress superficial cultures. Fluoroquinolone ear drops have been available for 20 years and are highly active against most strains of *Pseudomonas*. In the U.S., ofloxacin and ciprofloxacin/dexamethasone otic solutions were approved by the Food and Drug Administration (FDA) in 1997 and 2003, respectively.

It is important to consider that cultures taken from the ear canal may reflect colonizing bacteria, selected by use of antibiotic ear drops, rather than the pathogen causing MOE. For example, *Staphylococcus aureus* is found in 5–15% of positive cultures in some MOE studies [15, 17, 20, 23], including some isolates that are methicillin-resistant (MRSA) [16]. However, the ear canal is not sterile and *S. aureus* can be a normal colonizer. Other organisms, such as enteric Gram-negative bacilli, enterococci, and *Candida*, can also colonize an ear canal, especially after selective pressure from chronic antibiotic ear drops. Studies reporting a non-*Pseudomonas* etiology for some MOE cases cannot support this etiology if treatment includes an antibiotic active against *Pseudomonas* and the patient improves. One study reported that 50% of the cultures obtained in MOE patients grew an organism other than *Pseudomonas* (e.g., Enterobacteraciae 23%, *Candida* 13%, *S. aureus* 9%, streptococci 1%), but treated all patients with a *Pseudomonas*-active regimen (ceftazidime or ciprofloxacin) [35]. Studies of MOE prior to availability of fluoroquinolones reported *Pseudomonas* as the cause of over 95% of cases [3].

Failure of response to anti-*Pseudomonas* therapy in a patient with negative cultures should prompt concern for another pathogen. Bacterial pathogens such as *S. aureus*, MRSA, and Gram-negative bacilli other than *Pseudomonas* may be rare causes of MOE (probably <5% of cases). Fungi such as *Aspergillus* can cause MOE and are important causes of failure to respond to empiric anti-bacterial therapy. Again, occult malignancy should also be considered.

Fungi. *Aspergillus* and other fungi may cause MOE. The incidence of fungal MOE is <5%. Only 4 of the 15 studies listed in Table 10.1 reported any cases of fungal MOE [13, 17, 19, 20], and in total these comprised 4% of all MOE pathogens. Fungal MOE occurs in temperate as well as hot climates, and cases have been reported from the U.K. [20], France [17], Australia [19], and Israel [13] in addition to other countries.

Aspergillus is the most common cause of fungal MOE, usually accounting for over 90% of cases. Three series listed in Table 10.2 included only 1–2 fungal cases each (2–8%) and all were due to *Aspergillus fumigatus* or *A. flavus*. A study from Israel reported the highest incidence (15%) of fungal MOE, and these cases were due to *Aspergillus*, *Pseudallescheria boydii* (also known as *Scedosporium*), and the yeasts *Malassezia* and *Candida* [13]. Walton et al. studied 32 other cases of fungal MOE reported in the literature and found that *Aspergillus* accounted for 91% (29 cases) [36]. The remaining three cases were due to *Scedosporium*, *Malassezia*, or unknown. An immunocompromising condition such as malignancy (especially acute leukemia), AIDS, or solid organ transplant is a risk factor for fungal MOE and may be present in half of the cases [36]. Other cases are associated with diabetes; rare cases have no apparent risk factor [36].

Diagnosis of fungal MOE is difficult and often delayed. As a consequence, the patient may present with advanced infection. Two literature reviews found that cranial neuropathies were present in approximately 50% of patients with fungal MOE, a higher incidence than is usually seen in *Pseudomonas* MOE [36, 37]. Swab cultures of ear canal drainage often fail to make the diagnosis of fungal MOE and tissue biopsy of canal tissue may be helpful [36]. Cultures from a mastoidectomy are required to make the diagnosis of fungal MOE in many cases. Patients also may have a mixed infection in MOE, with both *Pseudomonas* and a fungus, so failure to respond fully to a course of antibiotics for *Pseudomonas* should raise this possibility. A recent case report illustrated this. A 79-year-old diabetic man initially stabilized on treatment for culture-positive *Pseudomonas* MOE but then had persistent dis-

ease [38]. Removal of a bony sequestrum from the ear canal revealed a mold (*Scedosporium*), and the patient improved after the addition of voriconazole [38].

Radiology

The CT scan is the radiologic study of choice for initial evaluation of MOE. A magnetic resonance imaging (MRI) study is also helpful in many cases to establish the extent of disease, and MRI is complementary to CT. Radionuclide studies such as the Tc99m bone scan and gallium citrate (Ga-67) scan may show inflammation earlier than CT or MRI but they lack anatomic specificity.

Common CT findings in MOE are listed in Table 10.3. Involvement of the external auditory canal is present in 90–100% of the cases, and bony erosion in the canal is seen in 70–100% of the cases [4, 15–17, 19]. Soft tissue in the ear canal and fluid in the mastoid or middle ear are also very common findings. Canal and mastoid or middle ear findings are considered evidence of localized extension of infection (called "minor" by some authors [25]). "Major" extension of infection includes involvement of the soft tissues of the infratemporal fossa, temporomandibular joint, parotid, parapharyngeal or nasopharyngeal space, petrous apex, and skull base (Figs. 10.2, 10.3, and 10.4). The infection can progress across the skull base, eventually extending to the center with erosion of the clivus (Fig. 10.3). Intracranial abnormalities are often missed on CT, and an MRI is indicated for these. Not all the patients with MOE have an abnormal CT on presentation. One study found a normal CT in 11% of cases [17].

Computed tomography findings of bony erosion persist long after clinical improvement. A study of nine patients with initial and follow-up CT scans demonstrated that clinical cure predated radiologic regression in all cases [39]. Follow-up CT scans were performed 8–37 months after completing antibiotics in this study. Progressive resolution of soft tissue abnormalities was noted while bony demineralization persisted in all cases.

Magnetic resonance imaging is complimentary to CT. Although MRI is less sensitive than CT for bony changes, MRI is better for detecting involvement of the central nervous system and for defining soft tissue abnormalities (Fig. 10.4). Al-Noury and Lotfy compared CT and MRI findings in 18 patients with MOE and found that CT was more likely than MRI to detect abnormalities of the infratemporal fossa but MRI detected more cases with nasopharyngeal extension or petrous

Table 10.3 Common findings on computed tomography (CT) in malignant otitis externa

Abnormality[a]	Loh [25] ($N = 19$)	Chen [15] ($N = 17$)	Al-Noury [14] ($N = 18$)	Stern Shavit [34] ($N = 61$)	Rubin [39] ($N = 11$)
EAC soft tissue swelling	94%	94%	89%	NR	100%
EAC bone erosion	88%	94%	25%	NR	NR
Mastoid involvement	94%	94%	56%	NR	89%
Infratemporal fossa involvement	24%	NR	44%	20%	54%
TMJ involvement	24%	29%	33%	41%	NR
Nasopharyngeal involvement	6%	NR	11%	13%	54%
Parapharyngeal involvement	18%	NR	NR	NR	54%
Petrous apex, skull base, or intracranial	26% clivus involvement (by CT or MRI)	NR	22% petrous apex	(NR: skull base in 11%)	9% clivus erosion; 9% intracranial

EAC = external auditory canal; TMJ = temporomandibular joint; NR = not reported; CT = computed tomography; MRI = magnetic resonance imaging

[a]Soft tissue swelling, bone erosion of the EAC, and mastoid involvement represent localized extension of infection while the remaining abnormalities listed indicate more extensive disease

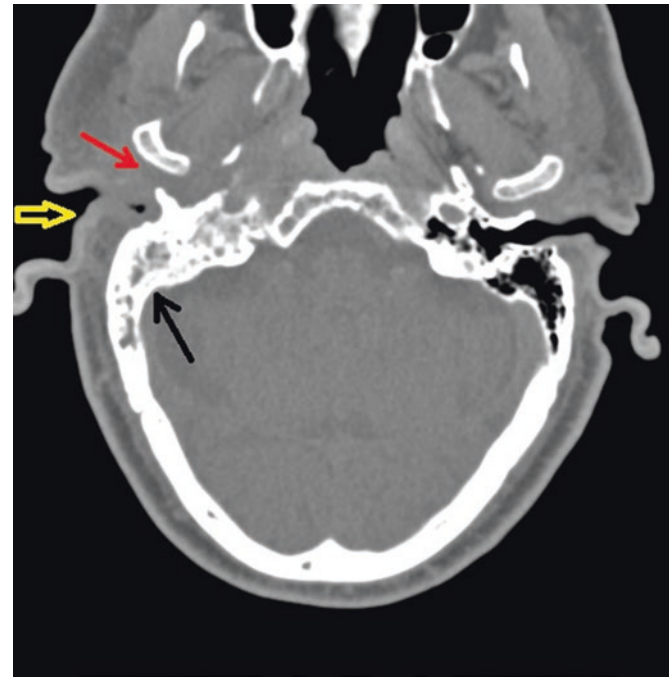

Fig. 10.2 Malignant otitis externa (MOE) with several abnormalities on computed tomography (CT) including abnormal tissue in the right external auditory canal (yellow arrow) and erosion of the adjacent bone, fluid in the mastoid (black arrow), and inflammation surrounding the temporomandibular joint (red arrow). *Pseudomonas* MOE in an 85-year-old diabetic man

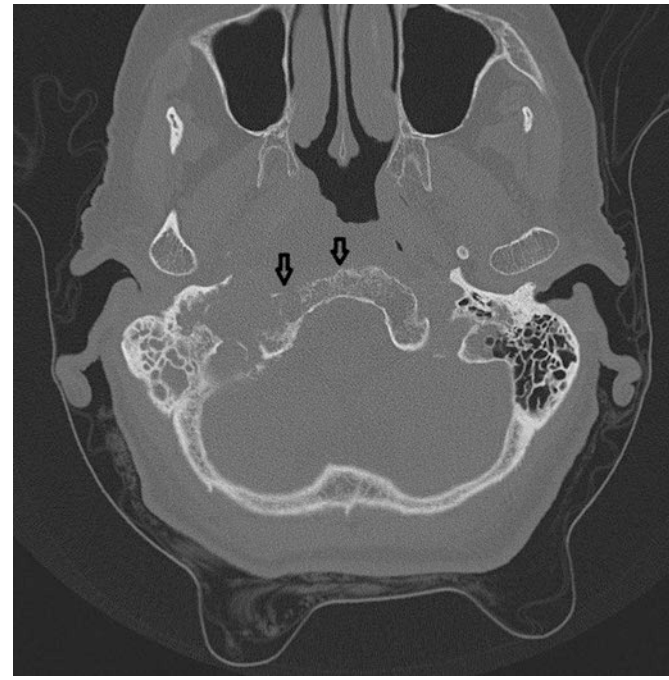

Fig. 10.3 Malignant otitis externa (MOE) with extensive soft tissue inflammation and erosion of the skull base, including the clivus (arrows). The patient, age 93 and diabetic, had been treated at another facility with antibiotic ear drops and short courses of ciprofloxacin prior to referral. She had 7 months of ear pain and 4 months of progressive cranial neuropathies (cranial nerve 7 followed by 9 and 10, then followed by 6)

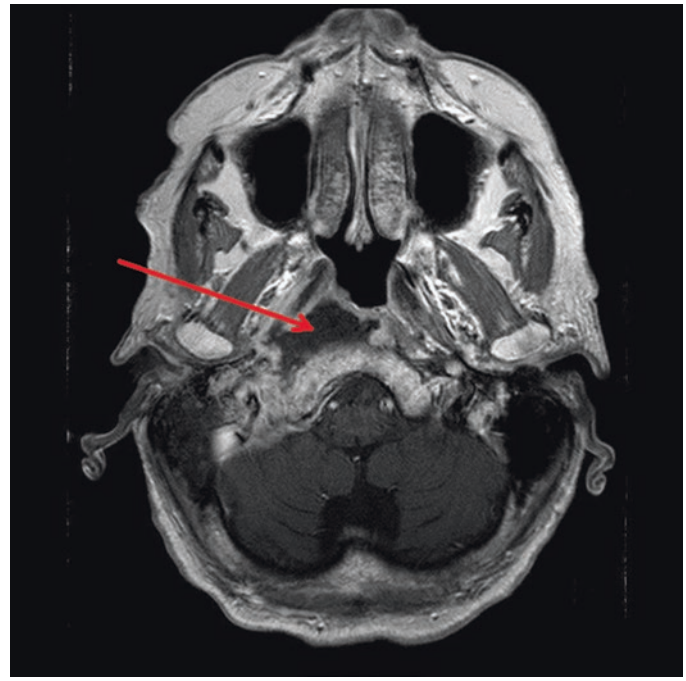

Fig. 10.4 Malignant otitis externa with a retropharyngeal abscess. Magnetic resonance imaging (MRI) of the patient described in Fig. 10.3; low density area (red arrow) was the abscess. Aspirate yielded pus and cultures grew *Pseudomonas*

apex involvement [14]. Magnetic resonance imaging but not CT detected intracranial or skull base involvement in one-third of study patients; this involvement included meningeal enhancement or inflammatory changes in the skull base or foramen ovale. Rarely, infection in MOE progresses to brain abscess, and an MRI would be the best study to detect this.

Differential Diagnosis

Cancer involving the external auditory canal and temporal bone can mimic MOE, with similar symptoms of persistent ear pain and drainage from the canal. Bony erosion in the ear canal may be seen with squamous cell cancer (Fig. 10.5) or with MOE, along with the extension of "inflammation" to the surrounding tissues. However, radiologic imaging cannot distinguish cancer from MOE. Patients with MOE are more likely to have a very elevated ESR and have a culture positive for *Pseudomonas*, but the presence of these features does not exclude cancer. In addition, it is possible to have both diagnoses concurrently, since cancer involving the ear canal may become superinfected, leading to MOE. Several such cases have been described [19, 40–43]. The cancer is usually squamous cell, but a case due to adenocarcinoma has been described [43]. It is important to consider cancer in patients with presumed MOE who fail to respond to antibiotics, or who appear to respond initially but then quickly relapse.

Malignant otitis externa can also mimic cancer, particularly in cases in which there is nasopharyngeal extension of infection (Fig. 10.6). A biopsy of the nasopharynx can be sent for both pathology and culture. In cases of MOE, the biopsy will show only inflammation and the culture will often grow *Pseudomonas*, as in the cases illustrated in Fig. 10.4. Skull base osteomyelitis arising from MOE may mimic advanced nasopharyngeal cancer, but radiologic imaging cannot distinguish these. There may be some radiologic clues but these do not apply to all cases. Rubin, Curtin, et al. observed that bone erosion in MOE may occur in several areas with intervening "skip" regions, while in carcinoma, bone erosions are usually contiguous [39]. Goh et al. reported that three MRI features were seen significantly more often in MOE-related skull base osteomyelitis than in nasopharyngeal cancer: "lateral" extension, such as to the parotid or

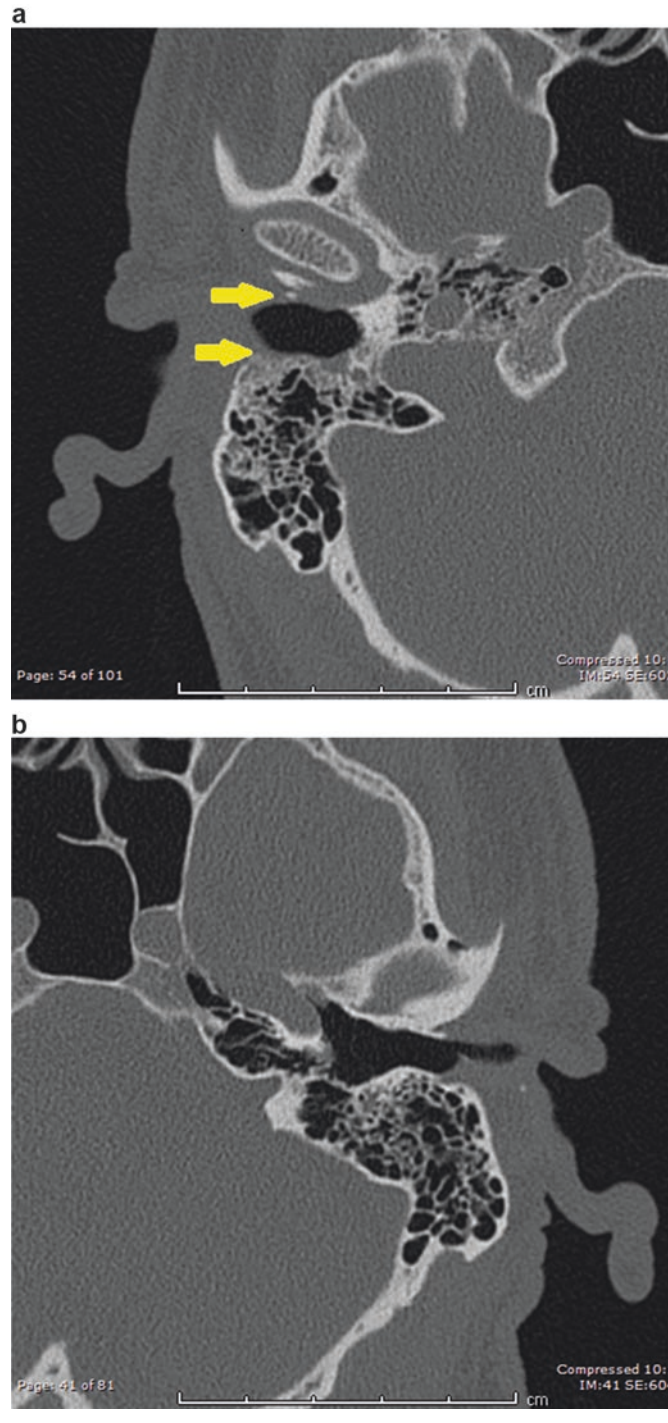

Fig. 10.5 Squamous cell cancer mimicking malignant otitis externa (MOE). The patient was diabetic and had several months of intermittent ear drainage, but no ear pain or headache. Computed tomography (CT) images. (**a**) Erosion (arrows) of the right external auditory canal (EAC). (**b**) Normal left side for comparison; note smooth line of the bone of the EAC

temporomandibular joint (92% versus 5%), increased T2 signal in adjacent soft tissues (92% versus 14%), and "significant" enhancement, meaning greater than or equal to nasopharyngeal or nasal mucosa (81% versus 5%) [44]. "Architectural" distortion (i.e., disruption of fascial planes and muscle fibers in masticator and prevertebral areas) was seen significantly less often in skull base osteomyelitis than nasopharyngeal cancer (4% versus 100%).

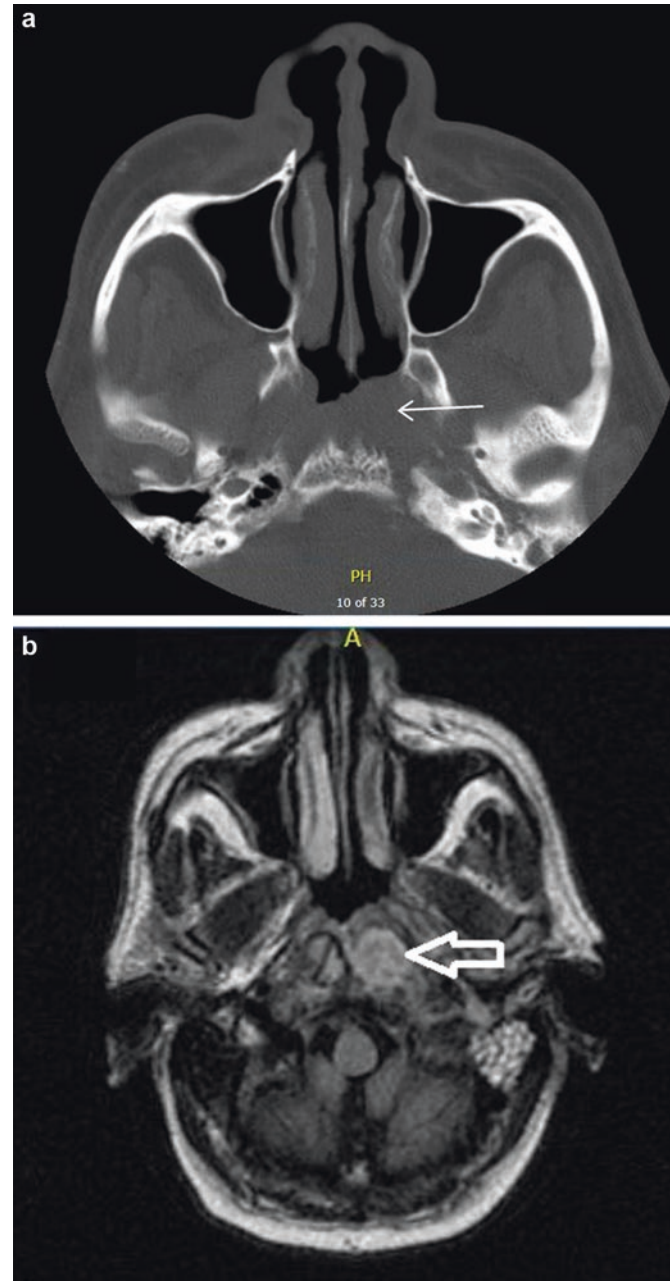

Fig. 10.6 Malignant otitis externa with extension of inflammation to the nasopharynx. This can mimic cancer on imaging. (**a**) Computed tomography (CT, non-contrast) showed a soft tissue mass (arrow). (**b**) Magnetic resonance imaging (MRI) showed enhancement of the mass (arrow). Cultures grew *Pseudomonas* and the patient improved with prolonged intravenous antibiotics

Treatment

With early diagnosis and appropriate management, cure is achievable in nearly all MOE cases. Indeed, 8 of the 15 studies listed in Table 10.1 had zero deaths due to disease. Even advanced cases can be cured, including those with extension of infection to the clivus. Antibiotics alone will cure most cases of MOE, but surgery may be required in some cases, as discussed later.

Antibiotics

Bacterial (*Pseudomonas*) MOE Treatment. Antibiotics should be started as soon as MOE is suspected and a culture of the ear canal (drainage or

granulations) is obtained. There are no randomized controlled trials to identify optimal therapy for this infection, but this author recommends initial empiric therapy with a combination of two anti-*Pseudomonas* antibiotics (from two different antibiotic classes, such as ciprofloxacin plus ceftazidime). Antibiotics can be tailored based on culture results. However, an antibiotic active against *Pseudomonas* should be included in the antibiotic regimen for nearly all cases of MOE even if the culture is negative or grows another organism. *Pseudomonas* may be the true pathogen while ear canal cultures may reflect bacterial colonizers.

For most MOE cases due to *Pseudomonas*, continuing two effective anti-*Pseudomonas* agents for at least the initial 2 weeks of the planned 6–8-week course seems prudent. There may be mixed populations of *Pseudomonas* isolates with different susceptibilities, but not all isolates will necessarily be detected on superficial cultures (e.g., ear canal drainage or granulations). Following this initial therapy, reducing to one effective intravenous (IV) antibiotic or to oral or IV ciprofloxacin (for ciprofloxacin-susceptible *Pseudomonas*) for the remaining weeks is reasonable if the patient is improving. Ciprofloxacin 750 mg given orally every 12 h can achieve blood levels equivalent to IV dosing of 400 mg every 12 h, provided gastrointestinal absorption is normal. If oral ciprofloxacin is chosen, the patient must avoid taking supplements or medications that can interfere with ciprofloxacin absorption, such as oral iron, calcium, antacids containing magnesium or aluminum, or sucralfate, for at least 2 h prior to taking ciprofloxacin. In patients in whom gastrointestinal absorption is questionable or in patients who present with severe MOE, IV therapy with ciprofloxacin or another antibiotic to which the *Pseudomonas* tests susceptible may be indicated for the entire antibiotic course.

Ciprofloxacin resistance in *Pseudomonas* has increased in recent years and is seen in up to one-third of MOE cases. This may partly reflect prolonged courses of fluoroquinolone ear drops prior to the diagnosis of MOE. Ciprofloxacin is the most effective fluoroquinolone against *Pseudomonas*, and resistance to ciprofloxacin confers bacterial resistance to other fluoroquinolones. Antibiotics besides ciprofloxacin that have activity against *Pseudomonas* include ceftazidime, cefepime, meropenem or imipenem, ticarcillin or piperacillin, and aztreonam. Aminoglycosides also have activity against *Pseudomonas* but are avoided due to renal toxicity and ototoxicity, important considerations particularly in older diabetic patients.

After the initial hospitalization, the patient is often discharged on home IV antibiotic therapy given via peripherally inserted central venous catheter (PICC line). Dressings must be changed weekly and the IV insertion site monitored for signs of infection. One patient in a series reported by Hobson et al. died not of MOE but of venous catheter-related sepsis [16]. Routine laboratory tests should be monitored at regular intervals (usually once weekly) while the patient is receiving home IV therapy. These tests typically include hematocrit or hemoglobin, white blood count and differential, platelet count, blood urea nitrogen (BUN) and creatinine, and liver function tests. Abnormalities may be early warning signs of antibiotic toxicity, and should prompt more frequent monitoring and potentially a change in antibiotic therapy. The patient should be seen in regular intervals to ensure there are no symptoms of toxicity. Toxicity may be serious even without any symptoms or evidence of antibiotic allergy. One series reported a patient who died from an intracerebral hemorrhage due to thrombocytopenia; the thrombocytopenia occurred as a complication of ceftazidime therapy [25]. Oral (or IV) ciprofloxacin may also cause significant toxicity (e.g., elevated liver function tests, tendinopathy, peripheral neuropathy, central nervous system side effects), and the clinician should monitor laboratory tests and symptoms in patients receiving this antibiotic.

Fungal MOE Treatment. Fungal MOE is due to a mold in almost all cases, most often *Aspergillus*. Fungal MOE due to yeast is very rare. Effective anti-fungal agents for molds include voriconazole, isavuconazole, and liposomal amphotericin. Liposomal amphotericin is preferred over amphotericin B because the former is less toxic. Voriconazole is the treatment of choice for *Aspergillus* infections. Voriconazole

has been available in the U.S. since 2002, when it was shown to be superior to amphotericin in treating invasive *Aspergillus* infections in a randomized prospective trial [45]. Clinical practice guidelines from the Infectious Diseases Society of America also recommend voriconazole for treating invasive aspergillosis, including the treatment of MOE due to *Aspergillus* [46]. Voriconazole is given initially as IV to quickly achieve blood levels, then as oral therapy for the duration of the course. It has excellent oral bioavailability. A few patients with *Aspergillus* MOE successfully treated with voriconazole have been described [47]. A new azole, isavuconazole, was FDA-approved in 2016 for treating invasive *Aspergillus* infections (and invasive mucormycosis). This approval was based on a randomized prospective trial demonstrating noninferiority to voriconazole in treating over 500 patients with invasive mold infections (80% due to *Aspergillus*) [48]. Isavuconazole, available IV or orally, has a broader spectrum of anti-fungal activity than voriconazole and potentially fewer drug-drug interactions. There are no reports of using isavuconazole to treat *Aspergillus* MOE yet, but efficacy should be similar to voriconazole. For patients who cannot tolerate voriconazole or isavuconazole or whose MOE is due to an azole-resistant mold, liposomal amphotericin should be given. The clinician should routinely monitor for symptoms and signs of potential toxicity with any of the antifungal agents for the duration of therapy.

For the rare cases of MOE that are due to *Candida*, azole treatment is also reasonable unless the isolate is resistant. Fluconazole can also be used if the isolate is susceptible, as most *C. albicans* isolates are. Non-albicans species of *Candida* may be fluconazole-resistant, but most are susceptible to voriconazole. Echinocandins and amphotericin are alternative treatments for invasive *Candida* infections.

Duration of Therapy. The duration of antibiotic treatment in MOE due to *Pseudomonas* is at least 6 weeks, often much longer. In some cases, IV antibiotics are required for the entire course of therapy, while in other cases, oral ciprofloxacin may comprise the later weeks of therapy. The duration of treatment for fungal MOE is a minimum of 6 weeks but usually several months. As noted above, *Aspergillus* MOE is usually treated by IV voriconazole initially followed by months of oral voriconazole therapy. Voriconazole levels are monitored periodically, along with routine laboratory tests for toxicity.

Surgery

Major surgical debridement is not indicated in MOE, with rare exception. However, simple procedures such as polypectomy if a polyp is obstructing the EAC, or biopsy of granulation tissue in the EAC for diagnosis and culture if necessary, should be performed without hesitation. All surgical specimens should be sent for pathology as well as for the following microbiology tests: Gram stain, fungal stain, aerobic, anaerobic, and fungal cultures. Mastoidectomy may be important to establish a diagnosis and obtain deep cultures in patients with MOE who are failing empiric anti-*Pseudomonas* therapy, or who improve then relapse. These cases are rare but many turn out to be due to *Aspergillus* or other fungi, yet diagnosis was delayed for weeks to months of empiric antibacterial therapy due to the lack of a surgical specimen. Approximately 10% of patients with MOE require surgery at some point, and outcomes in most recent series have been as good in these patients as in MOE patients who never required surgery. In a series by Chen et al., for example, 8 (42%) of 19 patients required surgery (mastoidectomy in 7, drainage of TMJ abscess in 1) and none died of MOE [15].

Hyperbaric Oxygen

The role of hyperbaric oxygen in MOE is unknown. There are case reports of improvement in refractory cases but no consensus. A Cochrane review of the literature concluded that there was no clear evidence to support the adjunctive use of hyperbaric oxygen in addition to the standard MOE therapy of prolonged antibiotics (with or without surgery) [49].

Outcome

Clinical Response. The first sign of clinical response to systemic antibiotic therapy is usually a decrease in ear pain. Most patients note some decrease in pain after 1 week of therapy, but full resolution of pain usually takes several weeks. Patients in one series reported improvement in pain an average of 6 days after starting therapy [50]. Resolution of pain required a mean of 18 days in one series [51] and 5 weeks in another [20].

The ESR, if very elevated initially, will also decrease with successful therapy. This decrease may be very gradual. Loh et al. reported that in patients whose MOE resolved, the mean ESR was 58 at diagnosis and 49 after 6 weeks of antibiotics [25]. C-reactive protein levels, if elevated at presentation, also typically decrease during the course of antibiotic therapy. Chin et al. reported that initial CRP was elevated in most patients (mean 38) and returned to normal in 91% of patients in whom a follow-up level was obtained [19].

Radiologic findings on CT and MRI lag behind clinical response, as noted above. Soft tissue abnormalities improve first, while changes of bony erosion may persist for years.

Cranial neuropathies usually resolve, but not always. Franco-Vidal et al. noted that none of the nine (of 46) patients in their series who presented with facial nerve palsies recovered normal facial function, even though they were cured of MOE [17]. The mean follow-up time in this series was 18 months. Meade et al. reported a higher rate of recovery of cranial nerve function, with 9 of 14 patients with various cranial neuropathies having resolution (29%) or improvement (36%) in cranial nerve function at 3–6 month follow-up [20]. Facial nerve palsy may be less likely to resolve than other cranial neuropathies. Mani et al. reported that all three patients in their study with lower (CN 9–12) cranial neuropathies recovered normal function, while four of six patients with facial nerve palsy had no improvement and two had only partial improvement [33]. Mortality in both the Meade and Mani series was zero. While some series have found that cranial neuropathies on admission for MOE signify a worse prognosis, other series such as the Meade and Mani studies have not found this to be the case.

Relapse. Relapse of infection after apparently successful therapy may occur in up to 20% of patients with MOE. Close follow-up is therefore essential. The first sign of relapse is usually recurrence of ear pain or a recurrent elevation in ESR after it had fallen to low levels. Relapse may occur many months after therapy although it usually occurs within 3 months. The evaluation and management of the relapse should be similar to the initial presentation of MOE, although often a deeper biopsy or mastoidectomy is required to determine the reason for relapse. The initial *Pseudomonas* isolate may have recurred with resistance to the prior antibiotics, or a new organism, such as *Aspergillus*, may be present.

Mortality. As noted above, mortality from MOE has declined over the past several decades. Doraghazi et al. reported a mortality of 36% in a review of 95 cases of *Pseudomonas* MOE reported before 1979 [52]. The MOE-related mortality now is <10%, and in many series, the mortality from MOE is zero. The overall mortality is usually higher because many patients with MOE are over age 80, and most have diabetes or other significant comorbidities. Cure of MOE, however, is possible in most patients.

Conclusion

Malignant otitis externa is an invasive infection, usually due to *Pseudomonas*, that arises in the ear canal and invades the temporal bone and adjacent soft tissues and bones. The infection primarily affects diabetic patients, men more often than women. The mean age of patients in nearly all MOE series is over 60. Unilateral ear pain is a hallmark of the infection, and this pain progresses over weeks to months despite topical antibiotic therapy. Facial nerve palsy develops in approximately 25% of patients by the time of diagnosis; other cranial neuropathies can also occur. Treatment with a minimum of 6 weeks of systemic antibiotics is indicated. Mortality from MOE used to be >30% but is now 5% or less in many series.

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Acute Bacterial Rhinosinusitis

11

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Introduction

Acute sinusitis, also known as acute rhinosinusitis, is an inflammation of the nasal cavity and paranasal sinuses that lasts up to 4 weeks [1, 2]. We preferentially use the term rhinosinusitis in place of sinusitis to acknowledge that the inflammation seen in sinusitis involves the nasal cavity as well. Although many patients present with rhinosinusitis that has lasted longer than 4 weeks, these more protracted forms of sinusitis—subacute and chronic rhinosinusitis—are discussed in Chap. 13. The definitions for the various types of rhinosinusitis are summarized in Table 11.1.

It is estimated that 12% of the U.S. population is affected by acute and chronic rhinosinusitis [3]. Women appear to be affected more than men, and the most commonly affected age group among adults is mid-40s to mid-60s [3]. Older age, smoking, air travel, exposure to changes in atmospheric pressure as with flying or diving, swimming in chlorinated pools, asthma and allergies, dental disease, and immunodeficiency are all considered risk factors for the development of ARS [4]. Direct costs from managing acute and chronic sinusitis are estimated at $11 billion dollars per year in the U.S., not accounting for significant indirect costs attributable to lost work productivity and reduced job effectiveness [5, 6]. Acute rhinosinusitis is the fifth most common diagnosis for which antibiotics are prescribed; thus correct diagnosis of ARS and judicious treatment with antibiotics are particularly important in an age of growing bacterial resistance [7].

Pathophysiology

Most patients suffering with sinus symptoms will have a viral etiology of their inflammation [8]. It can be quite difficult for a primary care physician to distinguish between simple upper respiratory infections (URI), episodes of acute viral rhinosinusitis (AVRS), and episodes of true bacterial rhinosinusitis (ABRS). Almost 90% of patients with viral URIs have evidence of AVRS [9]. The most common viruses that cause VRS are rhinovirus, influenza virus, and coronavirus; others include parainfluenza virus, adenovirus, respiratory syncytial virus, and metapneumovirus [10]. Patients with AVRS typically develop symptoms 1–4 days after infection. Viruses attach to the nasal epithelium and can spread from the nasal cavity to the paranasal sinuses. Once within the paranasal sinuses, viruses may exert direct toxic effects on mucociliary clearance, and may induce epithelial permeability and hypersecretion from inflammatory cytokines. These alterations lead to

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_11

Table 11.1 Types of sinusitis, as defined by the American Academy of Otolaryngology-Head and Neck Surgery [2]

Term	Definition
Rhinosinusitis	Inflammation of the paranasal sinuses and nasal cavity
Uncomplicated rhinosinusitis	Inflammation confined to the nasal cavity and sinuses, without extension (e.g., to surrounding soft tissues, orbit, or central nervous system)
Acute rhinosinusitis	≤4 weeks of purulent nasal drainage (anterior, posterior, or both) accompanied by nasal obstruction (e.g., congestion, blockage, stuffiness), facial pain-pressure-fullness, or both
Recurrent acute rhinosinusitis	≥4 episodes per year of acute rhinosinusitis, without intervening rhinosinusitis symptoms
Subacute rhinosinusitis	Rhinosinusitis symptoms persisting >4 and <12 weeks. Clinicians should determine whether to treat such patients as acute versus chronic rhinosinusitis
Chronic rhinosinusitis	≥12 weeks of at least two of four symptoms (mucopurulent drainage, nasal obstruction, facial pain-pressure-fullness, hyposmia) plus at least one objective evidence of inflammation (see Chap. 13 for details)

the mucosal edema, thickened secretions, and ostial obstruction characteristic of acute rhinosinusitis.

Acute bacterial rhinosinusitis most commonly occurs as a complication of viral infection, complicating 0.5–2.0% of cases of the common cold [10], However, other factors may also predispose to ABRS, such as allergy, immune dysfunction, impaired ciliary function, anatomic narrowing of the sinuses, or poor dentition [11]. The most common bacteria associated with ABRS are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Microaerophilic streptococci and anaerobic bacteria are commonly identified if the ABRS originates from an odontogenic source. When a sinus culture is positive in a patient with ABRS, a single pathogen is usually found in high concentration, although in approximately 25% of the patients, two pathogens can be found in high concentration [12]. The usefulness and validity of sinus cultures have recently been reconsidered as more is understood about the complex commensal bacterial community comprising the sinus microbiome. However, cultures are still helpful in some clinical situations such as complicated or nosocomial ABRS.

Nosocomial bacterial sinusitis may develop in patients on transplant services or in the intensive care unit, particularly in those who have had prolonged intubation or who have nasogastric tubes or feeding tubes. In contrast to community-acquired sinusitis, nosocomial sinusitis is more likely to involve resistant bacteria, including *Staphylococcus aureus* and Gram-negative bacilli such as *Pseudomonas* [13, 14].

Diagnosis

History and Physical Exam

Patients with acute rhinosinusitis typically complain of nasal congestion and obstruction, purulent nasal discharge, and facial pain or pressure that is worse when bending forward. Maxillary tooth discomfort may be present if the maxillary sinus is involved. Other less specific symptoms can include fever, fatigue, cough, hyposmia, ear pressure, headache, and halitosis. These symptoms apply to both AVRS and ABRS. Therefore, it is not possible for patients nor clinicians to discern a viral from bacterial infection based on symptoms alone. Another diagnostic fallacy is that if nasal drainage is colored it must be from a bacterial infection [2]. To discern AVRS from ABRS, the clinician should focus on the duration and course of the symptoms. Acute viral rhinosinusitis will typically have partial or complete resolution of symptoms by 10 days, with a peak at 3–6 days [15]. If symptoms persist beyond 10 days, or if symptoms improve but worsen again within 10 days ("double-worsening"), there is a higher likelihood that the patient has ABRS [2].

On physical examination, findings may include purulent drainage in the nose or posterior pharynx and nasal speech. Although many physicians have been taught to percuss the sinuses to evaluate for

pain, this has not been shown to be useful [16]. Similarly, transillumination of the sinuses to detect an air-fluid level is an insensitive test and not recommended [17]. Examination of the nasal cavity with either anterior rhinoscopy (performed with a handheld otoscope or nasal speculum) or nasal endoscopy (using a flexible or rigid endoscope) may show diffuse mucosal edema, narrowing of the middle meatus, inferior turbinate hypertrophy, and purulence. A complete head and neck examination is important to both confirm the suspected diagnosis of acute rhinosinusitis as well as rule out any other possible diagnoses and evaluate for any possible complications.

Complications

Complications from ABRS, less commonly seen in adults than children, are rare but can be potentially serious, even life-threatening. Bacterial sinusitis can spread beyond the paranasal sinuses and nasal cavity to the orbit or surrounding tissues directly, or to the central nervous system (CNS) either directly or hematogenously. Chapter 12 discusses complications of ABRS in children.

Orbital complications include preseptal cellulitis, orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombophlebitis. The Chandler classification, the most common method of characterizing orbital complications, organizes orbital complications in terms of progressive severity (see Fig. 11.1) [18]. Infection in preseptal cellulitis involves the eyelid skin in front of the orbital septum and tarsal plates of the eyelids, while infection in orbital cellulitis, subperiosteal abscess, and orbital abscess involves the orbit. In orbital cellulitis, there is diffuse inflammation of the orbital fat and extraocular muscles. In subperiosteal abscess, there is a collection of pus in the space between the orbital bony wall and periorbita, and in orbital abscess, there is a collection of pus in the orbital fat. It is important to distinguish preseptal cellulitis from orbital infection (cellulitis or abscess), because preseptal infections do not threaten vision while orbital infections do. Patients with preseptal cellulitis will present with lid swelling and redness of the periorbital region but will not have involvement of the orbit (postseptal compartment) so will not have any of the three "orbital signs": impaired extraocular motility, decrease in vision, or proptosis. Patients with orbital cellulitis or abscess will present with similar lid changes, but in addition will have one or more orbital signs as a result inflammation of the extraocular muscles and fat within the orbit. Patients with orbital cellulitis or abscess may also have chemosis (edema of the conjunctiva), pain with eye movement, and/or diplopia. In general, patients with subperiosteal or orbital abscess have more pronounced orbital signs than those with orbital cellulitis. Because most sinogenic orbital abscesses arise from the ethmoid or medial frontal sinuses, the inflammation in the orbit is often most pronounced medially and/or superomedially, and the eye may be displaced inferolaterally. Patients with chronic sinus obstruction with nasal polyps may develop a frontal sinus mucocele that silently erodes the frontal sinus floor (orbital roof); an acute superinfection may cause orbital cellulitis or abscess (Fig. 11.2). Cavernous sinus thrombophlebitis can sometimes be insidious, but advanced cases will be marked by cranial nerve palsies involving III, IV, VI (sometimes also V1 and V2), fever, photophobia, visual loss, and signs of contralateral orbital involvement.

Acute bacterial rhinosinusitis may also lead to CNS infections, including meningitis, epidural abscess, subdural empyema, or brain abscess. Symptoms of meningitis include fever, headache, photophobia, nuchal rigidity, and mental status changes. Symptoms of epidural and brain abscesses may include headache, mental status changes, lethargy, and nausea and vomiting. There may or may not be papilledema or unilateral neurological findings on examination.

Osteomyelitis of the paranasal sinus bones can occur as a consequence of ABRS but is a rare complication. Patients usually complain of dull pain at the involved site and have localized tenderness, warmth, erythema, and swelling; fever may be present. Chronic frontal sinusitis may lead to osteomyelitis of the anterior table of the frontal sinus with frontal "bossing"— i.e., swell-

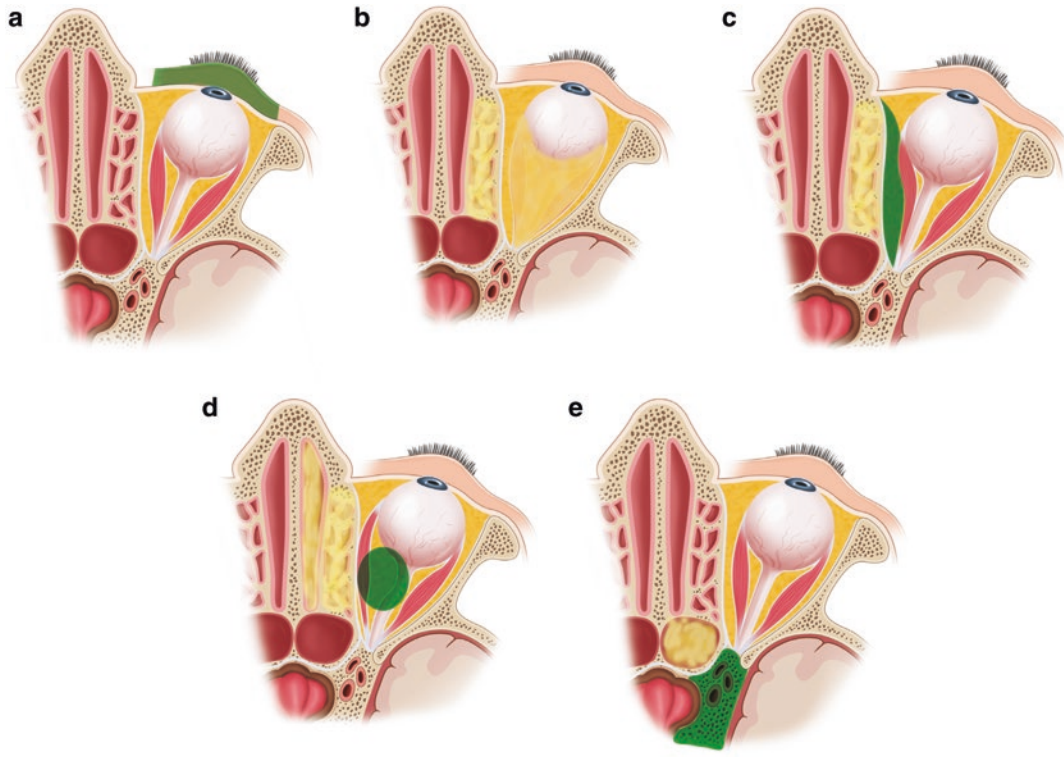


Fig. 11.1 Diagram of the orbital complications of sinusitis. (**a**) Preseptal cellulitis; (**b**) Orbital cellulitis; (**c**) Subperiosteal abscess; (**d**) Orbital abscess; (**e**) cavernous sinus thrombophlebitis

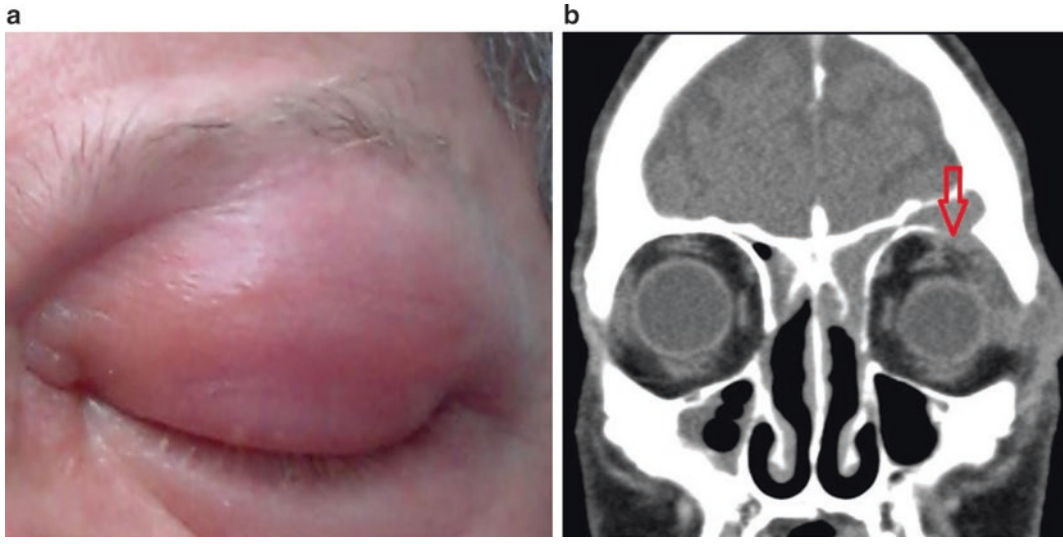


Fig. 11.2 Orbital cellulitis and acute frontal sinusitis due to *Staphylococcus aureus* in a patient with a history of chronic sinusitis and nasal polyps. The polyps had resulted in a chronic mucocele which eroded the floor of the left frontal sinus (left orbital roof), and acute superinfection resulted in orbital findings. (**a**) left eye. (**b**) computed tomography image; arrow shows bony erosion. *Courtesy of Dr. Marlene L. Durand*

ing of the forehead over the bone involved (also called "Pott's puffy tumor"); ABRS may cause abrupt worsening of symptoms.

Patients with any of the signs or symptoms suggesting a complication of ABRS should be urgently referred to an emergency department for evaluation and management. While preseptal cellulitis alone may respond to oral antibiotics, patients with any other orbital or any CNS complication require intravenous antibiotics, close inpatient monitoring, and may require emergency surgery to drain an abscess if one is present. An ophthalmologist should be consulted for patients with orbital complications, and consultation with a neurologist or neurosurgeon is usually indicated for patients with CNS complications. Orbital cellulitis or abscess may lead to permanent loss of vision if not appropriately and promptly treated. Neurologic complications may progress rapidly and lead to permanent disability or death if not recognized and treated promptly. Adequate clinical suspicion as well as prompt recognition and treatment of extrasinus complications are essential.

Imaging

Imaging is not indicated in uncomplicated ABRS. A practitioner should consider ordering an imaging study only to rule out a complication of ABRS or to establish an alternative diagnosis. It is important to remember that "abnormal" findings involving the sinuses do not necessarily confirm a diagnosis of acute rhinosinusitis, as 42% of normal individuals may demonstrate some form of abnormal mucosal thickening of the sinuses on CT [19]. Equally important, imaging cannot distinguish between viral and bacterial rhinosinusitis [19].

When there is sufficient indication, CT with contrast or magnetic resonance imaging (MRI) are the studies of choice. Computed tomography better delineates bony detail, while MRI provides superior delineation of soft tissue detail. When a complication is suspected, contrast-enhanced imaging is indicated to demarcate areas of extrasinus infection. Plain films are no longer indicated in evaluating adult sinusitis [2].

Cultures

No role has been established for routine cultures in uncomplicated ABRS. Cultures may be considered when there is concern for a complication of sinusitis, antimicrobial resistance, or an unusual organism—the last might be suspected in the case of an immunocompromised host. Nasal cavity cultures from blindly obtained swabs are not reliable indicators of true pathogens in the sinuses and are therefore not useful in the diagnosis of ABRS [19]. The gold standard in the diagnosis of ABRS is a maxillary sinus antral puncture and aspiration via an inferior meatal or canine fossa approach. However, sinus aspiration is invasive and not available to most primary care physicians. Endoscopic culture of the middle meatus is minimally invasive alternative and has been shown to correlate well with maxillary sinus cultures obtained by antral puncture [20].

Differential Diagnosis

There are many conditions that can cause symptoms of rhinorrhea, facial pain, or dental pain, mimicking the presentation of ABRS. The common cold, allergic and nonallergic rhinitis, and primary dental pathology are the most typical. Temporomandibular joint disorders, neuralgias, and other causes of atypical facial pain should also be considered, as well as primary headache disorders such as migraine, tension headache, and cluster headache. Importantly, in immunosuppressed patients, acute invasive fungal sinusitis must also be considered (see Chap. 15).

Treatment

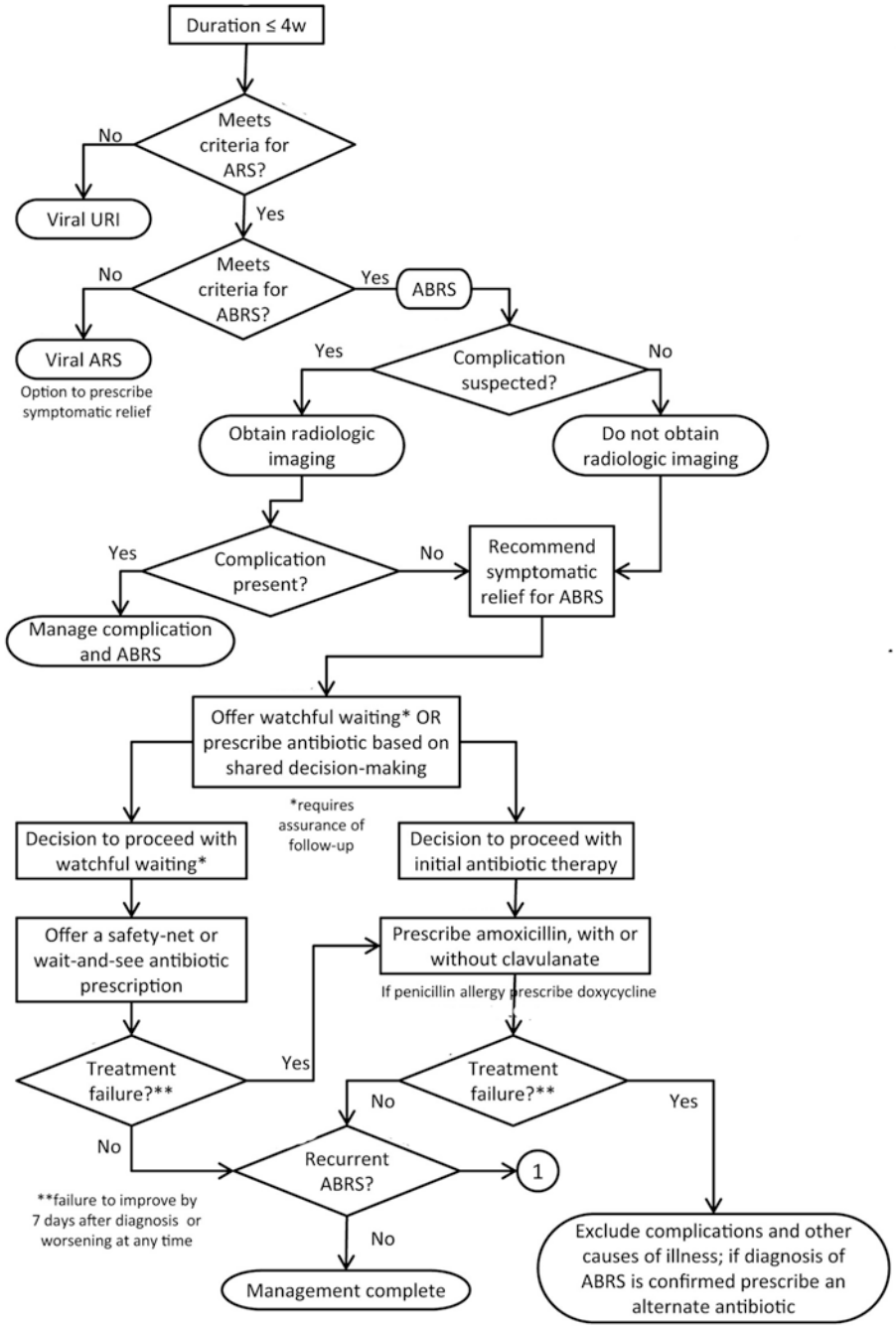
Acute bacterial rhinosinusitis is generally a self-limited disease and can resolve on its own without antibiotics. Systematic reviews and meta-analyses have found that the majority of patients with ABRS will resolve their symptoms without antibiotic therapy within 2 weeks [21]. Therefore, contrary to conventional wisdom, the successful distinction of ABRS from AVRS does

not equate with an automatic indication to prescribe antibiotics. In the first 10 days of symptoms, supportive therapy alone is indicated for uncomplicated ABRS in adults regardless of whether a diagnosis of AVRS or ABRS has been made, except for cases of "double worsening" or severe symptoms persisting for at least 3 days. Severe symptoms are defined as high fever (temperature 102 °F or higher) and purulent nasal drainage [19, 22]. "Double worsening" refers to worsening of symptoms after initial improvement. This is suggestive of an initial viral infection followed by a bacterial superinfection.

Guidelines regarding treatment of ABRS have been published for adults by the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) [2], for both adults and children by the Infectious Disease Society of America (IDSA) [19], and for children by the American Academy of Pediatrics (AAP) [22]. The IDSA and AAP guidelines are similar, but these differ from the AAO-HNS guidelines in that the latter offers the option of "watchful waiting" rather than antibiotics for up to 7 days beyond ABRS diagnosis for adults whose follow-up is assured. The AAP also offers the option of "watchful waiting" in children diagnosed with non-severe "persistent" uncomplicated ABRS but only up to 3 days. Figure 11.3 shows the AAO-HNS decision tree, Table 11.2 compares AAO-HNS and IDSA guidelines for adults with ABRS, and Table 11.3 summarizes the AAP guidelines for children with ABRS. The antibiotic options for children are further discussed in the AAP guidelines [22]. It is important to note that daytime cough is a symptom of ABRS for children, unlike adults, and the AAP recommends a clinical diagnosis of ABRS in children who have (1) nasal drainage or daytime cough persisting for more than 10 days without improvement, (2) worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement, or (3) severe onset, which is defined as fever ≥39 °C (102.2 °F) plus concurrent nasal discharge for at least 3 days.

Part of the risk-benefit analysis of treating ABRS with antibiotics involves an appreciation for potential complications of antibiotic therapy. A Cochrane review in 2014 found that although using antibiotics can help shorten the course of ABRS, the number of adults needed to treat to see that benefit is greater than the number needed to see adverse effects [23]. Meta-analyses of randomized controlled trials have found that, compared with placebo, adults with ABRS may benefit from antibiotics at the cost of increased adverse events. Estimates of the number needed to treat to benefit range from 13 to 18 patients, while the number needed to harm is approximately eight patients [24]. The clinician should consider that results of these meta-analyses may be influenced by inclusion and exclusion criteria. The 2014 Cochrane review analyzed ten trials that randomized antibiotics versus placebo to treat adults with clinically diagnosed ABRS [23], but many of these trials did not meet current criteria for ABRS so probably included AVRS as well as ABRS. For example, some trials included patients with only 5 or even 2 days of symptoms [25]. Exclusion criteria also may have influenced results, and common exclusion criteria in the ten trials were recent antibiotic use (80% of the trials), severe symptoms (30%), prior ear-nose-throat disease (50%), previous sinus surgery (20%), immune deficiency (50%), and comorbidities such as diabetes, heart failure, or pulmonary disease (50%) [23].

Of course, exceptions to clinical guidelines always exist, especially in immunocompromised patients and any patient in whom a complication is suspected. The individual clinical situation should dictate therapy above all and may warrant immediate antibiotic treatment and referral to a specialist. The clinician should decide if the risk of watchful waiting in the individual patient outweighs the benefit. This was illustrated by a complication that occurred in a patient randomized to the placebo arm of one trial of amoxicillin-clavulinate; the patient had persistent symptoms despite 2 weeks of placebo followed by 1 week of antibiotic and was found to have a brain abscess (the abscess pathogen was susceptible to the antibiotic) [25].



ARS, acute RS; AB, acute bacterial RS; CRS, chronic RS; KAS, key action statement; RS, rhinosinusitis; URI, upper respiratory infection

Fig. 11.3 Algorithm for the evaluation and management of acute rhinosinusitis in adults, according to the American Academy of Otolaryngology – Head and Neck Surgery. Adapted from Rosenfeld RM, et al. [2] with permission from Sage Publications

Table 11.2 Adult acute bacterial rhinosinusitis (ABRS): recommendations for evaluation and treatment by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) [2] and the Infectious Disease Society of America (IDSA) [19]

Recommendation	AAO-HNS	IDSA
Clinical diagnosis of acute bacterial rhinosinusitis (ABRS)	Symptoms of acute rhinosinusitis that: (1) persist ≥10 days or (2) worsen after initial improvement ("double worsening")	Same as (1) and (2) of AAO-HNS plus (3): (3) severe onset of symptoms ($T \geq 102$ °F plus either purulent nasal drainage or facial pain) lasting ≥3 days
Use of radiologic imaging (CT or MRI)	Only for suspected complication or alternative diagnosis	Same as AAO-HNS
Initial therapy of ABRS	"Watchful waiting" versus antibiotics[a].	Antibiotics
First line antibiotic choice	Amoxicillin or amoxicillin-clavulinate[b]	Same as AAO-HNS but preference for amoxicillin-clavulinate over amoxicillin[b]
Penicillin-allergy	(1) Doxycycline or (2) clindamycin plus cefixime or cefpodoxime (if non-type 1 hypersensitivity to penicillin)[c]	Doxycycline[c]
Duration of antibiotics	5–10 days	5–7 days if no risk for resistant bacteria (7–10 days if such risk)
Treatment failure	Exclude complications and other causes of symptoms; if ABRS confirmed, switch antibiotics	Same as AAO-HNS

[a]The AAO-HNS states that "watchful waiting" in adults "should be offered only when there is assurance of follow-up such that antibiotic therapy is started if the patient's condition fails to improve by 7 days after ABRS diagnosis or if it worsens at any time" [2].

[b]First-line therapy with amoxicillin-clavulanate rather than amoxicillin is generally recommended by the AAO-HNS for the following: older age (age >65 years), immunocompromise, comorbid conditions (chronic cardiac, hepatic, or renal disease), history of recurrent ABRS, moderate to severe symptoms, or risk factors for resistant organisms such as antibiotics within the past month, contact with health care environment, contact with child in daycare, high prevalence of resistant bacteria in the community. The AAO-HNS recommends high-dose amoxicillin (IDSA recommends high dose amoxicillin-clavulanate) for adults at increased risk for infection with amoxicillin-resistant organisms

[c]Both AAO-HNS and IDSA recommended either doxycycline or a respiratory fluoroquinolone such as levofloxacin in penicillin-allergic patients, but the Food and Drug Administration subsequently recommended against use of fluoroquinolones for ABRS unless no alternatives exist (see the text).

First-Line Antibiotic Therapy

As cultures are not indicated in ABRS, the initial choice of antibiotic treatment is empiric and is based on the most common pathogens (as outlined above). Therefore, first-line therapy for adults would be oral amoxicillin or amoxicillin-clavulanate (500/125 three times daily or 875/125 mg twice daily), depending on the resistance patterns within the community. In communities with a higher prevalence of beta-lactam resistance among *Haemophilus influenzae* and *Moraxella catarrhalis* isolates, amoxicillin-clavulanate is preferred [2, 19]. Macrolides and trimethoprim-sulfamethoxazole are not recommended due to high rates of *S. pneumoniae* resistance (and for trimethoprim-sulfamethoxazole, also *H. influenzae* resistance) [2, 19]. All doses given are for patients with normal renal function.

In adults with specific risk factors for antibiotic resistance, high dose amoxicillin with clavulanate (2 g/125 mg twice daily) would be indicated. Examples of risk factors for resistance include living in communities where the prevalence of penicillin-non-susceptible *S. pneumoniae* exceeds 10%; age >65 years; hospitalization in the last 5 days; antibiotic use in the previous month; immunocompromise; multiple comorbidities; or severe infection with evidence of systemic toxicity and threat of suppurative complications [2, 19].

For adults with penicillin allergy, oral doxycycline (100 mg twice daily or 200 mg daily) is a

Table 11.3 Pediatric acute bacterial rhinosinusitis (ABRS), patients age 1–18 years: evaluation and treatment recommendations by the American Academy of Pediatrics, 2013 [22]

Recommendation	AAP guidelines[a]	Comments
Clinical diagnosis of acute bacterial rhinosinusitis (ABRS)	Either: (1) persistent nasal drainage or daytime cough or both for >10 days ("persistent illness") **or** (2) worsening course (see text) **or** (3) severe onset of symptoms (*T* 102 °F plus nasal drainage) lasting ≥3 days	Cough is not included as a symptom of ABRS in adults (see Table 11.2)
Use of radiologic imaging (CT with contrast)	Only for suspected complication involving orbit or central nervous system	Similar recommendations for adults
Initial therapy of ABRS	Antibiotics for worsening course or severe onset ("2" or "3" above), but antibiotics **or** watchful waiting (for up to 3 days) for "persistent illness" ("1" above)	If watchful waiting is chosen for persistent illness, antibiotics should be started if there is clinical worsening at any point or if the child fails to improve by 3 days
First line antibiotic choice[a]	Amoxicillin or amoxicillin-clavulanate	Give high-dose amoxicillin if resistant bacteria are a concern; give high-dose amoxicillin-clavulinate for <age 2, attends child care, moderate to severe ABRS, recent course of antibiotics
Penicillin allergy[a]	non-type 1 allergy, mild ABRS: second or third generation cephalosporin (cefuroxime, cefdinir, cefpodoxime)[a]	Moderate to severe ABRS: clindamycin (or linezolid) plus cefixime (if non-type 1 allergy), or levofloxacin[a]
Duration of therapy	No recommendation but favors 7 days after symptoms resolve so at least 10 days	IDSA guidelines: 10-14 days for children with ABRS [19]

AAP = American Association of Pediatrics. IDSA = Infectious Disease Society of America
[a]This table is not comprehensive: see AAP Guidelines for details regarding treatment options

reasonable alternative, as is a combination of clindamycin plus a third-generation cephalosporin such as cefixime or cefpodoxime [2]. Fluoroquinolones have traditionally been another alternative, but are now highly cautioned against due to an increasing recognition of serious side effects, including tendinitis, tendon rupture, and peripheral neuropathy. The Food and Drug Administration has advised that fluoroquinolones should be used for ABRS only when no alternative options exist [26].

For children with ABRS, the first-line treatment recommended by the AAP is amoxicillin at standard pediatric dosing (45 mg/kg per day in 2 divided doses) for children aged 2 and older with uncomplicated ABRS of mild to moderate severity and who do not have risk factors for antimicrobial resistance (no antibiotics within 4 weeks and no day care), or high-dose amoxicillin (80–90 mg/kg per day in 2 divided doses, up to a maximum of 2 g per dose) in communities with high prevalence of resistant bacteria (i.e., penicillin non-susceptible *S. pneumoniae*) [22]. For children presenting with moderate to severe ABRS, as well as children under age 2 years, attending day care, or who have recently received an antibiotic, the AAP recommends high dose amoxicillin-clavulinate. A single 50 mg/kg dose of intravenous of intramuscular ceftriaxone may be given to children who are vomiting, unable to tolerate oral medications, or are unlikely to be adherent to initial doses of antibiotics [22]. Oral antibiotics may be started 24 h after this parenteral dose, to complete the course of therapy. For additional details regarding treatment of children with ABRS, including treatment in patients with penicillin allergies, the reader is referred to the AAP Guidelines [22]. Note that these guidelines do not apply to children younger than age 1.

The recommended duration of antibiotic treatment is 5–7 days in adults (longer in children), provided the patient is improving. Longer courses

of antibiotics (e.g., 10–14 days) have not been shown to offer greater efficacy in adults, yet are associated with higher rates of adverse drug effects.

Second-Line Antibiotic Therapy

If a patient does not improve or in fact worsens with first-line therapy, a change in therapy is indicated. There is not good evidence to guide the choice of second-line therapy, but one may consider either increasing the dose or changing class of antibiotics. Options in adults include high dose amoxicillin (2 g twice daily) with clavulanate, doxycycline, levofloxacin, and moxifloxacin. The latter quinolone options should again be prescribed with caution, with regard for potential adverse effects of fluoroquinolone use [26].

Failure of Response

If patients with ABRS have failed to respond to both first-line and second-line therapies, or if at any time a potential complication is suspected, they should be referred for further evaluation to a specialist and possibly undergo radiologic imaging.

Supportive Therapy

The use of over-the-counter antipyretics and analgesics can help to treat fever and pain in ABRS [2]. Saline irrigations offer the opportunity for symptomatic relief with a favorably low side effect profile (minor nasal burning and irritation) [27]. However, there are no randomized controlled trials of the use of saline irrigations in ABRS [2], so their benefit is unknown. In addition, patients cannot obtain sterile solutions for nasal irrigations so whether or not there is risk with nasal irrigations with non-sterile solutions is unknown. Intranasal glucocorticoid sprays can be helpful in ABRS. A meta-analysis of three studies has shown a minor benefit in adding nasal steroid sprays to the treatment regimen of patients with ABRS [28]. Other therapies that are sometimes used in supportive treatment of ABRS include oral and topical decongestants, antihistamines, and mucolytics. However, none of these therapies has good evidence to support its use; some may actually cause harmful side effects, such as raising blood pressure (associated with oral decongestants), and irritating or overdrying the nasal lining (associated with antihistamines) [2].

Conclusion

Acute bacterial rhinosinusitis is one of the most common infections treated by primary care providers. The distinction between ABRS and viral upper respiratory tract infections is usually made based on duration and time course of compatible symptoms, with ABRS characterized by either persistence of symptoms for at least 10 days, worsening of symptoms (or double worsening), or severe onset of symptoms including high fever for 3 days. Radiologic imaging and sinus cultures are not indicated for uncomplicated ABRS. Adults with non-severe, uncomplicated ABRS and whose follow-up is assured may be observed without antibiotics (watchful waiting) or treated with antibiotics. Patients with orbital or CNS complications require aggressive treatment with intravenous antibiotics and possibly surgery.

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Complications of Acute Bacterial Sinusitis in Children

12

Ellen R. Wald and Gregory P. DeMuri

Upper respiratory infections (URI) are the most common illnesses evaluated by the primary care physician. Observational studies have shown that 5–10% of URIs in children are complicated by acute bacterial sinusitis (ABS) [1–3]. Acute bacterial sinusitis and its complications are responsible for approximately 23 million visits to the health care provider annually and result in over 20 million prescriptions for antibiotics [4]. Complications of ABS are rare although their precise incidence is unknown. A population-based study from the Netherlands estimated that 1:12,000 pediatric episodes of ABS were complicated by an orbital infection [5], while a study from the U.S. found that only 0.7% of nearly 102,000 children with ABS seen in emergency departments had an orbital or intracranial complication [6]. Orbital complications are more common than intracranial complications, with 70–80% of all ABS complications involving the orbit and 20–30% involving the central nervous system [5, 6]. Complications of ABS may have severe sequelae, including loss of vision, hemiplegia, or death, if not treated appropriately. With aggressive management, including surgery as needed, outcomes are usually good. The mortality rate was 3% in a large recent systematic review of intracranial complications reported between 1947 and 2015 [7].

The peak prevalence of complications of ABS parallels the frequency of URIs and occurs in the winter months in temperate climates. The mean age is 3–6 years which likely reflects the greater prevalence of orbital involvement which occurs in young children compared to intracranial complications which occur more frequently in adolescents [8]. Males account for 60–70% of cases in nearly every survey of the complications of ABS.

Anatomy and Pathogenesis

The ethmoid and maxillary sinuses develop in the third to fourth month of gestation and although very small, are present at birth. The frontal sinuses develop from an anterior ethmoidal air cell and move from an infraorbital to a supraorbital position by the fifth or sixth year of life. The frontal sinuses progressively pneumatize the frontal bone; development of the frontal sinuses is not complete until late in adolescence. The sphenoid sinus starts to become aerated at age 5 years and expands in size into the second or third decade of life.

The outflow tract of the maxillary sinus is located at the superior most portion of the medial wall of the sinus (Fig. 12.1). This awkward

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_12

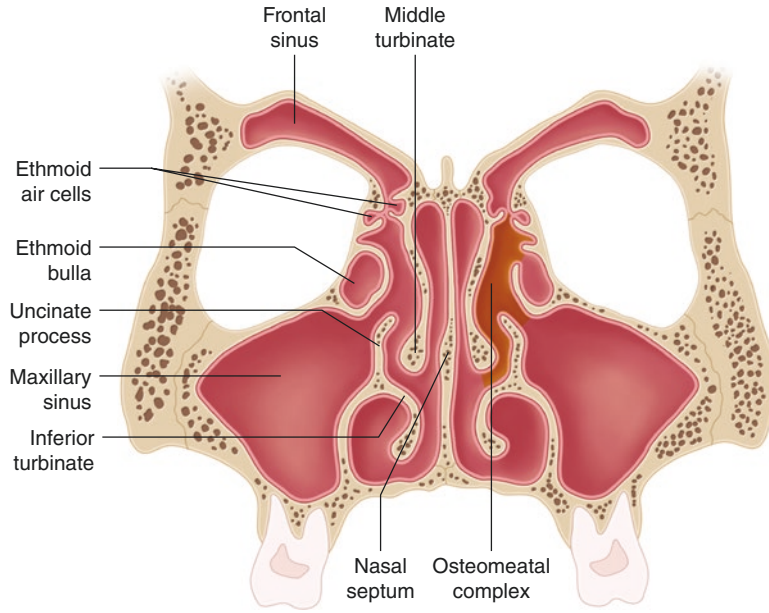

Fig. 12.1 Anatomy of the paranasal sinuses and orbits

positioning of the outflow tract makes gravitational drainage difficult. The clearance of secretions of the sinus is thus dependent on the mucociliary elevator of the mucosa. The maxillary sinus empties via the ostium into the middle meatus of the nasal cavity at a location known as the osteomeatal complex. The maxillary sinus ostia are small, tubular structures with a diameter of only 2.5 mm and a length of 6 mm. The anterior ethmoid and frontal sinuses also empty into the osteomeatal complex in the middle meatus; their ostia are even smaller in diameter, measuring 1–2 mm. The posterior ethmoid air cells and the sphenoid sinus drain into the superior meatus.

A key concept in understanding the pathogenesis of ABS is that the mucosa of the nose and nasopharynx is continuous with the mucosa of the paranasal sinuses. When there is a viral URI causing nasal inflammation, there is almost always inflammation of the membranes that line the paranasal sinuses as well. This pseudostratified columnar epithelium clears mucus and other material from the sinus by ciliary action. Unlike the nasal mucosa, which is heavily colonized with bacteria, the paranasal sinuses are usually sterile when evaluated by conventional microbiologic techniques [9].

Table 12.1 Factors that predispose to sinus ostia obstruction

Mucosal swelling	Mechanical obstruction
Systemic Factors	Choanal atresia
Viral upper respiratory infection	Deviated septum
Allergic inflammation	Nasal polyps
Cystic fibrosis	Foreign body
Immune disorders	Tumor
Ciliary dyskinesia	Ethmoid bullae
Tobacco smoke	
Local Insult	
Facial trauma	
Swimming, diving	
Rhinitis medicamentosa	
Nasal intubation	

The pathogenesis of sinusitis involves three key factors: obstruction of the sinus ostia, dysfunction of the ciliary apparatus, and thickening of sinus secretions. The narrow diameter of the sinus ostia allows for easy obstruction. The factors that predispose the ostia to obstruction may be divided into those that result in mucosal swelling and those that result in a direct mechanical effect and are listed in Table 12.1. Viral URI is the most common cause of ostial obstruction in children and frequently precedes the development of sinusitis. Obstruction of the ostia results

in a transient increase in pressure in the sinus cavity. As oxygen is depleted, the pressure in the sinus becomes negative relative to atmospheric pressure. This negative pressure allows for the introduction of bacteria from the nose and nasopharynx into the sinus during sneezing and nose blowing. When the ostium is obstructed, mucus production by the mucosa continues, resulting in the accumulation of fluid in the sinus cavity as well as the multiplication of bacteria and the initiation of an inflammatory reaction.

In addition to ostial obstruction, dysfunction of the mucociliary apparatus also contributes to the development of sinusitis. During a viral URI, progressive loss of ciliated cells may be observed in the respiratory mucosa. Lastly, the quality and character of sinus secretions play an important role in the pathogenesis of ABS. Cilia can only beat in a liquid media and diseases such as cystic fibrosis result in very thick, viscous secretions that diminish ciliary clearance of fluid and debris from the sinus. Infection of the sinus results in thickening of secretions, compounding this process. The result of a viral URI is that all three of these factors are present: ostial obstruction, ciliary dysfunction, and thickening of sinus secretions. The viral URI is the most common predisposing factor to the development of bacterial sinusitis in childhood and accounts for approximately 80% of the cases. Allergic inflammation underlies the remaining 20% of cases of ABS in children.

Anatomical Features Relative to Complications of Sinusitis

The complications of ABS relate directly to the proximity of the paranasal sinuses to the orbit and the brain. The orbit is surrounded on three sides by the paranasal sinuses (Fig. 12.1). The roof of the orbit is the same as the floor of the frontal sinus, the medial wall of the orbit is the same as the lateral wall of the ethmoid sinus, and the floor of the orbit is the same as the roof of the maxillary sinus. In particular, the wall that separates the ethmoid sinuses from the orbit is known as the lamina papyracea,—*paper thin plate* of bone. Naturally occurring bony dehiscences in the lamina papyracea, as well as vascular foramina, allow the passage of bacteria from the sinuses to the orbit. Alternatively, infection in the sinuses may lead to infection in the thin bones (osteitis) comprising the lamina papyracea [10].

It is also important to note that the posterior wall of the frontal sinus is immediately adjacent to the dura. This location allows for spread of infection from the frontal sinus to the meninges and the brain. The later development of the frontal sinuses explains the predilection for intracranial complications in older children and adolescents. The venous drainage of the frontal and sphenoid sinuses connects with the cavernous venous sinus (Fig. 12.2). This vascular structure, the so-called valveless venous network surrounding the paranasal sinuses, is at risk for

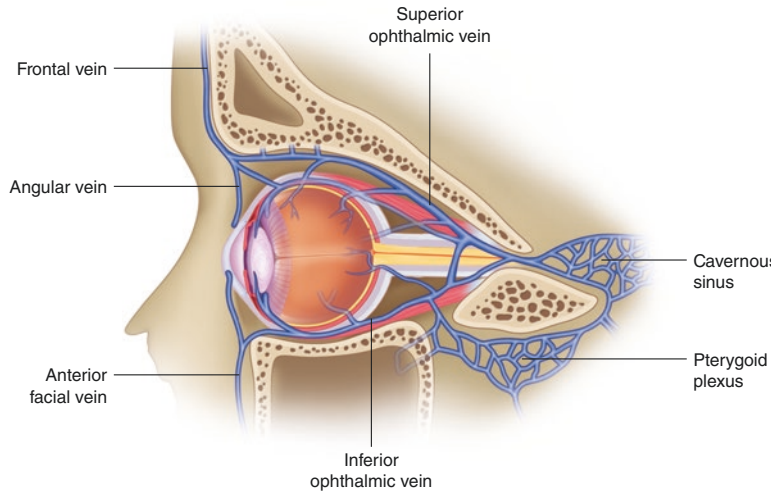

Fig. 12.2 Venous drainage of the sinuses and orbit

thrombosis and serves as another path for infection to spread from the sinuses to intracranial structures.

Complications: Orbital

Complications of ABS may be categorized as extracranial, intracranial and those involving the bone of the sinus wall (osteitis). Extracranial manifestations may be divided into preseptal or postseptal infections. The orbital septum is a connective tissue extension from the periosteum of the orbital rim into the tarsal plates of the eyelids and serves as a barrier to invasion of the orbital space from preseptal infections (Fig. 12.3). Inflammatory edema is a preseptal condition that usually arises from infection of the ethmoid sinus and is the most common complication of ABS in children, representing 80–90% of all the extracranial complications [11]. Inflammatory edema is often referred to as preseptal or periorbital cellulitis. This terminology can be confusing as the term periorbital cellulitis is also used to refer to infections of the skin and soft tissue of the lid and lid structures.

Inflammatory edema is caused by impaired venous and lymphatic drainage of an infected sinus. However, bacterial infection remains confined to the sinus cavity and does not involve the soft tissue surrounding the eye. Patients with inflammatory edema usually present with low-grade or no fever and redness and swelling of the eyelids and periorbital skin which evolves slowly over several days and accompanies signs and symptoms of an upper respiratory infection (Fig. 12.4). Often parents will note the occurrence of periorbital swelling in the morning for a day or two before clinical presentation. It may have been noted when the child awakens in the morning and then resolves over the next few hours. On the day of presentation, the periorbital swelling persists, prompting the parent to seek medical attention. On physical exam the child usually looks generally well. The soft tissue around the eye is swollen and erythematous but not usually tender to the touch. To be certain that the condition does not

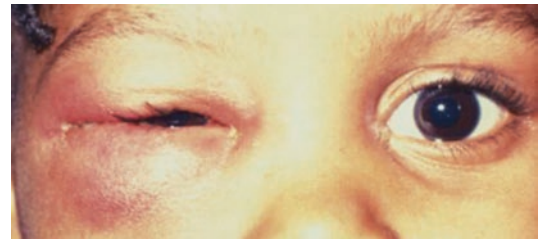

Fig. 12.4 Inflammatory preseptal edema in a child with acute bacterial sinusitis

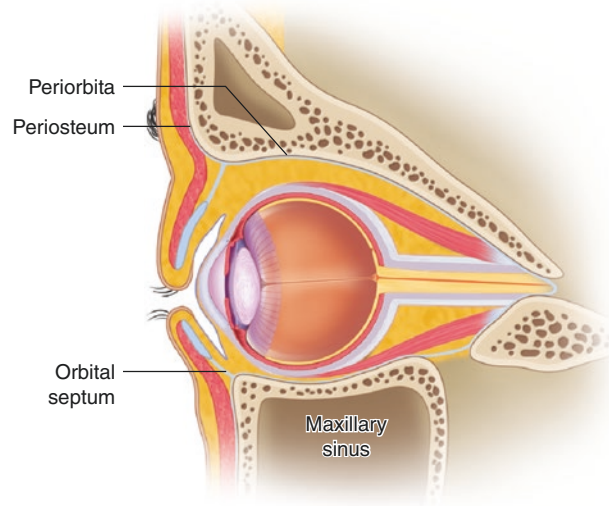

Fig. 12.3 The orbital septum

represent a true orbital infection, the globe must be inspected to determine that it is normal in position and that the extraocular eye movements are full and intact. If possible, visual acuity should be measured as well.

In contrast, orbital complications involve the orbital space proper and include orbital cellulitis, subperiosteal abscess, and orbital abscess. Cavernous sinus thrombophlebitis may occur as a complication of an orbital infection. The Chandler schema is most commonly used to classify the degree of orbital involvement, and divides infections into preseptal inflammatory edema, orbital cellulitis, subperiosteal abscess, orbital abscess, and cavernous sinus thrombophlebitis [12]. These divisions are not meant to necessarily imply that there is a progression between categories. In many cases it is probable that the bony wall of the ethmoid sinus becomes infected by contiguous spread from the mucosa resulting in an osteitis [10]. A subperiosteal abscess forms as the infection within the bone migrates toward the periosteum. If the periosteum ruptures and the purulent accumulation remains close to the bone, an orbital abscess results. If infection diffuses throughout the orbit, an orbital cellulitis evolves. Alternatively, orbital cellulitis may result from the direct spread of bacteria and purulent material from the ethmoid sinuses through natural bony dehiscences or vascular foramina.

The most common of the orbital infections is orbital cellulitis in some series and subperiosteal abscess in others. Botting et al. reported on 32 post-septal complications in children; orbital cellulitis occurred in 57%, subperiosteal abscess in 34%, orbital abscess in 6%, and only one patient (3%) had cavernous sinus thrombophlebitis [11]. In the series of 16 children with post-septal complications reported by Hansen et al., 81% were orbital cellulitis and 19% were subperiosteal or orbital abscess [5]. In contrast, Sharma et al. reported that the majority (72%) of 101 children who had computed tomography (CT) studies for orbital infections had a subperiosteal abscess, most of which did not require surgical intervention [13].

Orbital infections arise from the ethmoid and frontal sinuses in that order [11]. The preponderance of ethmoid sinusitis in orbital complications is likely due to the nature of the lamina papyracea noted above—a very thin bone with natural dehiscences. Patients with orbital infection present with lid swelling and erythema, similar to the appearance in preseptal cellulitis. However, in orbital infection, there is the critical addition of proptosis (usually anterior and downward displacement of the globe), ophthalmoplegia (usually impairment of upward gaze), and/or decrease in visual acuity. These are the distinguishing features of orbital disease compared to preseptal infection (Fig. 12.5). Accordingly, the clinician must make a determination regarding the presence of proptosis, although early proptosis may be missed if the determination is based solely on gross examination. Ophthalmologists consider proptosis as 2 mm or more difference in projection of the corneal surface of one eye versus the other, using a measuring device such as Hertel's exophthalmometer. If proptosis cannot be determined clinically, an image such as an orbital CT may be required. Because orbital complications may result in permanent visual loss or spread to intracranial structures, distinguishing this condition from preseptal involvement is essential. The clinical findings of ophthalmoplegia and proptosis each have a positive predictive value for orbital infection of 97% and their absence a negative predictive value of 93% [8]. If neither of these findings is detected, the chances of orbital involvement are low.

Complications: Central Nervous System

Complications of sinusitis that affect the central nervous system (CNS) include, in their relative order of prevalence, subdural empyema, epidural empyema, cerebritis, meningitis, brain abscess, and cavernous sinus thrombophlebitis [7]. Subdural empyema and epidural empyema are by far the most common and are roughly equal in frequency depending on the series. Each accounts for 35–49% of the intracranial complications secondary to sinusitis [7, 14, 15]. In a review of 179 patients with intracranial complications, the

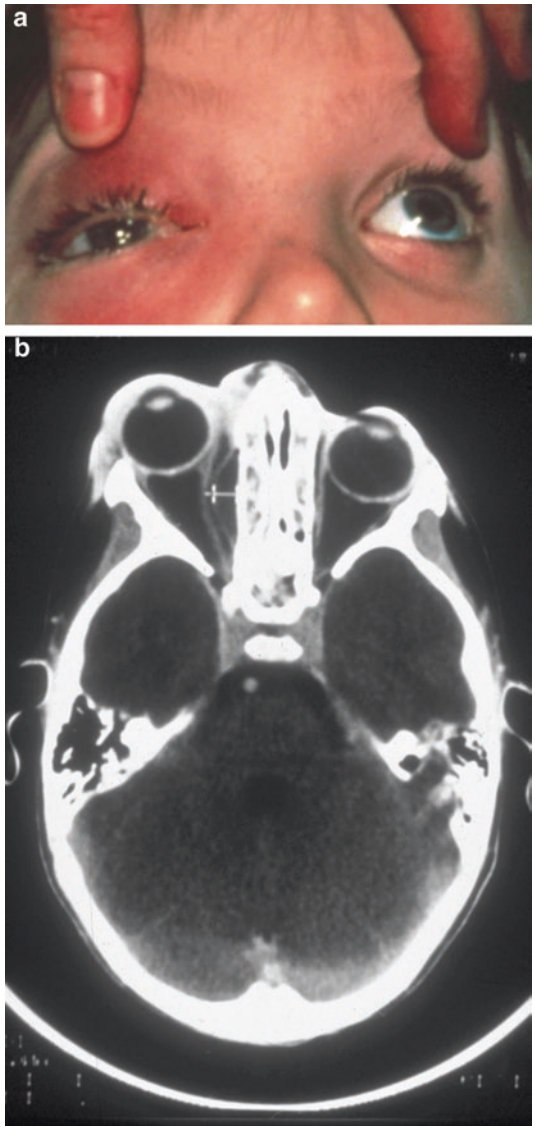

Fig. 12.5 (**a**) A child with a subperiosteal abscess due to *S. pneumoniae*. (**b**) CT scan showing subperiosteal abscess

composite mean age was 13 years (range 10 weeks to 18 years) and 70% of children were male [7]. The average duration of symptoms before clinical presentation was 13.4 days (range 7–16.2). Headache and fever are nearly universal findings at presentation and are often accompanied by mental status changes, seizures, or focal neurological deficits. Other findings include nausea and vomiting in 38% of children [7]. The array of symptoms is similar for each of these intracranial complications which may also be accompanied by orbital complications. Importantly, patients with intracranial complications may not have typical respiratory symptoms associated with URI or sinusitis (cough, nasal discharge, or congestion) or may have had them for only 5–7 days before presentation [16, 17]. Unfortunately, the absence of respiratory symptoms may delay the diagnosis or deter the clinician from associating the presenting symptoms with a preceding sinus infection. Symptoms referable to the CNS are often predominant and are the presenting illness.

The clinical presentation of children with epidural empyema is similar to that of subdural empyema, with headache and fever being predominant [18]. Likewise, there are no distinguishing clinical features for children who have the rare complication of brain abscess or cerebritis secondary to ABS. Fever, headache, and mental status changes usually prompt the performance of images of the brain which yields the specific diagnosis of brain abscess or cerebritis with or without epidural and subdural empyema.

Cavernous sinus thrombophlebitis is the least common complication of acute sinusitis [19, 20]. Classic signs of infection include unilateral periorbital edema, headaches, photophobia, chemosis, and proptosis. Approximately 50% of patients present with symptoms referable to cranial nerves III, IV, and VI, including impaired extraocular movement and VI nerve palsies [21]. Compression of the ophthalmic and maxillary branches of cranial nerve V results in facial sensory deficits, periorbital sensory loss, and/or an impaired corneal reflex [20]. Diagnosis is made with the performance of a contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) study. Complications include progression to bilateral involvement (due to an intercavernous communication), meningitis, subdural empyema, and sepsis [20]. Residual deficits are observed in approximately 25% of patients (blindness, ptosis, hemiplegia) and mortality in 8% [19]. Management includes drainage of any abscess

or empyema (if present) and antibiotics; use of anticoagulation is controversial [19].

Complications of the Frontal Bone

Pott's puffy tumor is an osteitis and subperiosteal abscess affecting the wall of the frontal sinus which presents with forehead swelling and tenderness. It is often associated with intracranial extension such as subdural and epidural empyema [22]. In the pediatric age group, Pott's puffy tumor usually presents in adolescents since the frontal sinuses are not fully formed until after puberty. However, younger children with Pott's puffy tumor have been described [20]. Symptoms include headache and fever; signs include tenderness, swelling, and erythema of the forehead.

Differential Diagnosis

Although preseptal inflammatory edema associated with ABS is one of the most common causes of preseptal erythema in young children, the differential diagnosis includes preseptal cellulitis from bacterial infections that may complicate a hordeolum, dacryocystitis, dacryoadenitis, or an infected cut or insect bite [23]. An additional, now rare, cause of preseptal cellulitis is bacteremic periorbital cellulitis caused by *Haemophilus influenzae* type b or *Streptococcus pneumoniae*. Before the near universal use of conjugate vaccines to prevent these infections, bacteremia caused by *H. influenzae type b* and *S. pneumoniae* occurred frequently in infancy and occasionally seeded the tissues around the eye. Children with bacteremic periorbital cellulitis have high fever (usually ≥39 °C) and present with very rapid progression of swelling and redness of the tissues around the eye leading to closure of the lids in 12–24 h [23].

Orbital abscess should be easily distinguished from mass occupying lesions of the orbit and from post-traumatic infections. Intracranial abscesses may be the result of trauma or bacteremic spread from a distant focus of infection.

Microbiology of Acute and Chronic Sinusitis

There has been relatively little direct investigation of the microbiology of acute sinusitis in the last several decades, as sinus aspiration via puncture is an invasive procedure which is not performed unless the patient has a complicated or non-responsive condition. Accordingly, most of the speculation regarding the usual microbiology of ABS in children is derived from data based on tympanocentesis performed on children with acute otitis media, capitalizing on the similarity of epidemiology and pathogenesis of ABS and acute otitis media. With this in mind, it appears that the bacterial species causing ABS, in their relative order of prevalence, are *H. influenzae* (non-typeable), *S. pneumoniae*, and *Moraxella catarrhalis* [24]. When complications of acute sinusitis occur, *S. pneumoniae* is the only one of this trio that is usually identified, although other Gram-positive organisms are prominent. Of interest, although *Streptococcus pyogenes* is an uncommon cause of ABS, it is a relatively common cause of subperiosteal abscess, underscoring the predilection of particular bacterial species to cause these complications.

The microbiology of chronic sinusitis includes those bacterial species found in children with acute sinusitis as well as *Staphylococcus aureus*, *Streptococcus anginosus*, and Gram-negative and Gram-positive anaerobic species [25, 26].

Microbiology of the Complications of Sinusitis

Appreciation of the microbiology of the complications of ABS is frequently confounded by partial antibiotic therapy before the site of infection is sampled, use of methods that may be prone to contamination from nasopharyngeal or nasal flora (sampling via the nasal endoscope), and inadequate culture methods to demonstrate the presence of anaerobes. The microbiology of orbital and intracranial complications of sinusitis reflects that of ABS to some extent, in that *S.*

Table 12.2 Microbiology of the complications of sinusitis

Gram positive
Staphylococci
Staphylococcus aureus
Coagulase-negative staphylococci
Streptococci
Streptococcus pneumoniae
S. anginosis and other viridans streptococci
S. pyogenes (Group A *Streptococcus*)
Group C *Streptococcus*
Gram negative
Haemophilus influenzae
Aggregatibacter aphrophilus
Moraxella catarrhalis
Pseudomonas aeruginosa
Klebsiella pneumoniae
Moganella morganii
Serratia marcesens
Citrobacter freundii
Anaerobes
Bacteroides species
Prevotella species
Eikenella corrodens
Fusbacterium species
Peptostreptococcus species
Porphyromonas species

pneumoniae is common although non-typeable *H. influenzae* and *M. catarrhalis* are relatively rare. However, other Gram-positive organisms, including staphylococci and *S. pyogenes*, Gram-negative and anaerobic bacteria, are also significant pathogens (Table 12.2). In the past decade, there has been increasing recognition of the importance of *S. anginosis* (formerly *S. milleri*) and methicillin-resistant *S. aureus* (MRSA) in these infections [11, 14, 27]. The increase in these pathogens has been associated with the decrease in *S. pneumoniae* presumably attributable to the widespread use of pneumococcal conjugate vaccines, PCV7, and most recently PCV13 [28]. Many of the complications of ABS are polymicrobial in nature. A comprehensive review of the microbiology of subperiosteal abscess by Brook details findings in the pediatric literature, although the site sampled in each case is not always noted [29].

Imaging

When an orbital or intracranial complication of ABS is suspected on clinical grounds, imaging studies are essential to confirm the diagnosis and to determine the need for surgical intervention. Computed tomography provides the best definition of bony structures and is most likely to show subperiosteal abscess and osteitis, particularly when orbital complications are suspected. In addition, CT will delineate the osteomeatal complex and sinuses themselves in great detail, which may provide important information when sinus surgery is planned. Despite the overall high sensitivity of CT to delineate the presence of subperiosteal abscesses of the orbit, when surgery is performed immediately post imaging, occasionally only a phlegmon is present [30]. Magnetic resonance imaging affords more detailed images of the brain and surrounding structures. Meningitis and local fluid collections such as subdural and epidural empyema are best imaged using MRI [31].

Management

The management of the complications of ABS consists of targeted antimicrobial therapy and surgical drainage. Empirical antimicrobial choice depends on the location of infection and suspected pathogens. For sinus, periorbital and orbital involvement, a combination of ceftriaxone (100 mg/kg/day in 2 divided doses) and vancomycin (60 mg/kg/day in 4 divided doses) should be used initially. Ampicillin/sulbactam (200 mg/kg/day in 4 divided doses) is an acceptable alternative if MRSA is not suspected and there is no intracranial extension. Therapy should usually be parenteral except in cases of mild preseptal inflammatory edema (without orbital involvement), in which case amoxicillin/clavulanate may be used orally. Intracranial complications should always be treated with intravenous antimicrobials and therapy must include agents that have adequate penetration into cerebrospinal

fluid and brain. Combination therapy with vancomycin, ceftriaxone, and metronidazole (40 mg/kg/day in 3 divided doses) provides coverage for most intracranial pathogens complicating ABS. In all cases, antimicrobial therapy should be dictated by microbiological data and changed to the most narrow spectrum agent(s) available.

Patients with very small orbital, subperiosteal, or epidural abscesses and minimal ocular and neurologic abnormalities may be managed with intravenous antibiotic treatment for 24–48 h while performing frequent visual and mental status checks [32, 33]. In patients who develop progressive signs and symptoms, as well as those who fail to improve within 24–48 h while receiving antibiotics, prompt surgical intervention and drainage of the abscess should be undertaken [34]. Surgery has two purposes: to provide microbiological data that will guide antibiotic selection and to drain significant fluid collections. Prompt surgical drainage is paramount when the CNS and ocular structures are threatened. Both aerobic and anaerobic cultures should be obtained in the operating room and transported to the laboratory immediately. For anaerobes, special transport media should always be used to optimize recovery of these pathogens.

Outcomes depend on prompt recognition of orbital and intracranial involvement and early intervention. Patients should be managed in consultation with the appropriate surgical subspecialties. Supportive care such as anticonvulsants, analgesics and measures to reduce intracranial pressure should be used as indicated. Since the complications of ABS are rare, it is difficult to establish that early treatment of ABS in the ambulatory setting reduces complications. However, treatment of uncomplicated ABS should follow established guidelines.

Conclusion

Acute bacterial sinusitis complicates viral URI in approximately 8% of cases. Orbital and intracranial complications of ABS are very uncommon impacting only between 0.5% and 1.0% of children. Orbital complications are observed most frequently (70%) and affect children <5 years of age while intracranial complications affect an older age group. True orbital complications are characterized by lid erythema and swelling but also one or more of the following: proptosis of the globe, impairment of extraocular movements, and decrease in vision. Intracranial complications include epidural empyema, subdural empyema, brain abscess, and cavernous sinus thrombophlebitis. Diagnosis is supported by the performance of a contrast enhanced MRI. Treatment includes antibiotics and surgical drainage if indicated. Residual neurologic deficits may occur although overall outcomes are improved with current diagnostic and therapeutic modalities.

Acknowledgement This work was supported by a grant from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (R01 AI097172).

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Chronic Rhinosinusitis

13

Ahmad R. Sedaghat

Introduction

Chronic rhinosinusitis (CRS) is a disease characterized by chronic inflammation of the sinonasal mucosa [1–3]. The clinical manifestations include not only chronic sinonasal symptoms but also symptoms of acute exacerbations and any comorbid pulmonary diseases [4–6]. Chronic rhinosinusitis impacts quality of life to a degree comparable to asthma or heart disease [4, 7], causes significant losses in productivity from missed days at work and school [7, 8], and leads to billions of dollars in direct and indirect costs every year [9, 10]. The impact of CRS is not only on afflicted individuals but also on society as a whole.

As discussed below, CRS is a complicated and heterogeneous disease. The exact pathophysiology likely differs from patient to patient, but recent studies suggest that CRS results from a dysregulated interaction between external stimuli and the host immune response. This chapter will review the diagnosis, pathophysiology, and treatment of CRS.

Diagnosis

Chronic rhinosinusitis is defined clinically based on consensus guidelines incorporating both subjective and objective criteria. Guidelines by the American Academy of Otolaryngology—Head and Neck Surgery, as shown in Table 13.1, recommend at least 12 consecutive weeks of symptoms including at least two of the following four major symptoms of CRS (nasal obstruction, drainage, facial pain/pressure, and hyposmia/anosmia), in addition to objective evidence of sinusitis on nasal endoscopy or sinus computed tomography (CT) [1]. Very similar diagnostic guideline criteria have been adopted throughout the world [2, 11]. Because CRS is defined clinically, there are likely many different pathophysiologic processes that converge upon the final clinical phenotype defined by consensus diagnostic criteria. In fact, multiple inflammatory mechanisms are believed to contribute to the development and persistence of CRS [3, 12].

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_13

Table 13.1 Clinical consensus guidelines criteria for the diagnosis of CRS from the American Academy of Otolaryngology—Head and Neck Surgery[a]

Diagnostic criteria for CRS
Subjective
At least 12 continuous weeks of at least two out of four symptoms of:
• Nasal obstruction
• Nasal drainage
• Facial pain/pressure
• Hyposmia or anosmia
Objective
• Nasal endoscopy findings
– Mucupurulent drainage, edema, polyps
Or
• Radiographic findings
– Mucosal thickening, sinus opacification, air-fluid levels

[a]Adapted from reference [1]

Pathophysiology

Genetic basis. There is ample evidence that dysregulated host inflammatory responses to various extrinsic inflammatory stimuli contribute to the pathophysiology of CRS [13]. In many cases, there appears to be a genetic basis for the host response that is inherited as a complex genetic trait. The heritability of CRS has been suspected for decades. Patients with cystic fibosis may have significant CRS and the association of CRS with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which cause cystic fibrosis, represents a special case of CRS [14, 15]. However, a genetic basis for CRS in other patients has been suspected for many years because CRS patients often relate a positive family history of CRS, even in the setting of dissimilar environment exposures [16, 17]. Recent studies of a large genealogical database linked to medical charts of almost ten million individuals have shown an increased risk for the development of CRS in individuals with family members who have CRS [18, 19]. There was an increased risk of developing CRS in adults with a first-degree relative with CRS (two to four-fold increased risk) and in siblings of pediatric CRS patients (>50-fold increased risk) [18, 19]. Genetic linkage studies have identified numerous gene loci that appear to be associated with the development of CRS [12].

Innate immune response. Supporting the important role of the host inflammatory response in the development of CRS is the identification of genes involved in the innate and adaptive immune responses associated with CRS. The immune system is comprised of an innate and an adaptive immune system. The innate immune system is more primitive and present in both animals and plants, while the adaptive immune system is only present in vertebrates. The innate immune system is a rapid response system and serves as the first line of defense against invading microbes. It also activates the adaptive immune response to provide a secondary response. The ability of the innate immune system to rapidly recognize pathogens is linked to the presence of Toll-like receptors (TLRs) in the cell membranes of various types of white blood cells (e.g., macrophages, dendritic cells) as well as epithelial and endothelial cells. These TLRs recognize molecules that are broadly shared by viruses, bacteria, and fungi. Several studies have identified polymorphisms in TLRs and their downstream signaling molecules that appear to be associated with CRS [20–23]. Another receptor that plays a role in the innate immune system is the bitter taste receptor T2R38, which helps protect the upper airway. This receptor is found in human sinonasal epithelial cells and when activated by certain molecules (quorum-sensing) produced by bacteria, T2R38 causes the epithelial cells to release nitric oxide, which in turn triggers bactericidal activity and increased mucociliary clearance. Several recent studies have identified polymorphisms in T2R38 that are associated with medically refractory CRS [24, 25].

Adaptive immune response. Although innate immunity is critical to the initiation of the immune response, the adaptive immune response often plays a more important role in chronic inflammatory conditions such as CRS. While the innate immune response is static—hard-coded in the genome to respond to specific microbial antigens—the adaptive immune system is variable from person to person and can evolve over the course of days to maximize its efficacy against

targeted antigens. The adaptive immune system, which confers long-term immunity, creates an initial response to a pathogen and then an enhanced response with each subsequent encounter with the same pathogen. The central regulators of the adaptive immune response are T lymphocytes, and these respond to pathogens once these are presented to them on the surface of a host antigen presenting cell (e.g., dendritic cell). To "present" these pathogens to T lymphocytes, the pathogens or components of pathogens must be combined with the cell's major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) complex in humans. The MHC (or HLA) is a set of cell surface proteins present on nearly all cells of the body that enables the immune system to recognize "self" from "non-self," and recognize invading pathogens such as bacteria. Presentation of HLA-antigen (e.g., bacteria or bacterial component) complex activates T lymphocytes, which in turn activate the adaptive immune system response. Numerous studies have now found that the genes responsible for these HLA proteins are strongly linked to CRS [26–30], and this in turn suggests that the pathophysiology of CRS is related to an antigen-driven inflammatory response. Figure 13.1 illustrates various actions of the innate and adaptive immune systems (and their interactions) that may play a role in CRS.

Cytokines and other inflammatory mediators. Cytokines and other inflammatory signaling molecules have been associated with CRS [12, 31]. Many of the cytokine genes associated with CRS can be classified as pertaining to specific T-helper lymphocyte (Th) inflammatory responses, with the prototypical responses being Th1 and Th2 [32]. The Th1 response, which mediates the immune response to intracellular bacteria and viruses, is characterized by interferon-γ and interleukin-12 production as well as recruitment of cytotoxic $CD8^+$ T lympho-

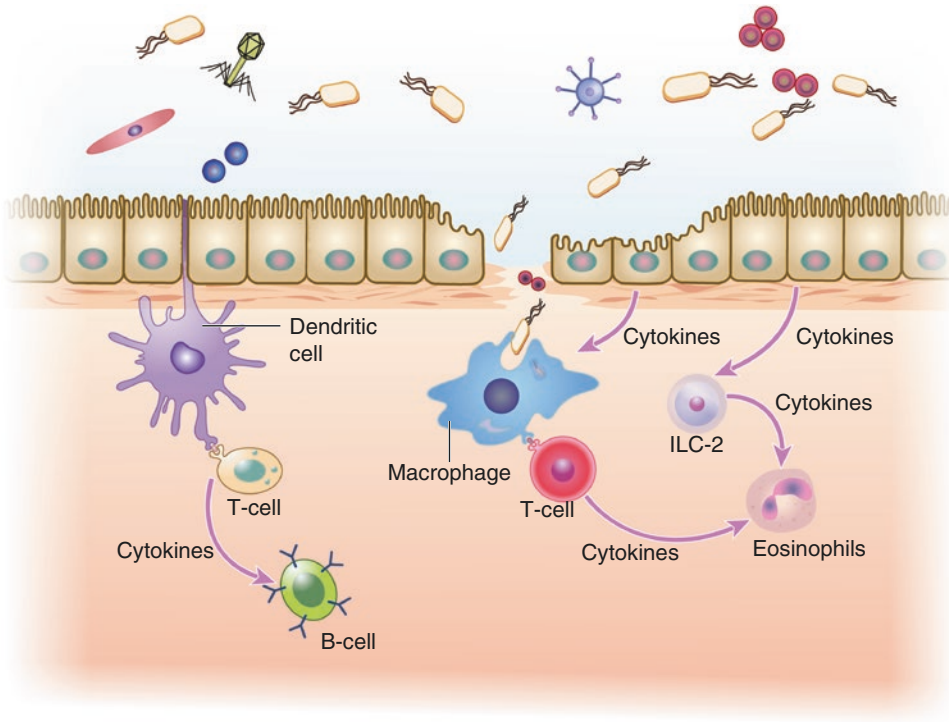

Fig. 13.1 Schematic of the contributions of—and interactions between—innate immunity (including epithelium, macrophages, dendritic cells, ILC-2s, and eosinophils) and adaptive immunity (including T cells and B cells) in the inflammation of the paranasal sinus mucosa in the setting of chronic rhinosinusitis

cytes and IgG-producing B lymphocytes [32]. The Th2 response, which mediates anti-parasitic and allergy immune responses, is characterized by interleukin-4, -5, and -13 production as well as recruitment of eosinophils and IgE-producing B lymphocytes [32]. Whether Th1 or Th2 cytokines predominate in the sinonasal mucosa of CRS patients correlates with nasal polyps: Th2 is predominant in patients with polyps and Th1 in patients without polyps [33–35]. It is not surprising that genetic linkage studies have identified polymorphisms in Th2-specific cytokines that are associated with the presence of nasal polyps in CRS patients [36, 37].

The dysfunctional sinonasal epithelium. Genetic studies and immunologic profiling studies of CRS patients have pointed to the importance of antigen recognition and the subsequent host immune response in the development of CRS [35]. These findings naturally lead to the subsequent question: what are these antigens and why do they drive chronic inflammation resulting in CRS in some patients but not in others? The answer to this question likely lies, at least in part, with the state of the sinonasal epithelium in CRS. In the setting of CRS, histologic evaluation of the sinonasal mucosa has shown the sinonasal epithelium to be frequently damaged and at various stages of healing with regeneration often occurring in a suboptimal manner (Fig. 13.2) [38]. This damage may be due to the direct impact of inflammatory cytokines as well as microbial products, allergens, and airborne irritants that can lead to breakdown of tight junctions and epithelial cell apoptosis [39–43]. The end result is that the sinonasal epithelium is highly porous, allowing leakage of allergens, environmental irritants, microbes and microbial products into the deeper layers of mucosa [44, 45]. These foreign substances may all serve as inflammatory stimuli that chronically activate the mucosal immune system in the paranasal sinuses.

Mechanical factors. The normal paranasal sinus mucosa, lined with pseudostratified epithelial cells that each have 50–200 cilia and mucus-producing goblet cells. The sinus mucosa continuously produces mucus that is moved up and out of the natural sinus ostia through the

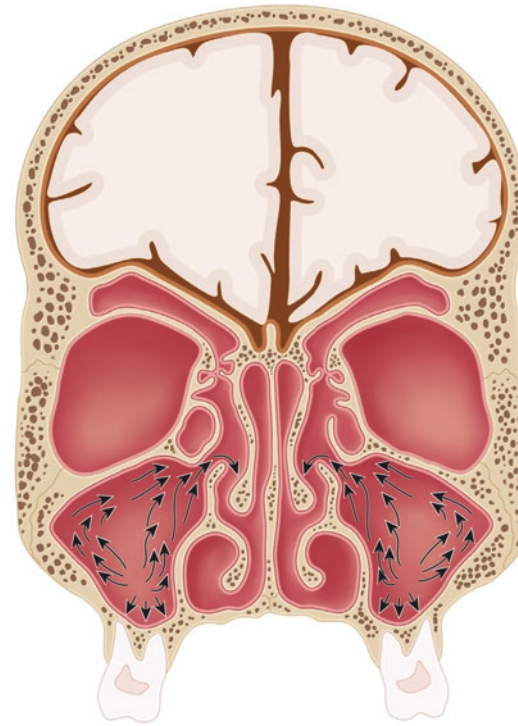

Fig. 13.2 Schematic of mucociliary clearance. A coronal section through the skull, including the paranasal sinuses. Mucociliary clearance from the maxillary sinus is represented by the arrows showing directional sweeping to move mucus out of the sinus by the ciliated sinonasal epithelium

action of the synchronized beating of cilia on sinonasal epithelium (Fig. 13.2) [46, 47]. Chronic inflammation may lead to a change in the composition of the sinus mucosa in CRS, with drop out of ciliated cells and an increase in mucus-producing goblet cells (Fig. 13.3). The cilia on the sinonasal epithelium, which normally beat in concert at 12–15 Hz, beat not only slower but also beat dyssynchronously in the setting of CRS (Fig. 13.4) [46, 47]. The sinus ostia may also be obstructed by inflamed mucosa, polyps, or inspissated secretions, which can further delay the natural movement of mucus out of the sinus (Fig. 13.5). The end result is that there is chronic mucus stasis in the sinuses, which can serve as a chronic inflammatory stimulus through accumulation of microbes and microbial products.

Alterations in the sinonasal microbial flora. It has been established for several decades that

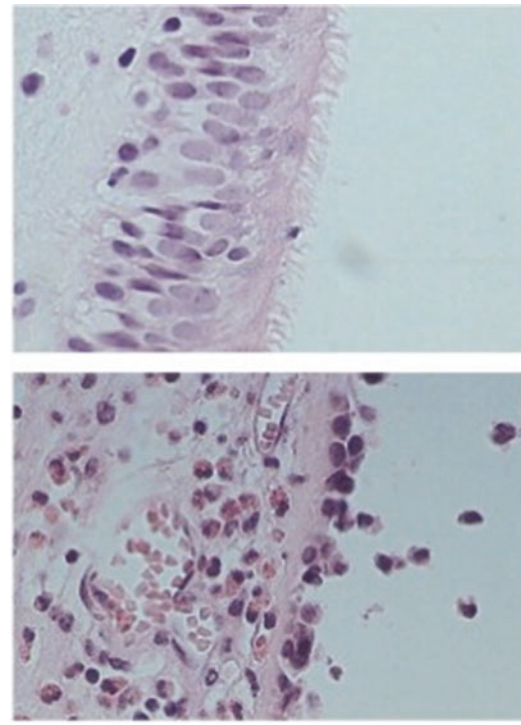

Fig. 13.3 Histologic images of normal healthy pseudostratified sinonasal epithelium (top panel) and sinonasal epithelium from a patient with CRS demonstrating complete erosion of the epithelium. Reproduced from Ponikau JU, et al. [121], with permission from Elsevier

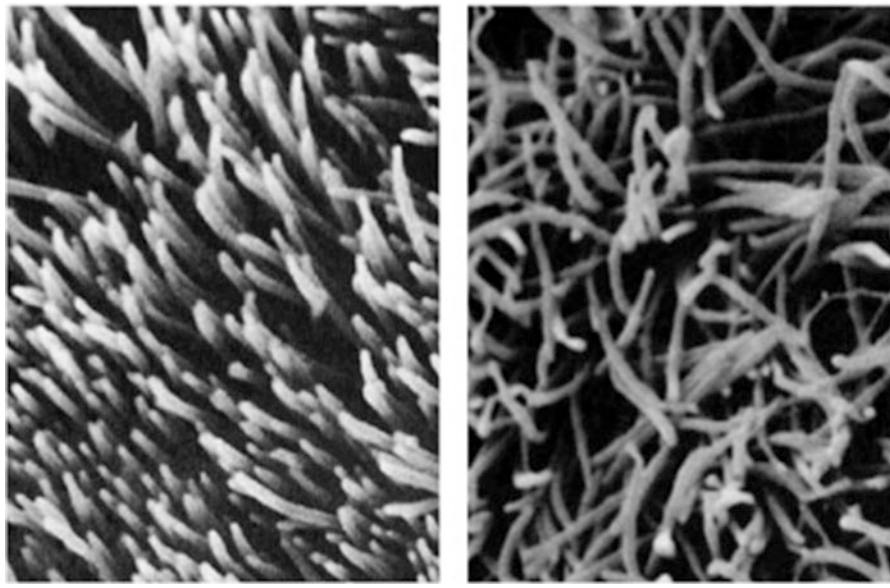

Fig. 13.4 Scanning electron microscope images (600×) nasal mucosa from patients with CRS, ranging from normal synchronous cilia beating at approximately 15 Hz (left) to complete ciliary beat disorientation at approximately 6 Hz (right). Reproduced from Joki S, et al. [122], with permission from John Wiley and Sons

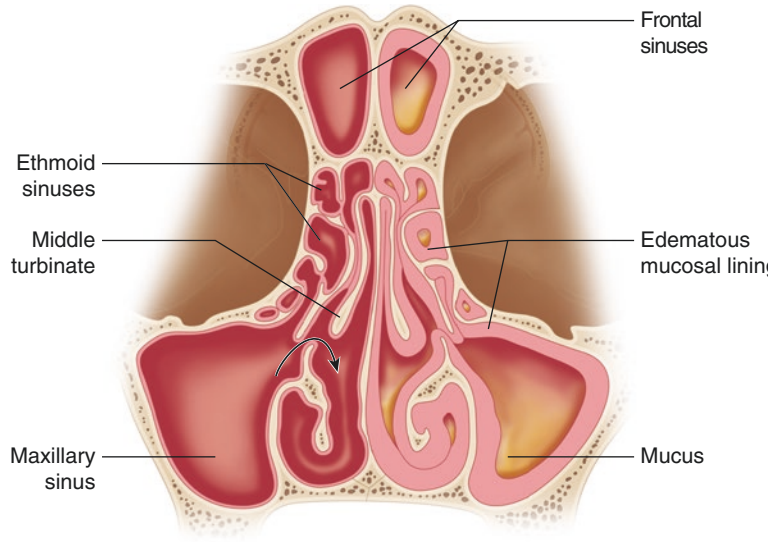

Fig. 13.5 Schematic showing obstruction of normal mucociliary clearance by sinonasal mucosal edema on a coronal section through the paranasal sinuses. On the left, there is normal mucociliary clearance of mucus through the natural opening of the maxillary sinus. On the right, edema of the sinonasal mucosa obstructs the natural opening of the maxillary sinus leading to resultant mucus stasis

the microbial flora colonizing the sinuses of CRS patients differs from that of non-CRS patients and from pathogens seen in acute sinusitis [48, 49]. Pathogens cultured from acute bacterial rhinosinusitis (ABRS) are primarily *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* [48–50] and these may be cultured in up to 15% of CRS patients as well, in some cases in the setting of an acute exacerbation [48, 49]. Sinus cultures from CRS patients, however, usually grow a mixture of aerobes and anaerobes, with aerobes consisting of *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and/or Gram-negative bacilli such as *Pseudomonas* and Enterobacteriaceae (e.g., *Klebsiella*). Anaerobes may be cultured in up to two-thirds of CRS patients when careful anaerobic cultures are obtained.

Interpreting sinus cultures can be challenging because microbes that colonize the nares and nasal passages may readily contaminate "sinus" cultures obtained via the nose, including those obtained endoscopically. Coagulase-negative staphylococci colonize nearly 100% of the nares of the general population but these bacteria are not respiratory pathogens. *Staphylococcus aureus* colonizes the nares of 20–30% of the normal population and MRSA colonizes approximately 3% (up to 6% of healthcare workers and patients with frequent healthcare contact).

Although fungi can be cultured from the nasal secretions of almost all the CRS patients, the same is also true of healthy individuals. This reflects the ubiquitous nature of fungal spores in the ambient air and the entrapment of these spores in the mucus of the upper airway [48]. In both CRS and healthy individuals, *Aspergillus*, *Cladosporium*, *Candida*, and *Alternaria* are commonly cultured from the nasal cavity [51, 52]. The pathogenic role of these fungi is unclear and increasingly unlikely (except for special cases discussed later) as the prevalence of detectable fungi from the paranasal sinuses (in contrast to mucus of the nasal cavity) of CRS patients is extremely low [53].

Given the similarities between CRS and asthma, there has been interest in the role of viruses in CRS. Viral respiratory tract infections are well-known contributors to asthma pathophysiology. Respiratory syncytial virus (RSV) infection during infancy and childhood is a risk factor for the development of wheezing and asthma later in life [54–56] and viral respiratory tract infections (RSV as well as others such as Human Rhinovirus) are associated with asthma exacerbations [57]. Advances in DNA sequencing technology have made detection of viruses more convenient and these approaches have been applied to study the prevalence of viruses in the paranasal sinuses of CRS patients. In one study

of 13 CRS patients undergoing sinus surgery, RSV was not found in the sinus mucosa of any patient and the authors concluded that persistent RSV infection is not a pathophysiologic mechanism of CRS [58]. In another study, RSV was detected at high levels in the middle meatuses of both CRS patients and in healthy controls [59]. Another study found a higher prevalence of respiratory viruses, such as rhinovirus, parainfluenza virus, and RSV, in the nasal washes of CRS patients compared to healthy controls [60]. These reported differences in the detection of viruses from the sinonasal cavities of CRS patients may be related to the source material (nasal washing, epithelial scraping, whole tissue/sinonasal mucosa) as well as the timing of the sampling (e.g., time of year). Nevertheless, these inconsistent findings raise more questions than provide answers and the role of viruses in CRS pathophysiology is still unclear.

Microbiome. The collection of microbial species, also referred to as the *microbiome*, in paranasal sinuses is clearly different between CRS patients and healthy individuals based on culture data alone. These culture-driven findings and our knowledge of the microbial flora in CRS have been taken a large step forward through advances in high-throughput ribosomal RNA sequencing technology. This has allowed characterization of the paranasal sinus microbiome through identification of thousands of microbial species that may be present at levels that are too low to detect by cultures. Several studies have now characterized the microbiome of the paranasal sinuses in CRS patients and healthy controls [61–63]. The results of these studies have been inconsistent, with some studies identifying a decrease and others an increase in bacterial and fungal diversity in the paranasal sinuses of CRS patients compared with controls. Some differences in results may be explained by differences in methodology, but others may be due to the fact that the microbiome of the paranasal sinuses is not static and can instead change in response to, for example, acute bacterial superinfections or environmental exposures [64, 65].

Some studies have found a correlation between the sinonasal microbiome in CRS and clinical outcomes. Ramakrishnan et al. found that CRS patients whose sinus cultures had less microbial diversity had worse clinical outcomes after endoscopic sinus surgery but patients with abundant *Corynebacterium* species, particularly *C. tuberculostearicum*, had improved postoperative outcomes [61]. Abreu et al. found that, in comparison with CRS sinuses, the sinuses of healthy patients had more microbial diversity, more *Lactobacillus* species, and fewer *C. tuberculostearicum* [62]. Abreu et al. also demonstrated the pathogenic potential of their microbiome findings by animal experiments, producing histopathologic changes in the sinonasal mucosa of mice suggestive of CRS (e.g., goblet cell hyperplasia) through intranasal inoculation with *C. tuberculostearicum*, and protecting against those changes through co-inoculation with *Lactobacillus species* [62]. Aurora et al., in contrast with the studies by Ramakrishnan and Abreu, found that the microbiomes of CRS patients and controls were similar, but that CRS patients appeared to be hyperreactive to their colonizing flora [63].

Biofilms and antigenic stimulation. With CRS increasingly recognized as an inflammatory condition that is driven by an aberrant host immune response, the role of microbes in CRS is likely as a chronic inflammatory stimulus [13, 45]. Many of the bacterial species, such as *S. aureus* and *P. aeruginosa*, that are found in the paranasal sinuses of CRS patients can form biofilms which is one particularly robust mechanism of bacterial persistence. In contrast to the isolated or free planktonic bacterial forms that can be isolated from mucus, biofilms are adherent complexes of extracellular matrix composed of polysaccharides and proteins, within which bacteria are embedded. Biofilms may also serve as a mechanism for enhanced survival. Although biofilms may be found on the sinonasal mucosa of healthy individuals, some studies have found that biofilms are enriched on the sinonasal mucosa of CRS patients and so may serve as a reservoir for bacterial stimulation of the mucosal immune system [66]. Because microbes may easily penetrate into the subepithelial layers of the sinonasal mucosa in CRS patients, they may provide direct antigenic stimulation to the host mucosal immune

system. One study found that biofilms adjacent to breaks in the sinonasal epithelium in CRS patients were accompanied by a focal enrichment of T lymphocytes and macrophages [67]. Other studies have shown that CRS patients have higher numbers of memory and fungal-specific T lymphocyte responses, suggesting a greater history of antigenic exposure [68, 69]. Bacteria and fungi that are routinely found in CRS are agonists for TLRs which, as described above, activate cells of the innate immune response and also modulate the adaptive immune response [32]. Additionally, *S. aureus*, which is cultured in up to a quarter of CRS patients, produces a superantigen that is believed to be a major driver of nonspecific inflammation in the sinonasal mucosa of CRS patients [70]. In support of this, one study found evidence for oligoclonal expansion of T lymphocytes in the polyps of all 18 CRS patients studied, while another study showed that in CRS patients with polyps, there was evidence of significant enrichment of T lymphocytes responsive to staphylococcal superantigens in 35% of nasal polyps [71, 72]. However, these studies did not include analysis of sinonasal mucosa of non-CRS controls.

Treatment

Saline irrigation and corticosteroids. The mainstay of treatment for CRS is medical management consisting of nasal saline irrigation and topical intranasal corticosteroids [2, 3]. Randomized controlled trials (RCTs) have shown that low-pressure, high volume (240 mL) nasal saline irrigation alone may improve sinonasal symptoms in up to 50% of CRS [73–75]. These studies have also found that low-pressure, high volume irrigation is superior to intranasal saline sprays. While isotonic and hypertonic saline irrigations appear to be equally effective [76, 77]. hypertonic saline irrigations may lead to more patient discomfort (e.g., complaints of burning) [78]. Evidence for the clinical efficacy of intranasal topical corticosteroid sprays in CRS, both for patients with nasal polyps and for patients without, comes from numerous RCTs that have identified a clear benefit for improving CRS symptoms as well as objective sinonasal mucosal inflammation [79, 80].

Antibiotics. The role of antibiotics in treating CRS is unclear [48, 81]. Table 13.2 summarizes the evidence to date. Antibiotics have historically been used for CRS due to the belief of an underlying bacterial etiology. When used for CRS, the typical route of antibiotic administration for CRS is by mouth as there are no studies to date that show an advantage for intravenous or topical antibiotics, with these latter routes of antibiotic administration used on a patient-by-patient basis [2, 3, 48, 81]. There is, in fact, little evidence for the use of antibiotics for CRS in general [48, 81]. However, despite surprisingly scant evidence, antibiotics have traditionally been used as a component of maximal medical therapy [82]. Typically, endoscopically obtained culture-directed antibiotics are administered for up to 3 weeks in the treatment of CRS. This duration is based, in part, on a study that demonstrated a pla-

Table 13.2 Summary of the role of antibiotics in uncomplicated chronic rhinosinusitis

	Level of evidence	Result	References
Topical antibacterials	• RCTs (N = 14–50) • Cochrane review	No benefit vs. placebo	[81, 106–109]
Topical antifungals	• RCTs (N = 24–116) • Cochrane review	No benefit vs. placebo	[97, 99, 110–113]
Oral antibacterials	• RCTs (N = 43–66) • Cochrane review	Possible benefit of macrolides vs. placebo but high quality studies still needed	[81, 84, 88, 89, 114–118]
Oral antifungals	• RCT (N = 53) • Cochrane review	No benefit vs. placebo	[99, 119]
Intravenous antibiotics	• Retrospective reviews • Consensus statement	No clear benefit	[3, 120]

RCT = randomized controlled trial

teau of radiographic improvement of sinus disease after 3 weeks of treatment with antibiotics [83]. Unfortunately, RCTs to study antibiotics in the treatment of CRS are lacking. One small RCT has also shown that a 3-week course of doxycycline may reduce sinonasal symptoms and reduce polyp size in CRS patients [84]. However, these beneficial effects may have been due to the anti-inflammatory—rather than antibacterial—properties of doxycycline [85]. In support of this, one recent open label study showed that long-term low dose doxycycline, which is a dose that is subtherapeutic as an antibiotic but is used as an anti-inflammatory medication in a variety of diseases, was beneficial for improving subjective CRS symptoms and improving objective radiographic CRS severity [86].

The majority of studies on antibiotics for CRS have examined the effect of macrolide antibiotics. Macrolide antibiotics are also known to possess anti-inflammatory properties and it is these properties that have been the subject of much interest for the treatment of CRS [87]. Many retrospective or uncontrolled studies have reported macrolides to reduce sinonasal symptoms and polyp size when used as long-term medical therapy for CRS [88–90]. A recent meta-analysis of RCTs supported the use of long-term macrolide antibiotics in the medical management of CRS patients with polyps who have had endoscopic sinus surgery, stating that more high quality studies are still necessary to determine which additional CRS patients would most benefit from macrolides [91]. While macrolide antibiotics may benefit a subset of CRS patients, the possibility of adverse events—such as development of *Clostridium difficile* colitis—must also be considered. As such, long-term macrolide antibiotics are an option but not necessarily recommended for the long-term treatment of CRS [3].

Another role for antibiotics in CRS may be for acute exacerbations of CRS. However, there is no consensus agreement as to what represents an acute exacerbation of CRS. Instead, the diagnosis of CRS exacerbations is patient-driven and often described in the literature as, for example, "sudden worsening of symptoms with return to baseline after treatment" [2]. Presently, acute exacerbations of CRS are treated like episodes of acute rhinosinusitis using observation, and/or antibiotics [1, 2]. Chapter 11 discusses acute rhinosinusitis in detail. In fact, bacterial isolates from CRS with acute exacerbations are similar to those seen in ABRS, including, *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* [92]. However, bacterial isolates that are more consistent with CRS, such as anaerobes, are also found in acute exacerbations of CRS [92]. The only RCT to study the treatment of CRS exacerbations found no evidence for improved sinonasal symptomatology after 2 weeks of antibiotics compared to placebo [93]. This finding is analogous to a recent RCT of antibiotics for acute rhinosinusitis, which showed that although antibiotic therapy accelerated the resolution of symptoms, both the antibiotic and placebo groups had the same degree of improvement after 10 days of antibiotics [94]. It is therefore possible that antibiotics may accelerate the resolution of acute exacerbations of CRS, but it remains unclear if they have any other benefit over observation alone. It should be noted that the above findings apply only to acute exacerbations of CRS in which there is no evidence for a complication of sinusitis (e.g., no high fever, orbital cellulitis, bacteremia, central nervous system infection).

Early studies that found fungi in the sinonasal cavities of CRS patients suggested that fungi might be a dominant driver of CRS [95, 96]. Additional smaller randomized clinical trials also seemed to show a benefit for the treatment of CRS with systemic and topical antifungals [97]. However, this line of investigation has since been disproven as studies have shown an equivalently high prevalence of fungi in the sinonasal cavities of non-CRS controls and several subsequent randomized clinical trials have found no benefit for antifungals in CRS [98]. At present, there is no evidence to suggest a role for antifungals in CRS [99].

Surgery. Endoscopic sinus surgery may serve as another treatment modality for CRS. There are absolute and relative indications for endoscopic sinus surgery in CRS. Absolute (or emergent) indications for endoscopic sinus surgery include orbital or intracranial complications of CRS

requiring surgical drainage procedures. These complications usually occur in the setting of an acute sinus infection, and are discussed in detail in Chaps. 11 and 12. In these cases, the goal of endoscopic sinus surgery is to gain source control of the infection, decompress any abscess, and obtain cultures for directed antibiotic therapy. Relative indications for endoscopic sinus surgery primarily include persistently decreased quality of life due to CRS despite appropriate medical management (i.e., medically refractory CRS). In the treatment of medically refractory CRS, the goals of endoscopic sinus surgery are to remove excessive inflammatory tissue (such as polyps), enlarge the natural drainage pathways of the paranasal sinuses for improved ventilation, and improve access to the paranasal sinuses for topical medications (e.g., saline irrigation or topical corticosteroids). Although there are no RCTs for the efficacy of endoscopic sinus surgery, one multi-center prospective observational cohort study has reported that endoscopic sinus surgery leads to a greater improvement of CRS symptoms and objective endoscopic findings than continued medical therapy in patients with medical refractory CRS [100].

Special Considerations

Because CRS is defined based on clinical criteria, many different pathologic processes, with distinct underlying pathologies, may be categorized as CRS. There are two special cases of CRS that are worth discussing in the context of infectious disease. The first is odontogenic CRS related to the upper teeth, the roots of which are in close proximity to the floor of the maxillary sinuses. There is usually a history of antecedent dental surgery or odontogenic infection (e.g., a periapical dental abscess) with secondary maxillary sinusitis that, if untreated, can progress to odontogenic CRS [101, 102]. Odontogenic CRS can usually be cured by eradicating the infection—usually oral flora—with antibiotics, addressing the odontogenic source and establishing drainage of the affected paranasal sinuses [101, 102].

The second special consideration is allergic fungal rhinosinusitis (AFRS). This is a special form of CRS, most common in warm and humid locales such as the southern United States, caused by an allergic response to fungi trapped in the paranasal sinuses [103]. In addition to the standard diagnostic criteria for CRS, a diagnosis of AFRS also includes type I hypersensitivity to fungi, nasal polyps, characteristic CT findings of serpentine areas of high density scattered within low density sinus opacification, and eosinophilic mucus within the paranasal sinuses that contain fungi on fungal stain or fungal culture but without evidence of fungal invasion [104]. The treatment of AFRS is much the same as standard CRS: intranasal saline irrigation, topical intranasal corticosteroids, and endoscopic sinus surgery—with meticulous removal of fungal mucin to lower the antigenic burden as much as possible—when medical management fails. Even though AFRS is hypothesized to be driven by allergic inflammation to fungi, antifungals and allergen immunotherapy are not a routine or standard treatment for AFRS due to only low quality evidence supporting their use [3, 105]. Allergic fungal sinusitis is discussed further in Chap. 14.

Conclusions

CRS is a complex disease that is likely driven by a combination of both aberrant host-specific inflammatory responses and extrinsic inflammatory stimuli, which likely interact with each other in a dysregulated manner within the paranasal sinus mucosa of affected patients. The role of microbes remains unknown but is most likely as a chronic inflammatory stimulus. No studies to date have demonstrated any benefit of treating CRS with antibiotics other than possibly those antibiotics with anti-inflammatory properties (e.g., macrolides). The treatment of CRS remains saline irrigations, topical corticosteroids, and surgery to remove obstruction of the natural sinus ostia and re-establish sinus drainage.

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Noninvasive Fungal Sinusitis

14

Ashleigh A. Halderman and Matthew W. Ryan

Introduction

The first case of fungal rhinosinusitis was reported by Plaignaud in 1791. Since that initial description, the classification system for types of fungal sinusitis and our understanding and management of these diseases has evolved. The difference and importance of distinguishing between these two forms was highlighted by Hora in 1965 [1]. The two noninvasive forms, allergic fungal rhinosinusitis (AFRS) and sinus fungus ball, differ significantly in the type of immune response they elicit from the host. This chapter will focus on these noninvasive forms of fungal rhinosinusitis with an emphasis on the pathophysiology, diagnosis, and management.

Fungus Ball

One of the more common forms of fungal sinus disease encountered, a fungal ball is dense mat of fungal hyphae appearing as a firm, dark, dense mass of debris within a sinus. "Mycetoma" is often used interchangeably for this disease process, but this is a misnomer as a mycetoma is a granulomatous, subcutaneous fungal infection with draining sinus tracts that usually involves the foot. The incidence of sinus fungal balls is largely unknown as many are discovered incidentally on imaging performed for other purposes. A review of pathology specimens sent from nearly 800 surgeries performed for inflammatory sinus disease over a 10-year period reported fungus balls in 3.7% [2].

Paranasal sinus fungal balls have been reported in patients from adolescence to nearly age 90, but the mean age is approximately 50. A series of 173 patients from France found a mean age of 49 (range 14–87) [3], and a study of 160 cases from Italy found a mean age of 53 [4]. Patients with noninvasive sinus fungal balls are nearly always immunocompetent, although the incidence of medical conditions such as diabetes has not been reported in large series [3–5]. Immunoglobulin levels are no different in patients with fungal balls and those with chronic sinusitis [6], and *Aspergillus*-specific IgE levels do not appear to be elevated [5].

Interestingly, it appears that prior endodontic treatment may be a risk factor for developing a maxillary sinus fungal ball. One case-control study showed that 89% of patients with maxillary sinus fungal balls had prior endodontic treatment versus 37% in a matched control group [7]. Another study reported 50% of patients with maxillary fungal balls had prior endodontic pro-

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_14

cedures [5]. It is thought that zinc promotes fungal growth and that the zinc oxide (a common endodontic sealer) placed in a maxillary tooth root canal may extrude into the maxillary sinus and promote the development of a fungus ball [7, 8]. One study, noting that copper and zinc are the most common elements in endodontic materials, found high levels of these elements in maxillary sinus fungus balls of patients with evidence of prior endodontic procedures in adjacent teeth [8].

Given the fact that fungi are universally present in the nasal cavity [9], why then do some patients develop a fungal ball yet others do not? Aside from the potential role of zinc in root canal cavities highlighted above, fungal balls may form when fungal spores get "trapped" within a paranasal sinus cavity and then propagate. While acute or chronic inflammatory infiltrates may be present in the adjacent mucosa on pathology, tissue invasion by fungus or granulomatous reactions are absent [2]. This is therefore more of a "passenger" process with a robust immunologic response notably absent. Therefore, other factors such as anatomic features and mucociliary clearance may variably contribute to the development of a fungal ball.

A person may be completely asymptomatic from a fungal ball. In a series of 173 cases, 10% of the patients were asymptomatic [3]. Other patients may present with nonspecific rhinosinusitis symptoms such as nasal discharge, post-nasal drip, nasal obstruction, or facial pressure [3]. On sinonasal endoscopy, approximately 40% of the patients will have purulent drainage from the involved sinus and 10% will have polyps [3]. More commonly, patients will have a normal endoscopic exam. More than 90% of cases involve a single sinus, most frequently an isolated maxillary (80–85% of cases) or sphenoid sinus (10–15% of cases) [3, 4]. Involvement of two sinuses has been described, with bilateral maxillary sinus involvement in 1–4% of cases in two large series [3, 4]. Additionally, frontal and ethmoid fungal balls have also been described, but these are uncommon (<5% of cases).

Radiographically, sinonasal fungus balls have distinct characteristics that aid in making the diagnosis. On computed tomography (CT) scans, a single opacified sinus with central areas of hyperattenuation and calcifications is highly suggestive of a fungal ball (Fig. 14.1). These calcifications and areas of hyperattenuation correspond to dense fungal debris. There may be mild or no sinus expansion and bone erosion is possible but uncommon. Alternatively, there may be surrounding osteitic bony changes secondary to the presence of the chronic disease process. Magnetic resonance imaging (MRI) typically shows hypointense sinus contents on both T1 and T2-weighted images with hyperintense surrounding mucosa on T2 or contrasted images [10] (Fig. 14.2). This MRI finding is not seen in all cases however, and was absent in five of ten cases in one series [4].

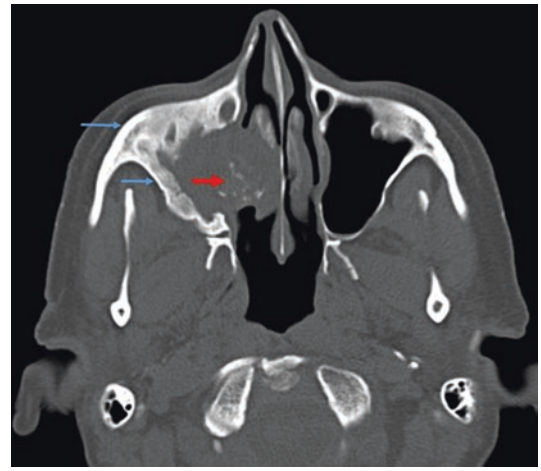

Fig. 14.1 Fungus ball, computed tomography (CT). Axial CT shows an opacified right maxillary sinus with hyperdense material medially (red arrow). Note the pronounced sinus wall hyperostosis (blue arrows) resulting from chronic inflammation

Ultimately, diagnosis is confirmed on histopathologic examination of the sinus contents. Microscopically, fungus balls consist of dense tangles of fungal hyphae with calcifications and oxalate crystals [2]. Acute or chronic inflammatory infiltrates may be seen in the nearby mucosa; however, fungal invasion of tissue is absent [2]. The most common pathogen is *Aspergillus* with *Aspergillus fumigatus* the most commonly identified species. A fungus ball is always identified on histopathology but cultures are only positive in 20–30% of the cases [3, 4]. One series of 160

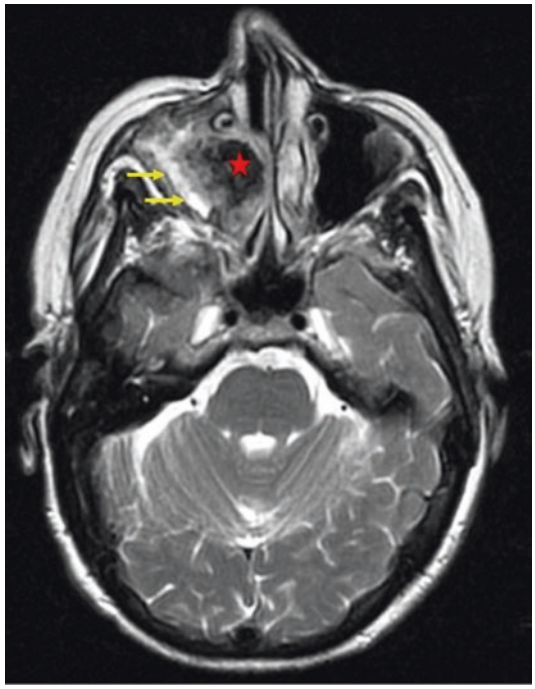

Fig. 14.2 Fungus ball, magnetic resonance imaging (MRI). Axial T2 MRI from the same patient as in Fig. 14.1, showing low signal (red star) corresponding to the region of the medial sinus and nasal cavity containing the fungus ball, and bright signal (yellow arrows) from inflamed mucosa on the lateral sinus walls

patients reported positive cultures in 20%, with *Aspergillus fumigatus* accounting for 75% of positive cultures and *Alternaria* 10% [4]. Other isolates included single cases of *Penicillium*, *Bipolaris*, and *Paecilomyces*. A series with 161 cases with positive cultures identified *Aspergillus* in 66%, dematiaceous fungi (e.g., *Alternaria*, *Bipolaris*) in 9%, others (e.g., *Paecilomyces*, *Penicillium*) in 21%, and multiple fungal species in 4% [11].

A sinus fungal ball is considered a surgical disease since oral and topical antifungal agents are ineffective in treating this condition. Grossly, fungal balls are dense conglomerations of thick inspissated debris variably colored brown or green with a consistency similar to peanut butter or clay (Fig. 14.3). They can partially or completely fill the sinus cavity and purulent drainage may be present within the sinus due to the obstruction from the fungal ball. The sinus

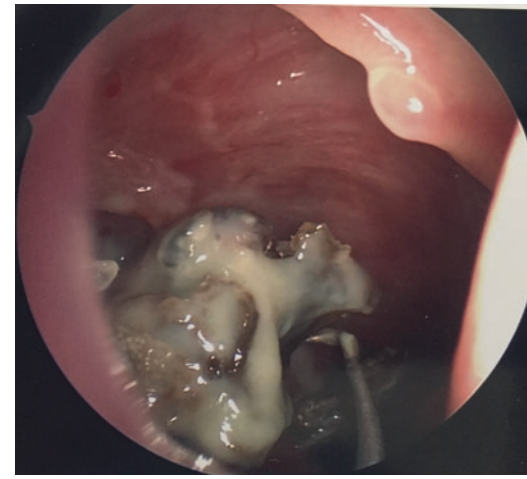

Fig. 14.3 Fungus ball in the maxillary sinus, endoscopic view. Note the variegated debris with variable consistency and surrounding purulent exudate

mucosa may show a variable amount of edema. The goal of surgery is to remove all fungal elements and reestablish drainage of the involved sinus. Typically, an endoscopic mucosal-preserving technique is utilized. The debris can prove quite difficult to remove but a combination of variously sized curved suctions, curettes, and copious warm irrigation can achieve complete removal. It is often helpful, especially in the maxillary sinus, to examine the cavity with 30° and 70° endoscopes to assure all debris has been removed. The 30-degree scope can also be helpful when examining the lateral portion of the sphenoid.

Postoperative care consists of saline irrigations and endoscopic debridements until such a time as the cavity is completely healed. If all fungal debris is removed, a complete cure can be achieved. Recurrences after complete removal are uncommon.

Allergic Fungal Rhinosinusitis

The most common form of fungal sinusitis is AFRS. This disease accounts for between 4% and 7% of chronic sinusitis surgical cases each year in the United States [12, 13]. Allergic fungal rhinosinusitis is most common in young adults (mean

age 20–30) [14, 15]. In the United States, there may be a geographic predominance with the highest rates of AFRS seen in the Mississippi river basin and the South, based on the findings of a survey study of 20 otolaryngology practices [16].

Type 1 hypersensitivity reactions to fungi were thought to contribute considerably to the pathophysiology of AFRS. However, in recent years, this has become a topic of debate. Some studies have shown that up to 90% of patients with AFRS do demonstrate a type 1 hypersensitivity to fungal antigens on skin prick testing [17]. Other studies, however, have shown that 10–30% of patients with AFRS do not, and hence the current debate over the role of type 1 hypersensitivity in this disease process [17, 18]. This subset of patients with AFRS but no demonstrable allergy to fungal antigens may represent a different disease process known as eosinophilic mucin rhinosinusitis or eosinophilic fungal rhinosinusitis [19].

Currently, the predominant theory of the pathogenesis of AFRS is that the disease develops in certain patients where particular genetic, environmental, and local factors converge, a concept adopted from the current understanding of allergic bronchopulmonary aspergillosis [14]. Inflammation induced by fungi entering the nose and paranasal sinuses of such patients may produce stasis of secretions, thick allergic mucin, and ostial obstruction of the sinuses. As the fungi are essentially trapped, this cycle persists through continual stimulation of the adaptive immune system [14].

Further supporting an underlying immunologic response in the pathogenesis of AFRS is evidence of a potential role for IgE and IgG-dependent mechanisms mediating a hypersensitivity response to fungus in these patients. Patients with AFRS usually demonstrate elevated serum total IgE and fungal-specific IgE compared to normal controls and to patients with chronic sinusitis (either with and without polyps) [20]. In two separate studies, fungal-specific IgE and IgG were shown to be significantly elevated in AFRS patients for *Alternaria* and *Bipolaris* respectively [20, 21]. Interestingly, local sinonasal IgE production may also play a role as multiple studies have demonstrated elevated fungal-specific IgE both within the sinonasal mucosa and mucin in AFRS patients [22–24]. Additionally, CD8 T cells and eosinophils are elevated in the nasal mucosa of AFRS patients and it has been theorized that fungal-activated eosinophils may be capable of eliciting a fungal-specific Th2 immune response through induction and proliferation of CD4 and CD8 cells [25–27].

Staphylococcus aureus produces enterotoxins capable of inducing a Th-2 skewed inflammatory reaction such as that seen in AFRS. These "superantigens" can elicit both an inflammatory reaction and polyclonal activation of T and B lymphocytes [28]. Superantigens can further induce formation of local polyclonal IgE against inhalant allergens such as fungus [28, 29]. *Staphylococcus aureus* has been shown to be significantly more prevalent in AFRS patients when compared to patients with chronic sinusitis with polyps, supporting a role for superantigens in this disease process and yet another immunologic factor in the pathogenesis [30].

Symptoms of AFRS develop and progress very slowly. The development of polyposis over time leads to symptoms of nasal obstruction/congestion and hyposmia developing over a period of months to years. Additionally, patients may report anterior or posterior rhinorrhea, facial pressure, or even blowing out dark chunks of mucus or rubbery mucus out of their noses. Given the insidious onset, the disease process can be quite well advanced at the time of diagnosis with up to 20% of patients presenting with telecanthus or proptosis and/or complaints of diplopia or visual loss from mucocele formation and expansile pressure from the disease [31].

On examination, as stated previously, some patients with advanced disease may present with proptosis or telecanthus [32]. Nasal endoscopy typically reveals polyposis and/or inspissated yellowish allergic mucin or even dark, firm fungal debris (Fig. 14.4). The disease can be unilateral in up to 50% of cases with the uninvolved side showing a normal nasal endoscopic examination.

There are several key radiographic features that, when present, indicate AFRS. Computed tomography scan typically shows opacification

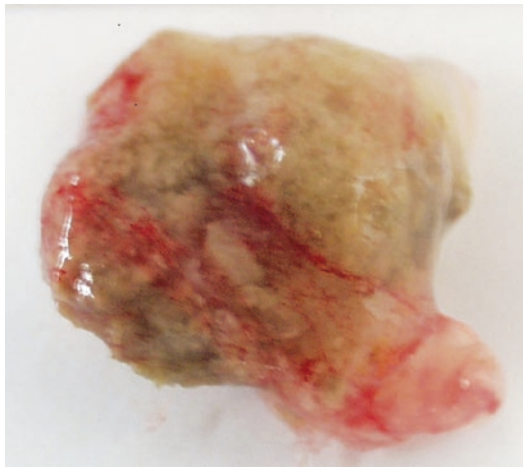

Fig. 14.4 Allergic fungal rhinosinusitis (AFRS). This surgical specimen of sinus contents demonstrates the typical eosinophilic mucin. The gross appearance can be similar to a fungus ball

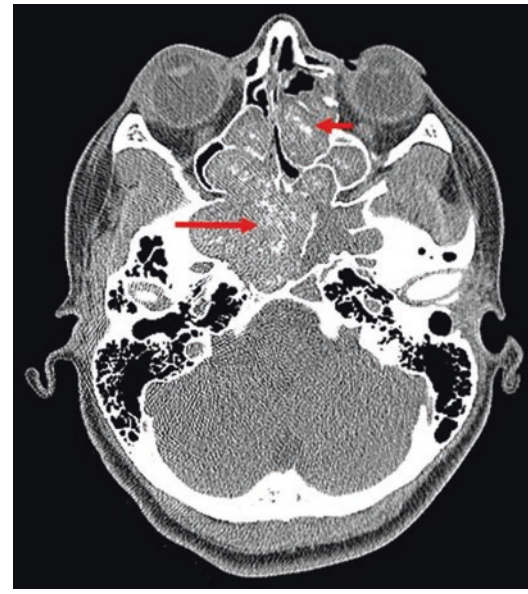

Fig. 14.5 Allergic fungal rhinosinusitis (AFRS), computed tomography (CT). Axial CT shows mucocele formation with hyperdense sinus contents (arrows)

of multiple sinuses (either unilateral or bilateral) with central attenuation secondary to dense fungal debris and calcifications. Characteristic extensive remodeling of the paranasal sinus boney architecture is a radiographic feature of AFRS. Mucocele formation with erosion of either the lamina papyracea or skull base with a pushing border is frequently seen (Fig. 14.5). MRI typically shows peripheral mucosal hyperintensity on both T1 and T2 consistent with mucosal inflammation. Sinus contents will demonstrate T1 hypointensity and specifically, T2 hypointensity known as "drop out" (Fig. 14.6).

The diagnostic criteria for AFRS were first outlined by Bent and Kuhn in 1994 and updated by a consensus conference in 2004 [31, 32]. The criteria are listed in Table 14.1.

Histologically, fungal invasion of sinonasal tissue is not seen in AFRS. Findings on microscopic examination of mucin include both "onionskin laminations" consisting of clusters of necrotic and degranulating eosinophils, and hexagonal and bipyramidal crystals known as Charcot-Leyden crystals (crystals found in eosinophil cytoplasm) [14]. Fungal cultures may be positive in up to 80% of cases that meet AFRS criteria, and these cultures usually grow *Aspergillus* or a dematiaceous fungus such as *Alternaria*, *Bipolaris*, or *Curvularia*. More than

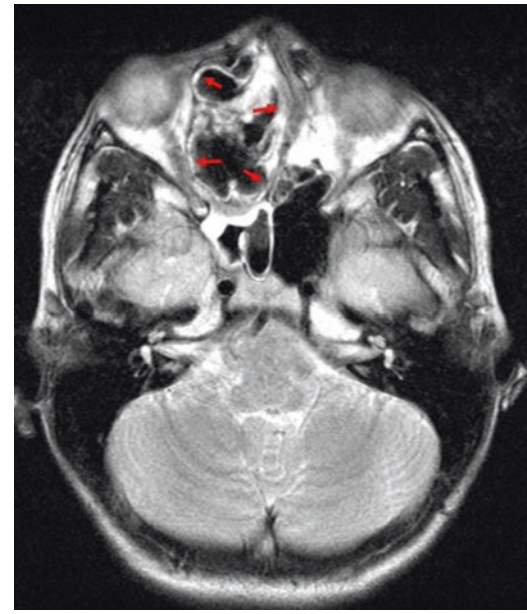

Fig. 14.6 Allergic fungal rhinosinusitis (AFRS), magnetic resonance imaging (MRI). Axial T2-weighted MRI in a patient with AFRS shows an expanded right ethmoid compartment (arrows) with signal void (black areas) in multiple ethmoid sinuses, corresponding to dense eosinophilic mucin in the sinuses

Table 14.1 Criteria for allergic fungal rhinosinusitis

Bent and Kuhn diagnostic criteria [31]
1. Type 1 hypersensitivity confirmed by history, skin test, or serology
2. Nasal polyposis
3. Characteristic CT scan findings
4. Positive fungal stain of sinus contents
5. Eosinophilic mucus without fungal invasion of sinus mucosa
Consensus Conference criteria [32]
1. Symptoms: ≥1 of the following: nasal drainage, nasal obstruction, decreased sense of smell, facial pain/pressure/fullness, PLUS
2. Objective findings (all required):
– Endoscopic evidence of rhinosinusitis (polyps, edema)
– Histopathology of allergic mucin showing fungal hyphae and eosinophils
– CT or MRI evidence of rhinosinusitis
– Evidence of fungal-specific Ig E (skin test or in vitro test)
– No histologic evidence of invasive fungal disease

one type of fungus grows in one-third of cases. In a series of 127 AFRS cases with positive cultures, *Aspergillus* (34%) or a dematiaceous fungus (30%) accounted for nearly all cases in which a single fungus grew [11]. The histopathologic diagnosis of AFRS can be further supported by demonstration of type 1 hypersensitivity on skin or radioallergosorbent testing (RAST) to multiple fungal allergens [14].

The treatment of AFRS is multimodal with surgery often representing a necessary first step in management. Endoscopic sinus surgery is generally employed to achieve the goals of removing allergic mucin and widely marsupializing involved sinuses to aid in the delivery of topical medications [14]. It is important to note that the disease may erode bony barriers including the orbit and skull base or distort normal intranasal landmarks potentially increasing the risk of surgery. Owing to this, image guidance is helpful for orientation and confirming the distorted anatomy.

Postoperatively, patients with AFRS must be followed closely as recurrence is unfortunately common in this disease process. Incomplete surgery either leaving behind allergic mucin or retained cells appears to increase the risk for recurrence. Recurrences can be treated with aggressive medical therapy including brief courses of systemic corticosteroids. When massive polyposis or significant reaccumulation of allergic mucin has occurred, revision surgery may again be necessary to reconstitute adequate drainage pathways and reduce the burden of both polyp and allergic mucin disease.

Medical therapy for AFRS should be directed toward suppressing inflammation, which allows for maintaining sinus drainage and preventing accumulation of allergic mucin. Maintenance therapy consists of saline irrigations and topical intranasal steroid sprays. Bursts and tapers of oral corticosteroids may be necessary to address exacerbations.

Regarding antifungal therapy for AFRS, large double blind randomized placebo controlled trials are lacking. However, one small prospective study demonstrated that preoperative itraconazole was associated with improved symptom scores, Lund Mackay scores, and improved endoscopic exam grades [33]. Treatment with oral itraconazole has not been compared to the current "gold-standard" of oral corticosteroids and it is important to note that improvements in all of these parameters could also have been achieved by an equal if not greater degree with corticosteroids. Other studies have demonstrated that oral itraconazole, used to treat postoperative recurrences, improves both symptoms and endoscopic findings and can decrease need for systemic steroids and even revision surgery [34–36]. Given that these studies were limited in size, meaningful recommendations regarding the use of oral antifungals in AFRS cannot be made until larger, high level studies have been conducted.

Given that type 1 hypersensitivity to fungal antigens appears to play a role in the pathogenesis of AFRS, immunotherapy is another treatment modality that has been proposed to treat this disease process. Uncontrolled studies have supported the use of immunotherapy as an adjunct treatment postoperatively for AFRS by showing improved endoscopic examination and lower chronic rhinosinusitis survey scores

[37]. Additionally, treatment with immunotherapy was associated with fewer courses of oral corticosteroids and less reliance on nasal corticosteroids [37]. However, over an average 82-month follow-up period, the immunotherapy group did not differ in either symptom scores or endoscopic staging nor was there a difference in the number of revision surgeries or courses of antibiotics [38]. Given the lack of double blind placebo controlled trials, the use of immunotherapy in the treatment of AFRS remains controversial.

As stated previously, AFRS is unfortunately notorious in its propensity to recur. Similar to the initial onset, symptoms may develop gradually over time and patients may not seek medical attention until the intranasal polyposis is so extensive as to cause complete nasal obstruction. With massive polyp recurrence, revision surgery may be required. Given the risk of recurrence, patients should be followed closely with regular endoscopic examination to identify early recurrence. This follow-up should be conducted for several years. There is some evidence that disease quiescence may occur in a majority of patients after several years of follow-up [38]. However, some patients continue to be plagued by recurrence and exacerbations and must be followed over much of the course of their lifetime.

Conclusion

Noninvasive forms of fungal sinusitis come in two widely divergent forms: fungus ball and AFRS. While the two disease processes share a common foundation of fungal involvement, they differ considerably in regards to pathogenesis, presentation, treatment, and prognosis. Surgical management of fungal balls is considered curative in the vast majority of cases while surgery in AFRS is viewed as one step in the overall management scheme. Moving forward, the medical management of AFRS with the use of oral antifungals and emerging biologics will remain an intriguing area of research.

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Invasive Fungal Sinusitis in Immunocompromised Hosts

15

Andrew W. Chao and Dimitrios P. Kontoyiannis

Introduction

Acute invasive fungal sinus disease (IFS) is an uncommon disease that often has rapid and destructive clinical progression. Primarily, a disease of the immunocompromised, IFS is typically associated with patients undergoing chemotherapy, stem cell transplantation as well as in patients with uncontrolled diabetes mellitus and patients using corticosteroids or other immunosuppressive therapies (e.g., following organ transplantation) [1–3]. It is less commonly described in HIV-infected patients, in whom invasive aspergillosis rather than mucormycosis is usually described [4]. The estimated mortality of IFS varies markedly, with a range from 20% to 80% with an estimated aggregate mortality of approximately 50% [5–7]. Invasive fungal sinusitis can also have profound effects on malignancy-related survival by delaying or resulting in dose-reduction in chemotherapy regimens [8]. Limited available interventions as well as slow development of new anti-fungal agents have led to incremental improvements in outcomes.

Causative Organisms

The fungi responsible for IFS are ubiquitous in the environment, filling the niche of saprophytic microbes feeding on detritus. They can be found as colonizing and commensal organisms in humans as well, with invasive disease rarely developing, and typically in the setting of significant immunosuppression. Many fungi can potentially cause IFS; however, molds predominate as causative agents. The majority of causative molds belong to the *Aspergillus* genus and Zygomycetes phylum. *Aspergillus* species include *A. fumigatus*, *A. niger*, and *A. terreus* among others [1, 6]. Of the *Aspergillus* species, *A. fumigatus* is the most commonly identified cause of invasive infection [9]. Pathogenicity of these isolates is attributed to smaller conidial size facilitating inhalation and penetration [10] as well as blunting host defenses including opsonization and complement activation [11].

The most common Zygomycetes causing IFS are from the *Mucorales* order and include important genera such as *Mucor*, *Rhizopus*, and *Absidia* [1, 12]. These species are increasingly encountered in patients receiving Aspergillus-active antifungals such as voriconazole or echinocandins [13].

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_15

Fusarium species are also implicated in IFS, though less commonly than *Aspergillus* and *Mucor* [14].

Acquisition of Infection

For an opportunistic pathogen to cause disease it must first reach the nasal sinus cavity, adhere to mucosal surfaces, and then bypass local and systemic host defenses to invade tissue. Although the underlying immunodeficiency of the host has received much attention, increasingly studies have highlighted the roles of anatomic abnormalities and environmental characteristics in facilitating disease pathogenesis [15].

The nasal mucosal membrane is the first physical and immunologic barrier in the infectious process [16]. Anatomic abnormalities such as a deviated nasal septum or nasal obstruction have been identified as predisposing host factors to developing IFS [15]. Specifically, it has been postulated that turbulent airflow as a consequence of these abnormalities, along with impaired ventilation, helps facilitate fungal spore deposition on the mucosa [17]. The nasal cavity flora has been demonstrated to interfere with bacterial upper respiratory infections and can resist spore deposition, but in turn can be disrupted by antimicrobial use [18]. Whether an altered composition of nasal microbiome is a permissive factor for invasive fungal infection remains to be shown. Nevertheless, studies have indicated that a preceding upper respiratory infection and prolonged antibacterial use are risk factors for IFS, likely due to the disturbance of the local microbiome [18]. With severe suppression in local and systemic innate host immunity, fungi can then invade in response to environmental cues, causing extensive necrosis and tissue infarction depending on the angioinvasive ability of the fungus.

Risk Factors and Pathogenesis

Several conditions are associated with diverse defects in the innate, more so than the adaptive immune system, which predispose to IFS. Thus, a heterogeneous population of patients is at risk including those with poorly controlled diabetes mellitus, chronic corticosteroid use, iron overload, HIV/AIDS, stem cell or organ transplant recipients, and patients with cancer [5]. Furthermore, practices such as inhaled cocaine abuse can cause erosion of nasal mucosa and structural abnormalities which then facilitate further fungal deposition and invasion [19]. Sporadic cases of IFS in apparently immunocompetent patients have been rarely reported [20, 21].

Hyperglycemia, secondary to diabetes mellitus or glucocorticoids use, results in a decrease in neutrophil and macrophage chemotaxis, impaired phagocytosis, and decreased oxidative and non-oxidative killing of fungi [22]. Furthermore, the acidemia of diabetic ketoacidosis (DKA) has been demonstrated to enhance the angioinvasion of *Mucorales* [23]. Ketoacidosis due to elevations of β-hydroxybutyrate in DKA facilitate *Mucorales* growth while further attenuating neutrophil-mediated responses. This is due to facilitation of fungal adherence to endothelium as well as disruption of host functions that lead to elevated free iron levels [24]. Iron overload and use of exogenous iron have been well described as an independent predisposing cause for mucormycosis [25, 26] and is part of the constellation of physiologic derangements seen in DKA.

Patients with hematological malignancies in particular have long been identified as being at risk for IFS due to primary dysfunction of the immune system as well as immunosuppression from cytotoxic chemotherapy. Cases of IFS have been described even during induction treatment shortly after the diagnosis of a primary hematological malignancy. This is further exacerbated by relapsed or recalcitrant disease, necessitating additional cycles of cyto-reductive chemotherapy. Hematopoietic stem cell transplant recipients can have a degree of neutropenia compounded by lymphocyte dysfunction and lymphopenia due to their immunosuppressive regimens used to prevent graft vs. host disease. Despite improvements in antifungal armamentarium, the incidence density of IFS has not decreased in this patient population.

Clinical Presentation

There is marked variation in the presenting symptoms, partially depending on the degree and perhaps the nature of the underlying immunosuppression. There may be few, if any, symptoms early in the clinical course which results in IFS misdiagnosed as a bacterial or viral upper respiratory tract infection. Symptoms can include, but are not limited to, fever, facial swelling, nasal congestion, facial pain, and headaches. A study from Thailand comparing 35 patients with IFS with 65 patients who had orbital complications of bacterial sinusitis found no significant differences between the two groups with regard to these nonspecific symptoms, although the IFS group had significantly higher incidence of diplopia and cranial nerve involvement [27]. Of note, fever was present in only one-third of patients with IFS, and the absence of fever or leukocytosis does not exclude IFS. Tissue with angioinvasion may be discolored and have a red, violaceous, or black appearance; the presence of discolored mucosa is suspicious for mucormycosis. Involvement can be seen in the nasal cavity and turbinates as well as facial lesions, including necrosis of the nasal bridge. However these findings, while typical for IFS, are not solely reliable for early diagnosis and their absence does not rule out disease. Necrotic eschars may be seen in only 50% of patients in the first 3 days of the onset of infection [22].

Patients with IFS often have invasion into contiguous structures [1] and present with additional complaints. There is a significantly higher rate of ocular symptoms associated with IFS, as noted above, indicative of invasion into the orbit and/or cavernous sinus [22, 27]. Fungal invasion into the orbit tends to be unilateral can result in decreased visual acuity, and dysfunction of extraocular movements. Such patients will often have proptosis and chemosis with periorbital and orbital edema with a cellulitis appearance (see Fig. 15.1). Sense of smell may be lost as well but may not necessarily reflect nerve dysfunction. Careful examination of the oral cavity, including the gingiva and hard palate, may demonstrate ulcerations and eschars as evidence of extending ischemia or necrosis. Erosion through bony and mucosal structures is occasionally seen, generally in late and progressive IFS. Patients with infraorbital nerve involvement can exhibit paresthesia in the malar/V2 distribution of the trigeminal nerve. Decreased sensation or paresthesias over the forehead and/or upper cheek suggest involvement of V1 or V2 and may occur from orbital apex or cavernous sinus invasion. Rarely, invasion into the central nervous system (CNS) can result in meningitis with associated symptoms of confusion, seizures, headache, and nuchal rigidity [5, 7]. Patients will need close monitoring and examination as the pace of disease progression can range from as short as hours (especially for Mucorales) to as long as days or weeks.

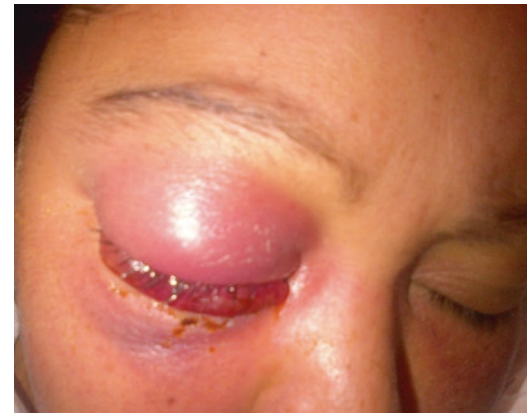

Fig. 15.1 A woman with relapsed acute myeloid leukemia and resultant 2 months of neutropenia presented complaining of 1 week of right-sided headaches with right eye photophobia and facial swelling. She was found to have sino-orbital mucormycosis due to *Rhizopus* species. Note the extensive orbital cellulitis and proptosis due to invasive fungal sinusitis with orbital invasion

Invasive mold infection beyond the sinuses is often concurrently found in immunocompromised patients who present with IFS; however, it is poorly described in the literature. In these instances, pulmonary involvement can be seen in addition to extension into the orbit or cranium [28] and is seen in over half of IFS cases [29]. Cutaneous involvement in IFS is usually a consequence of contiguous extension out of the sinuses into the skin but can also be rarely seen in remote sites [30].

Diagnostics

As symptoms can be nonspecific with significant overlap between viral or bacterial infections, clinicians must maintain a high index of suspicion for IFS in immunocompromised patients. Timely diagnosis is important for improved patient outcomes. Radiology studies, early ENT evaluation with procurement of material for microbiology and histopathological studies are all essential for diagnosis and to aid decision-making.

When IFS is suspected, a computed tomography (CT) scan of the sinuses is usually the first and easiest diagnostic imaging test to obtain. Plain film radiography may demonstrate air-fluid levels when sinusitis is suspected, but its role has been superseded by CT scan except in resource-limited settings. The most common early finding on CT is sinonasal mucosal thickening that is often unilateral [31]; however, this is a nonspecific finding that can be seen in all forms of rhinosinusitis. Characteristic invasion into soft tissue can be missed on CT, and bony destruction occurs late in the clinical course. Magnetic Resonance Imaging (MRI) is a more sensitive tool for determining early IFS changes in the soft tissue [32], evaluating for necrotic tissue that can be correlated with nasal endoscopy findings (see Fig. 15.2). Loss of contrast enhancement with gadolinium is strongly suggestive of tissue ischemia secondary to angioinvasion by fungal organisms [33] (see Fig. 15.3). An MRI can help establish the extent of disease by assessing for any intracranial or cavernous venous involvement, or invasion into other surrounding structures. This then helps determine appropriateness and extent of surgical excision. Persistent areas with loss of contrast enhancement on repeat imaging after debridement have been associated with worse outcomes [32].

Despite its usefulness, radiographic imaging will only indicate the extent of disease but cannot identify the causative etiology. Therefore, definitive diagnosis based on examination of tissue culture and pathology is required to guide the need and type of systemic antifungal therapy. Evaluation by an ENT specialist when IFS is suspected should be considered a surgical emergency, given the potential for rapid disease progression. Specifically, nasal endoscopy with biopsy is essential in the workup and management of these patients. Examination can be directed by radiographic findings toward the foci of greatest disease burden. Macroscopic findings of ischemic or necrotic tissue on nasal endoscopy are suggestive for IFS. The middle turbinate was

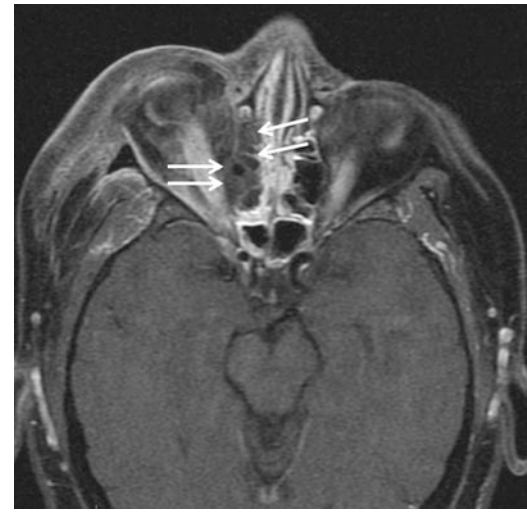

Fig. 15.2 MRI of the head of the patient in Fig. 15.1. There is hypodense material within the right nasal passage concerning for necrotic tissue. There is destruction of the medial wall of the right orbit

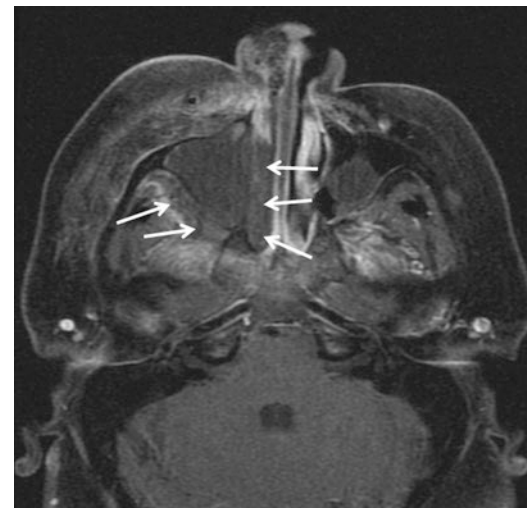

Fig. 15.3 MRI of the head with contrast of the patient in Fig. 15.1. There is a large hypodense mass within the right maxillary sinus. The loss of contrast enhancement in the posterior right maxillary sinus as well as nasal cavity is highly suggestive of tissue necrosis, suggesting an angioinvasive infection

the most common site of abnormality in over two-thirds of cases [34]. After samples are collected for further analysis, local debridement of necrotic tissue can be done.

Tissue obtained from biopsy of these areas should be sent for rapid pathology review by frozen section, and for culture. Samples should be of adequate amount to allow such evaluation and should be placed in saline for frozen section (also in saline or sterile cup for culture). Formalin-fixed samples should also be sent for permanent sections. Frozen section techniques for tissue can be done quicker than conventional methods [35] to help facilitate early diagnosis by identifying the presence of invading fungal hyphae in the sample. Small size case series indicate that this approach generally has a sensitivity of 60–80% and a specificity approaching 100% [34, 36]. Our own institutional experience with frozen section is excellent with 26 out of 27 cases showing evidence of IFS (>96% sensitivity) [1]. Beyond the fresh frozen section, histopathology techniques include fixation and processing with special staining such as Gomori methenamine silver (GMS), though they take longer than a day. Occasionally, characteristic fungal morphologies are distorted during the fixation process which may make identification of fungal more challenging. However important clues for organism identification can be found, specifically if there is evidence of perivascular or perineural invasion [37]. Samples sent for microbiology should not be swabs but should be tissue biopsies, placed in a sterile cup or saline and rapidly delivered to the microbiology laboratory. The microbiology laboratory should be alerted not to grind all the tissue prior to plating, as grinding can decrease the chance of growing molds. Traditional identification of fungal organisms comes from microscopic examination of growth from fungal cultures.

Laboratory Testing

Cultures remain the gold standard for confirming fungal growth and identification. However, the utility of cultures in early diagnosis remains limited as molds grow slowly or not at all [29], even when invasive tissue disease is seen on biopsy [38]. Given these limitations in pathological and microbial identification of fungi, there is an urgent need for non-culture-based diagnostics that can be done on a timely basis and can be used to supplement other clinical evidence to diagnose specific fungal infections.

A number of commercially available laboratory tests for fungal biomarkers could help as adjunct diagnostics in cases of possible IFS, though data on their performance remain limited. Many yeasts and molds have (1-3)-β-D-glucan as a component of their fungal cell wall which can be detected in serum. This test has shown utility in detecting invasive yeast and mold infections (although not mucormycosis) with an estimated sensitivity of 76.8% and specificity of 85.3% [39, 40]. There are limited data to suggest that trends in (1-3)-β-D-glucan can be used for evaluating response to therapy [41]. False positive (1-3)-β-D-glucan tests have been associated with factors that include blood transfusions, gauzes containing glucan, and some antibiotic suspensions.

Galactomannan is another fungal cell wall component found in hyalohyphomycetes, including *Aspergillus* species, also detected in serum. Like the (1-3)-β-D-glucan assay, a negative result does not rule out disease, especially in patients who are already receiving mold-active antifungals [42]. Galactomannan is a useful adjunct diagnostic for invasive aspergillosis but does not detect *Mucorales*. Choi et al. identified a sensitivity of 91.3% and specificity of 71.7% [43], though other studies note poorer results, ranging from 20% to 60% sensitivity and specificity [6, 44]. False positives can occur in the presence of other, usually non-pathologic, fungi such as *Penicillium* and *Paecilomyces* species.

Additional assays are available including quantitative, qualitative, and real-time PCR. PCR testing has been conducted on biopsied tissue as well as other sources including bronchoalveolar lavage fluid [45], serum [46], and even prior tissue samples that have been formalin-fixed and embedded in paraffin [47, 48]. Molecular testing in tissue via PCR, immunochemistry, and in situ hybridization has the advantage of assessing broadly for specific genera or could utilize specific primers or probes to detect individual

species [47]. Limitations to these methods include variable sensitivities, ranging from 60% to 90%, and a lack of standardization in primers, reagents, and overall methodology. Nevertheless, methods of molecular testing of fungi in tissue are promising and deserve further study.

Management

Not surprisingly, there are no randomized studies for the management of IFS in view of the rarity of the condition, the heterogeneity of afflicted hosts, site and degree of sinus involvement, offending fungi, comorbidities, and multiple concurrent surgical and medical interventions. The literature reflects single-institution retrospective experiences that encompass a limited number of patients that have significant variability in their presentation and prognostic factors. Therefore, such literature needs to be viewed with caution in light of significant publication and reporting biases. Nevertheless, surgical debridement continues to be regarded as an important part in the management of IFS as a part of the standard of care [49]. The scope of surgery can be variable, ranging from attempts at local resection all the way to radical resection. Endoscopic and open surgery have been compared, and given the complexity and sequelae of open surgery, the endoscopic approach is preferred in patients with early, limited disease or with significant medical comorbidities [34, 50].

Earlier studies suggested reserving open surgery for extensive disease, particularly with the involvement of the CNS or orbits [50, 51]. Surgeries in such cases have included maxillectomy, orbital exenteration, and/or craniofacial resection. However, more recent data suggest that "radical" surgeries did not result in any statistically significant improvement in survival, especially in patients with limited life expectancy [1, 5, 49]. Moreover, surgical resection of disease in such cases may be impractical when considering the morbidity and mortality of such extensive surgery, the underlying cytopenias that are often present, and the post-surgical complications that will arise. However, debridement of necrotic tissue may be important therapeutically in rapidly progressive IFS due to mucormycosis, particularly in diabetic patients where chance of survival is good. Surgical resection (beyond biopsy for diagnosis and minor debridement of necrotic tissue) is usually not necessary in invasive aspergillosis in diabetic or other minimally immunocompromised patients. The pace of aspergillosis is slower than in mucormycosis and these cases usually respond to antifungal therapy. As mortality from IFS in severely immunocompromised patients is still very high despite surgical intervention, a careful assessment of the risks and benefits of surgery should always be done.

Medical treatment of IFS focuses on addressing the active infectious process while simultaneously reversing the underlying immunosuppression, if possible. Selection of antifungals should be heavily influenced by local epidemiology with consideration for pharmacodynamics and adverse reactions [52]. For breakthrough cases on mold-active prophylaxis, changing class and initiation of broad-spectrum amphotericin B-based therapy, pending identification of the offending fungus seems prudent. Due to nephrotoxicity of amphotericin B-deoxycholate, liposomal amphotericin is preferred, at a dose of 5 mg/kg/day. Higher dosages of liposomal amphotericin have been studied prospectively at doses of 10 mg/kg/day [53] in patients with mucormycosis, including patients with IFS. No improvements in survival at 12 weeks were detected; on the other hand, high dose liposomal amphotericin was associated with increased frequency of adverse reactions especially renal injury and electrolyte derangements.

Triazole antifungals are a class of antifungal agents that deplete ergosterol from the fungal cell membrane. With their availability in both IV and PO formulations, they have an important role in bridging the initial management of IFS to long-term treatment. When dealing with invasive mold infections, the triazoles voriconazole, posaconazole, and isavuconazole/isavuconium sulfate offer good activity against many implicated organisms. Voriconazole has activity against both *Aspergillus* and *Fusarium* species but exhibits no activity against *Mucorales* [54]. The other new triazoles, posaconazole and isavuconazole, do have activity against both hyalohyphomycetes and *Mucorales* and are better empiric treatment options in IFS when no causative organism is

successfully identified [55]. Triazoles are known to have a significant number of drug-drug interactions due to their inhibition of the cytochrome P450 system, and in turn can have their pharmacokinetics altered by the presence of other drugs that induce the P450 system [56]. This can be particularly challenging in transplant recipients taking immunosuppressive agents and HIV patients on therapy with anti-retrovirals. It is important to develop a closely coordinated, multidisciplinary and individualized therapy tailored to patient circumstances [57].

Combination therapy, typically of liposomal amphotericin with another antifungal class, has been reported in the literature with varying success [1, 6]. While ineffective as monotherapy, an agent such as an echinocandin or terbinafine can improve outcomes when given as part of combination therapy [58–60]. Successful usage of local, retrobulbar injections of antifungals in selected cases of invasive sino-orbital infections in patients unable to tolerate intravenous amphotericin or as an adjunct to treatment of systemic amphotericin has been reported in small series [61–63].

It should be stressed that there are no clear definitions of antifungal breakpoints obtained in vitro for the fungi causing IFS. In vitro susceptibility breakpoints are not based on clinical data, but rather on pharmacokinetic and epidemiological concepts [64]. Care must be taken as results indicating in vitro susceptibility may not necessarily correlate with clinical success [65].

Adjunctive Therapies

Several strategies have been utilized to correct underlying the neutropenia found in many IFS patients. Granulocyte infusion has been used over several decades; however, results are drawn from experiences with small numbers of patients and have mixed outcomes [66]. In addition to having an unclear benefit, there are risks with therapy which include transfusion reactions, leuko-agglutination reaction, or even pulmonary edema. Therefore, no firm recommendations exist regarding use of granulocyte infusions but they may have a role in selected patients who fail to respond to initial surgical and anti-fungal interventions. Usage of granulocyte-stimulating factors to both resolve neutropenia and enhance neutrophil phagocytic activity against fungi has been shown to be successful in anecdotal reports [67, 68].

Use of hyperbaric oxygen therapy has been reported in small numbers with some degree of success. Hyperbaric oxygen therapy increases oxygen tension in tissues, leading to an increase in generation of oxygen-free radicals that can have fungicidal activity [69]. In vitro studies show inhibition of fungal growth in both aspergillosis and mucormycosis [70–72]. Limited data suggest that short-term survival is improved [71] though the effect on long-term outcomes is still unclear. No benefit has been found in cases of disseminated invasive fungal disease, suggesting that its use should be limited to only local infections. Aside from pneumothorax, there are few contraindications or complications from hyperbaric oxygen therapy and it offers a relatively low-risk adjunct to management with suggestion for improved outcomes. However, its use is limited to institutions with the facilities to administer it.

Reversal of Underlying Immunosuppression

As most IFS infections are associated with immunocompromised hosts, controlling the underlying condition to help restore normal immune function should be an important part of the treatment along with concomitant medical and surgical management. Patients with HIV/AIDS can be started on anti-retroviral therapy. Patients with immunosuppression from corticosteroids can be tapered off or transitioned to alternative non-steroidal therapy.

Patients with uncontrolled diabetes and/or diabetic ketoacidosis are a challenging population as there are a number of physiologic derangements at work that facilitate IFS. Aggressive glycemic control is an important part of treatment. Reversal of acidemia by the administration of sodium bicarbonate has been shown to partially block the ability of *Rhizopus oryzae* to invade endothelial cells, as well as to restore host iron chelation and neutrophil function. Sodium bicarbonate use is a treatment consideration even

in the absence of acidemia [24]. Treatment with iron chelators is a potential adjunctive therapy; however, caution is needed as some agents such as deferoxamine act as a siderophore for species of *Mucorales* and are historical causes of IFS [73–75]. New iron chelators such as deferasirox have no siderophore capability, but have not shown any benefit from their use as initial therapy for mucormycosis in hematological malignancy [76]. They still remain a potential therapy in other at-risk populations, especially in patients with uncontrolled diabetes and/or diabetic ketoacidosis.

Management of hematological malignancy patients with invasive fungal infections requires complex decision-making. It is common for the underlying malignancy to cause neutropenia and the production of non-functional phagocytic cells. Yet the treatment of leukemia and lymphoma by means of cytotoxic chemotherapy can have just as great a suppression on overall immune status. The challenge therein lies in determining the best time to re-initiate chemotherapy treatment. On one hand, some practitioners opt to delay or even postpone antineoplastic treatment to allow time for treating and controlling the infection, at the risk of having the malignancy becoming ultimately less amenable to chemotherapy. On the other hand, some proceed with early chemotherapy at the same time IFS is treated, in the hope of achieving cancer into remission sooner, allowing for earlier immune reconstitution and more effective clearance of infection. This carries the risk of having IFS worsen in the setting of heightened immunosuppression. In a case-control study, 57% of leukemia patients with probable or proven invasive fungal disease had a delay in chemotherapy with a median of 11 days [8]. Additionally, 28% of them had a change in their chemotherapy, either an earlier switch to maintenance, transition to palliative treatment or reduction in dose of chemotherapy. Decisions regarding timing of subsequent immune suppression in the setting of IFS should be made on a case-by-case basis.

Treatment Duration and Follow-Up

There is no fixed duration of treatment for IFS as therapy is dependent upon the severity and extent of IFS, the causative fungus, and the magnitude of clinical improvement on antifungal agents while reversing the underlying immunosuppression. In immunosuppressed patients with IFS due to *Mucorales*, clinicians should be conservative with a high threshold for discontinuing antifungal therapy as relapses of IFS off therapy often occur [77]. Similarly, there are no firm recommendations for frequency of follow-up or repeat studies. At a minimum, patients should have resolution of radiographic evidence of disease. Treatment is typically given for months, with initial intravenous therapy for many weeks followed by months of oral antifungal therapy.

We recommend routine outpatient follow-up on a monthly basis in patients undergoing treatment for IFS. An infectious disease specialist should be involved very early in the course of the disease and follow the patient closely, in conjunction with their other specialists. Close follow-up with otolaryngology initially is also helpful to monitor the endoscopic appearance of the nasal cavity and sinuses. Special attention is needed for monitoring changes in patient symptoms and tolerability of long-term antifungal therapy. If there are any concern signs or symptoms observed, repeat endoscopy should be performed by the otolaryngologist. Monitoring of drug serum levels in patients on chronic azole therapy, especially voriconazole, can help monitor compliance and adequacy of therapy. Although there are no data specifically for *Aspergillus* sinusitis, a baseline titer and monitoring of *Aspergillus* galactomannan trends can be useful to monitor therapeutic response [78]. If therapy is discontinued, patients should continue to have routine follow-up for monitoring for relapsed infection. Figure 15.4 depicts an algorithmic approach to management of IFS in immunocompromised hosts.

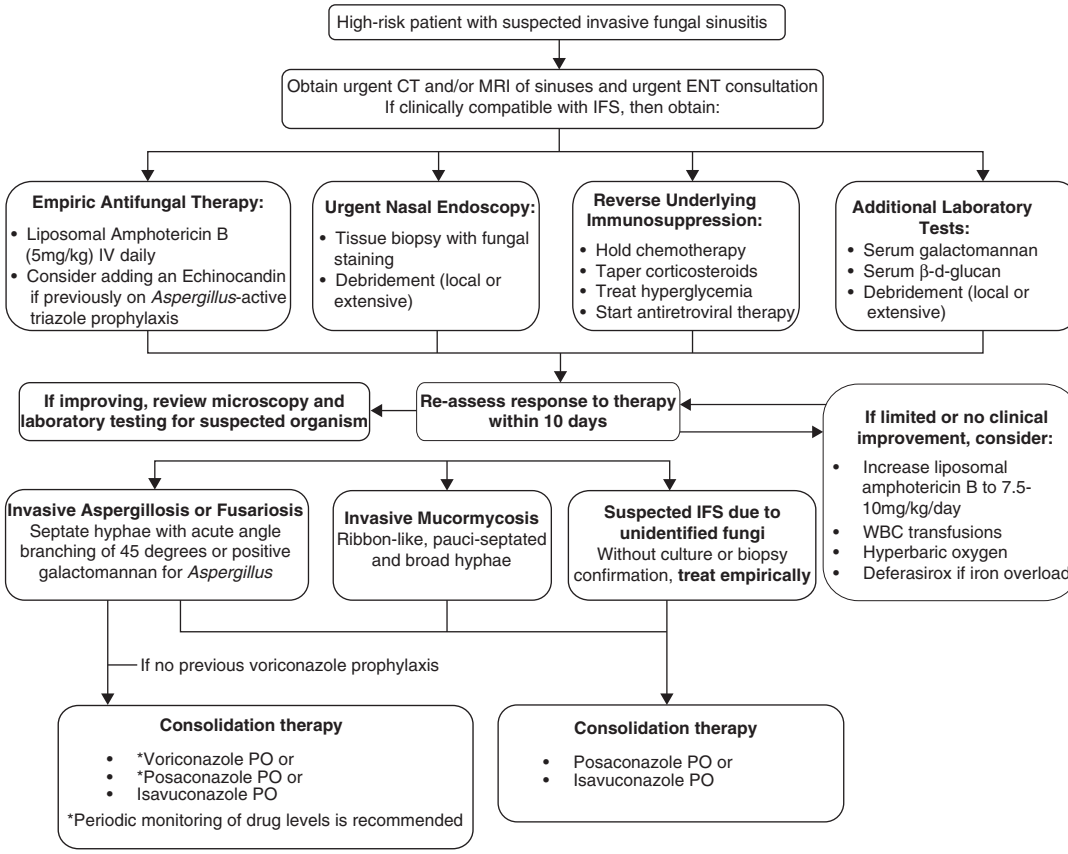

Fig. 15.4 Algorithm for evaluating and managing invasive fungal sinusitis

Outcomes

Despite the advances made in treatment options in antifungal agents and testing, long-term outcomes for patients with IFS still remain poor with 1-year mortality of approximately 50% [5]. This is particularly marked in patients with hematological malignancies as they often require further chemotherapy for refractory underlying disease [1]. Several studies have assessed negative prognostic factors in IFS patients. Factors associated with poor survival were leukemia, prolonged periods of neutropenia ≥10 days, advanced age, concomitant renal disease, as well as delays in treatment [1, 5]. Area and extent of IFS has also been demonstrated to have higher mortality [79]. For example, patients with IFS in only the lateral nasal wall had a mortality of 33%, but this figure climbed to 67% with involvement of the nasal septum and 100% when extending beyond the nasal cavity [80].

On the other hand, surgical or endoscopic debridement has been consistently shown to be a positive prognostic factor for patients with IFS [5, 49, 81] as it is associated with an earlier diagnosis and therefore earlier treatment for the disease [82]. It should be stressed that medical and surgical treatments are performed to manage the disease in the short term while attempting to reverse the underlying immunosuppression in patients who are immunocompromised.

Conclusion

Despite advances in medical and surgical therapy, IFS remains an opportunistic infection with a high morbidity and mortality. The disease most commonly occurs in patients with hematological

malignancies, receiving chronic corticosteroids or other immunosuppressive therapies, or uncontrolled diabetes mellitus. Presenting symptoms and clinical signs lack sensitivity and specificity for IFS. Early CT and endoscopic-based diagnosis along with combined surgical and medical treatment are important for improved survival. To this end, physicians should have a high index of suspicion for IFS and low threshold for consultation to ENT for additional evaluation. During this period, the plan for reversal of immunosuppression should be discussed. Treatment plans should be multidisciplinary and personalized. Patients should be given routine follow-up to monitor response to therapy and to re-evaluate for disease progression as needed.

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Nasal Infections

16

Marlene L. Durand

Introduction

The most common nasal infections are due to viruses, such as rhinoviruses, that cause the common cold. These are self-limiting unless a bacterial superinfection occurs. Acute bacterial nasal infections, such as cellulitis or vestibulitis, are also common and usually caused by *Staphylococcus aureus*, a normal colonizer of the skin and nasal vestibule. Aside from acute viral and bacterial infections, most other nasal infections are rare. Some infections primarily affect the nasal septum, such as post-traumatic nasal abscess, while others involve multiple sites and present as chronic masses, ulcers, or atrophic rhinitis. Some nasal infections, such as mucosal leishmaniasis, are very rare outside of an endemic region. However, many of these infections are chronic or have a long latency so may appear in a patient who immigrated from an endemic country months or years earlier. This chapter reviews the diagnosis and treatment of common and rare nasal infections due to bacteria, fungi, and parasites.

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Anatomy

The structure of the nose and nasal septum is comprised of bone and cartilage, with bone proximally and cartilage distally (Fig. 16.1). A small portion in the roof of the nasal cavity contains the cribriform plate, through which olfactory neurons extend to the overlying olfactory bulb. The nasal cavity is lined with respiratory epithelium that secretes mucus. Turbinates along the lateral walls of the nasal passages increase the mucosal surface area and help direct the inhaled air. Inhaled air is heat-regulated, humidified, and cleansed of foreign particles and microbes during passage through the nose. The nasal vestibules, areas just inside the nostrils, are lined with skin which contains small hairs (vibrissae). The hairs trap large inhaled particles. The venous drainage of the nose communicates indirectly with the cavernous sinus. The veins draining the nose were previously thought to lack valves, but recent research has proved otherwise [1]. However, infections involving the nose can spread rapidly to the cavernous sinus, and usually do so via the ophthalmic veins.

"The danger zone". For over 160 years, there has been recognition that seemingly minor infections in the mid-face could lead to fatalities.

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_16

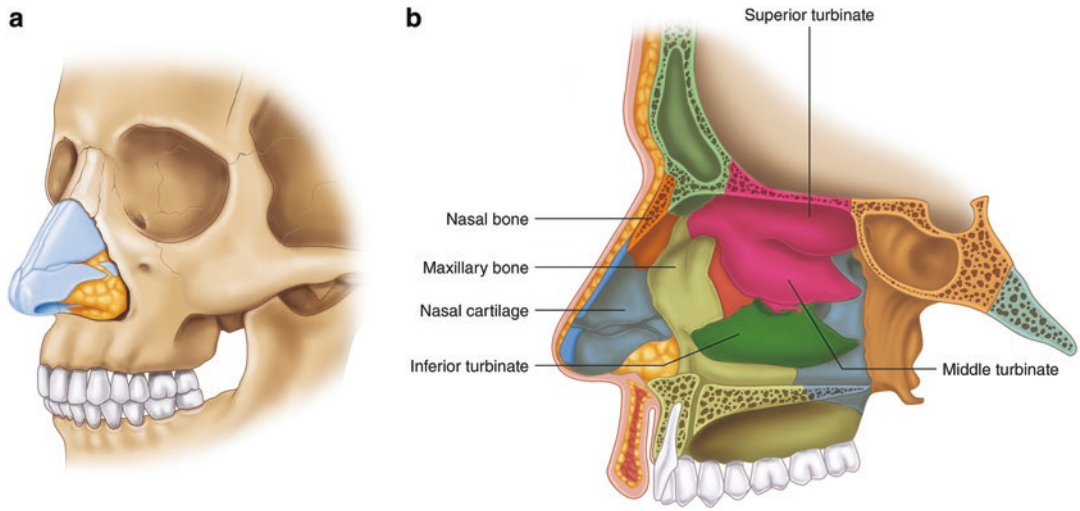

Fig. 16.1 (**a**, **b**) Anatomy of the nose. (**a**) External view, demonstrating nasal bones and cartilage. (**b**) Lateral wall of the nose, demonstrating the superior, middle, and inferior turbinates

Infections in the "dangerous area" of the face were first mentioned in 1852, when Dr. Harvey Ludlow, a general surgeon in London, reported six cases including three fatalities that followed a simple pimple or "boil" on the upper lip [2]. The pathophysiology was explained in 1883, when Sir Frederick Treves noted that a "carbuncle of the face or other diffuse and deep-seated inflammatory conditions, especially of the upper lip and in the neighborhood of the alae nasi, may induce fatal thrombosis of the cerebral sinuses." [3] In 1922, Walton Martin wrote a classic paper on the subject and described the risk from *S. aureus* infections in a danger triangle extending from the angles of the mouth to the bridge of the nose [4]. In 1937, Urban Maes reported 20 fatal cases of cavernous sinus thrombophlebitis that arose from lesions in the "danger triangle" that had been described by Martin, as well as 24 cases that arose from lesions in the face outside this triangle [5]. Maes noted that these cases typically occurred in young, previously healthy patients, often began as a trivial skin infection ("carbuncle or simple boil"), and were nearly always caused by *S. aureus*. Maes also noted that progression to septic cavernous sinus thrombosis typically occurred rapidly (days).

Recent reports corroborate Maes's observations. Pannu et al. described a healthy 55-year-old man who developed a minor furuncle and cellulitis on the nasal tip, then presented 15 days later with persistent fevers and third and sixth cranial nerve palsies due to cavernous sinus thrombophlebitis [6]. Munchkoff et al. described a healthy 26-year-old man who developed a post-traumatic pustule on the skin adjacent to the nares and then presented 3 days later with bilateral ophthalmoplegia and proptosis due to methicillin-resistant *S. aureus* (MRSA) cavernous sinus thrombosis [7] (Fig. 16.2). Varshney et al. reported a series of eight children in India who developed septic cavernous sinus thrombosis 4–10 days following minor nasal or sinus infections (furuncles, vestibulitis, ethmoiditis) [8]. All eight children were febrile on presentation, 75% presented with orbital signs and symptoms, and *S. aureus* was the pathogen in most—all features typical of cavernous sinus thrombosis following nasal infections. Cavernous sinus thrombophlebitis can be caused by bacteria besides *S. aureus*, and cases have been described due to streptococci (e.g., *Streptococcus anginosis/milleri* group, *S. pneumoniae*), Gram-negative bacilli, and anaerobes [9].

Microbiome of the Nose

The nasal passages are not sterile. *Staphylococcus aureus* is part of the normal microbiome in up to one-third of the population, and MRSA colonizes

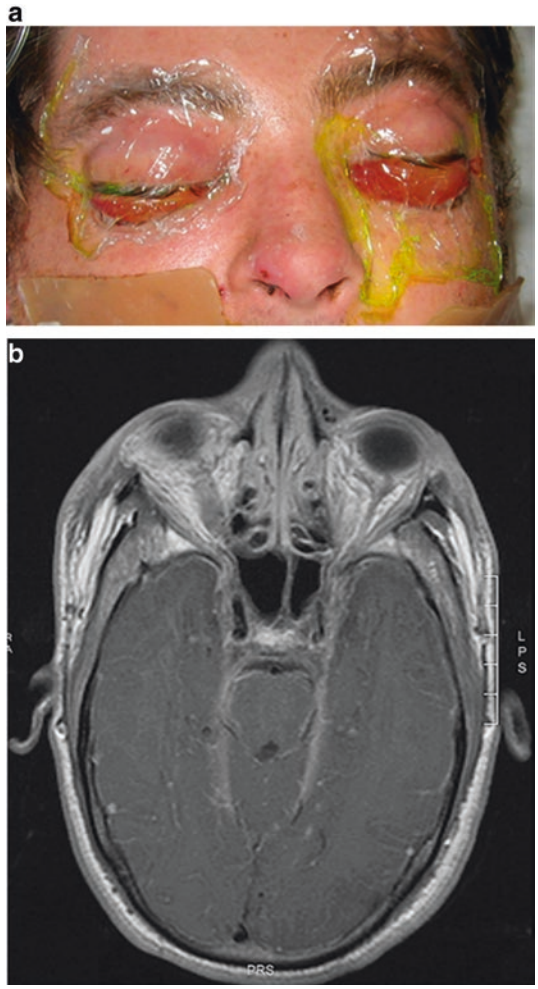

Fig. 16.2 (**a**, **b**) Cavernous sinus thrombosis from methicillin-resistant *Staphylococcus aureus* (MRSA). The patient was a previously healthy man who suffered a minor injury to the skin next to the right nostril 3 days earlier. (**a**) Examination showed bilateral ophthalmoplegia, proptosis, and a right nasal skin lesion. (**b**) Magnetic resonance imaging (MRI) demonstrated enhancement of the cavernous sinuses and prominence of the right superior ophthalmic vein, suggesting early thrombus formation. Reproduced from Munckhoff et al. [7], with permission from John Wiley and Sons

the noses of approximately 2% of the U.S. population [10]. The rate of MRSA colonization is often higher in healthcare workers and others with frequent contact with the healthcare system, as well as residents of long-term care facilities. The location of various microbes in the nose varies by location along the nasal passage. The technique used to detect microbes will influence results, and genetic sequencing techniques have demonstrated a much wider variety of organisms than was previously appreciated. Wos-Oxley et al. performed genetic sequencing on samples at four intranasal locations of 79 individuals (some with chronic sinusitis) and found nearly 450 distinct bacterial phylotypes, although 20 of these accounted for 75% of the total standardized sequence readings [11]. Predominant species included *Corynebacterium*, *Propionibacterium acnes*, *S. aureus*, coagulase-negative staphylococci, *Cupriavidus/Ralstonia*, *Dolosigranulum pigrum*, Enterobacteriaceae, and *Moraxella lacunata/nonliquefaciens*. Some of these bacteria, such as coagulase-negative staphylococci and *P. acnes*, do not appear to cause intranasal infections. The types of bacteria colonizing the nose may vary depending on whether the patient lives in the country or a city. Shukla et al. compared the intranasal microbiota of dairy farmers and urban dwellers and found that dairy farmers had a significantly greater microbial diversity and lower rate of staphylococcal colonization [12].

Fungal spores are present in the air we breathe, and one of the functions of the nasal mucus is to trap these spores and other allergens. It is not surprising, therefore, that cultures of the nasal mucus will grow fungi. A study by Ponikau et al. found fungi, especially molds, in cultures of the nasal mucus of nearly all patients with chronic rhinosinusitis and in all healthy control patients [13].

Nasal Vestibulitis

Nasal vestibulitis usually arises from an infection around one of the hairs in the vestibule. Most cases are caused by *S. aureus* (including MRSA). The clinical presentation is usually redness, swelling, and pain around the involved nostril (Fig. 16.3) [14]. Extension to the tip of the nose may occur. Systemic symptoms such as fever are rare, and if present suggest a more extensive infection. Minor, localized vestibular infections may be treated with a combination of oral and topical antibiotics, or in some cases with topical antibiotics alone. The antibiotic chosen should have activity against *S. aureus*, including MRSA in regions where MRSA is prevalent. Any antibiotic with activity against MRSA will also be

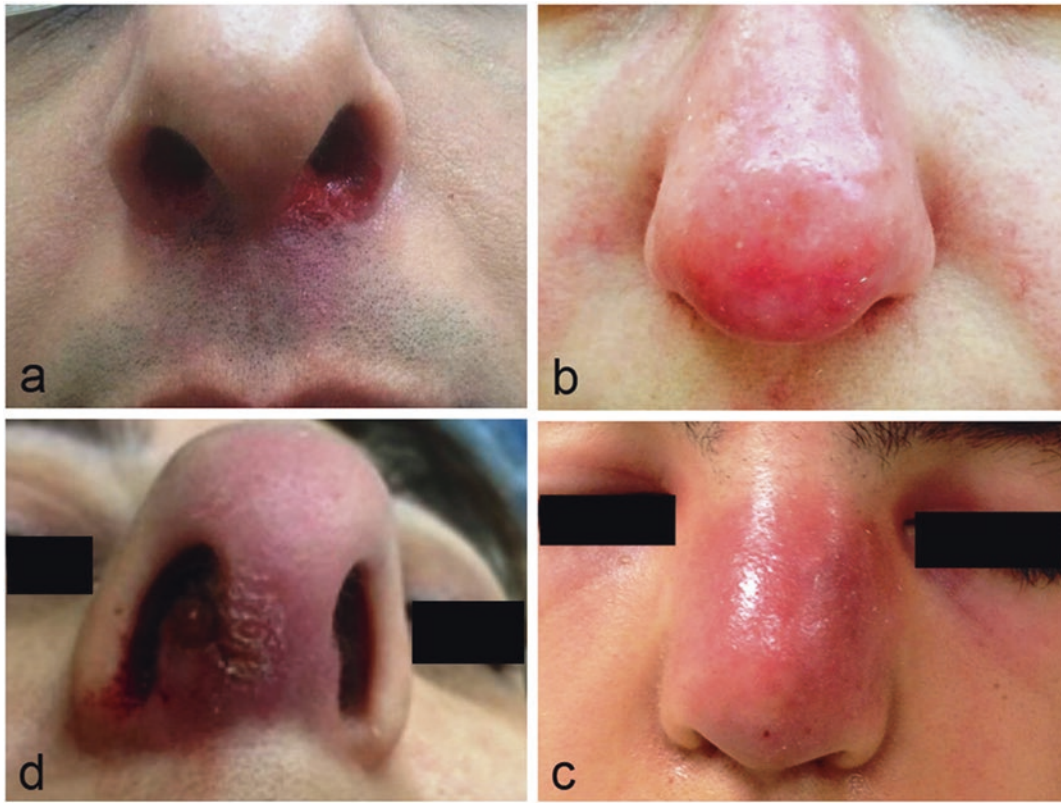

Fig. 16.3 (**a**–**d**) Nasal vestibulitis. (**a**) Left nasal vestibulitis with crusting. (**b**) Nasal vestibulitis with localized cellulitis. (**c**) Mid-face cellulitis. (**d**) Vestibular abscess. Reproduced from Lipschitz et al. [15], with permission from Sage Publishing

active against methicillin-sensitive *S. aureus*. Topical mupiricin generally has excellent activity against MRSA and may be more effective for nasal vestibulitis than triple antibiotic ointments (e.g., combination of bacitracin, neomycin, polymixin). A patient with nasal vestibulitis and nasal tip cellulitis has been described who failed initial treatment with triple antibiotic ointment plus oral doxycycline but rapidly responded to topical mupiricin ointment [15]. Cephalexin will treat methicillin-sensitive *S. aureus* but not MRSA, while trimethoprim-sulfamethoxazole will generally treat both although local susceptibility patterns should be considered.

More significant infections will require intravenous antibiotics. Patients with intranasal abscess and extension of cellulitis to the nasal bridge or face should be admitted for drainage of the abscess and intravenous antibiotics. Lipschitz et al. reported results of 115 patients admitted to a tertiary care center in Israel 2008–2015 for nasal vestibulitis [15]. The average age was 44 (range 8–96), and 40% of the patients had received oral antibiotics (most often amoxicillin-clavulinate) prior to admission. Indications for admission included failure to improve on oral antibiotics, mid-face cellulitis (present in 79%), or nasal vestibular abscess (present in 48%). Patients were treated with intravenous antibiotics and drainage of any abscess. Nasal abscess cultures were positive in 15 patients and grew *S. aureus* (87%), MRSA (7%), and *Prevotella* (7%). All infections resolved with treatment. Ruiz et al. reported a series of nasal vestibulitis in 115 cancer patients referred for outpatient dermatology consultation in New York City and the Netherlands [16]. Most were receiving "targeted therapy" for their cancer with an agent such as an

epidermal growth factor receptor inhibitor, a therapy associated with dermatologic side effects. Positive nasal vestibule cultures grew *S. aureus* (43%) or MRSA (3%), Group A or B streptococci (2%), Gram-negative bacilli (13%), and normal skin or respiratory flora; 28% of cultures were polymicrobial. Most vestibulitis cases in this series were considered mild or moderate and the majority responded to a topical antibiotic.

While *S. aureus* is the major cause of nasal vestibulitis and abscess and most patients present acutely, recurrent cases may be due to an unusual microbe or due to an underlying tumor. Rudramurthy et al. described a diabetic patient in India who presented with a vestibular abscess that was drained, only to relapse with fever, nasal erythema, and vestibular abscess 1 month later [17]. The abscess was again drained and branching, Gram-positive and partly acid fast organisms were seen on stains; a *Nocardia*-like organism (*Nocardiopsis dassonvillei*) grew on culture. The infection responded to 4 weeks of combination antibiotic therapy. Some patients diagnosed initially with chronic nasal vestibulitis have been found to have underlying cutaneous neoplasms such as basal cell or squamous cell cancer [18]. Patients with chronic or relapsing vestibulitis should have cultures of the vestibule for routine and unusual organisms, along with evaluation for a local malignancy.

Nasal Septal Infections

Acute Nasal Septal Abscess

A nasal septal abscess is uncommon, and usually develops in the anterior portion of the septum between the septal cartilage and the overlying mucoperichondrium. Rarely, the abscess is more posterior and develops between septal bone and mucoperiosteum. Most septal abscesses occur in children and adolescents. The most common etiology is trauma. Typically, a posttraumatic septal hematoma develops and becomes superinfected. Nasal septal trauma may occur following accidents, falls, or fights, and septal abscesses may be difficult to diagnose initially. Other causes of septal abscess include dental or sinonasal infections, such as nasal vestibulitis, and postoperative complications following nasal surgery. Rarely, septal abscess occurs spontaneously [19] (Fig. 16.4). Because the septal cartilage receives its blood supply by diffusion from the overlying mucoperichondrium, damage to the mucoperichondrium, as often occurs with trauma, can lead to rapid cartilage damage and subsequent septal perforation [20]. Secondary infection accelerates this process.

Septal abscesses are often bilateral, particularly in posttraumatic cases, and patients complain of bilateral nasal obstruction [20]. Symptoms typically develop within 1 week of the

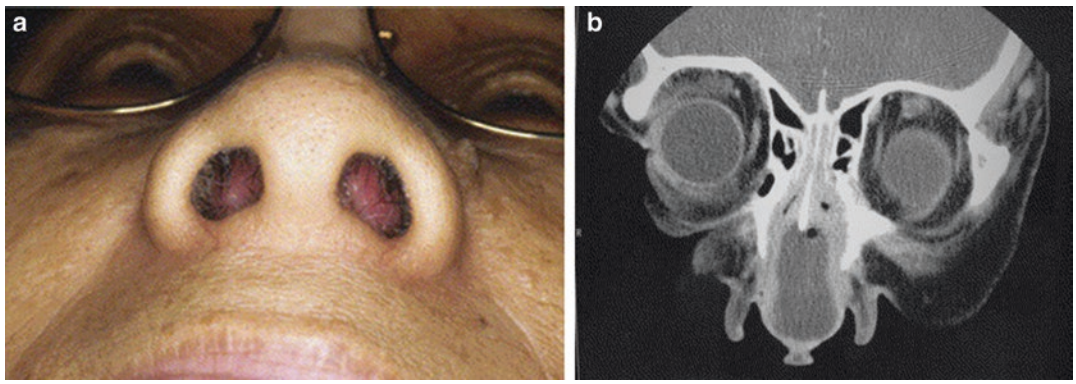

Fig. 16.4 (**a**, **b**) Nasal septal abscess. A 69-year-old woman presented with 4 days of nasal obstruction and pain. (**a**) Examination showed bilateral septal swelling causing obstruction. (**b**) Coronal computed tomography (CT) showed septal abscess with gas bubble. Surgical drainage revealed necrotic septal cartilage and pus, and culture grew penicillin-sensitive viridans streptococci. Reproduced from Huang et al. [19], with permission from Sage Publishing

trauma. Nasal pain, including over the bridge of the nose, is often present in septal abscesses but fever is uncommon and purulent nasal drainage may be absent. Examination reveals a swollen tender nose and bilateral dusky-appearing nasal septal swelling, often obstructing the nasal airway [20]. Most cases involve the anterior nasal septum, but rare cases involve the posterior septum [21]. Radiologic imaging should be performed as part of the evaluation. Computed tomography (CT) with contrast should be performed first, followed by magnetic resonance imaging (MRI) if there is concern for central spread of infection.

Nasal septal abscesses require immediate drainage to prevent further destruction of the cartilage. Samples of the abscess should be sent for Gram stain and culture. The most common cause of septal abscess is *S. aureus*, which accounts for approximately 70% of the cases [20]. Other etiologies include MRSA [22], streptococci (e.g., Group A *Streptococcus*, *S. pneumoniae*, *S. anginosis/milleri*), *Haemophilus influenzae*, anaerobes, and rarely Enterobacteriaciae [20]. Cases of septal abscess due to molds (e.g., *Aspergillus*, *Fusarium*) have been described but are very rare [23, 24]. Tuberculosis and leprosy, both mycobacterial infections, may cause septal infection and perforation, as discussed later.

In addition to urgent drainage of the abscess, treatment should include broad-spectrum intravenous antibiotics (e.g., vancomycin plus ampicillin-sulbactam, or vancomycin plus metronidazole plus ceftriaxone), with subsequent narrowing of the antibiotic regimen based on culture results. The optimal duration of antibiotics following surgical drainage has not been established, but a minimum of 2 weeks is recommended. Some cases require much longer (e.g., 4–6 weeks), since infections in cartilage can be difficult to eradicate. In cases with slow or no improvement on antibiotics after drainage, repeat cultures and imaging should be obtained. Further surgical drainage may be necessary, including in the operating room. Once the acute infection has been treated, cartilage grafting of any septal perforation may be necessary in growing children to prevent the later development of a facial deformity.

Cocaine Abuse, Septal Perforation, and Superinfection

Cocaine causes vasoconstriction, and intranasal abuse of cocaine often leads to osteocartilaginous destruction of the nasal septum due to ischemic necrosis. Secondary infection as well as chemical irritation from adulterants in the cocaine can add to the destructive process [25]. Septal perforations are well described in patients who use intranasal cocaine. However, persistent cocaine use can also lead to perforation of the palate and an oral-nasal fistula [25], or even a midfacial cavity resulting from the destruction of the turbinates and medial maxillary walls [26]. Secondary infection leading to acute or chronic osteomyelitis of the septum or hard palate may occur. In one advanced case, a biopsy of the bone at the edge of the central cavity revealed acute osteomyelitis, and cultures grew a mixture of bacteria including staphylococci, streptococci, and *Serratia* [26]. Although bacteria, especially *S. aureus*, are the usual cause of superinfection, molds can play a role. Cases of cocaine-related septal and palatal perforations with chronic invasive *Aspergillus* superinfection have been described [27].

Snorted narcotics can also lead to septal perforations. In a series from 50 years ago, Messenger found that all but seven of the 2185 drug users he examined over an 8-year period snorted heroin rather than cocaine (cocaine was more expensive), and that the incidence of septal perforations was 4.8% [28]. A recent report described a patient who developed total destruction of the septum, soft palate, and sinus walls from snorting crushed tablets of sustained release oxycodone [29].

Rare Intranasal Infections

Bacterial Infections

Tuberculosis

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis*, is prevalent worldwide but primarily affects the lungs. Extrapulmonary TB is less common and rarely involves the nose. A review of the twentieth cen-

tury literature found only 35 cases of nasal TB [30]. Nasal TB may occur without pulmonary involvement, although this is uncommon. Nasal TB involvement is usually unilateral, and symptoms include nasal obstruction and discharge [30]. Physical examination reveals a granular intranasal mass in most cases, with the most common site of involvement being the cartilaginous septum followed by the inferior turbinate (Fig. 16.5). Polyps and nasal ulceration may be rarely seen (6% of patients in one study) [30]. The mass of nasal TB can mimic malignancy, and a septal perforation may be present [31]. A biopsy of the nasal mass, rather than a swab culture, should be sent for acid fast bacilli (AFB) stains and mycobacterial cultures. Patients with TB affecting any part of the airway, including the nasal passages, should be placed on airborne precautions to prevent transmission to others. An infectious disease expert should be consulted to help with isolation precautions and TB treatment. Treatment for TB can lead to resolution of the nasal lesion and the septal perforation.

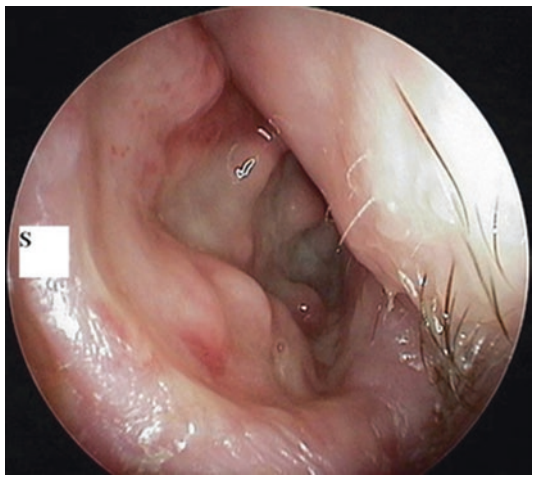

Fig. 16.5 Nasal tuberculosis. A 79-year-old woman presented with 6 months of unilateral nasal obstruction, crusting, and epistaxis. Chest x-ray was clear. Rhinoscopy revealed an irregular, friable, "apple jelly" consistency mass on the left side of the nasal septum (S = septum). Four biopsies over 18 months were required to make the diagnosis; one finally showed caseating granulomas and culture for mycobacteria grew *Mycobacterium tuberculosis* (TB). The infection resolved on anti-tuberculous therapy. Reprinted from Masterson et al. [31], with permission from Cambridge University Press

Leprosy

Leprosy, a bacterial infection caused by *Mycobacterium leprae*, has been known since 600 BC but is now rare in developed countries. Over the past 20 years, 16 million people with leprosy have been successfully treated and the prevalence of the disease has decreased by 99% [32]. However, there are still approximately 200,000 new cases per year worldwide, with 94% of cases occurring in 13 countries [32]. Three large population countries (Brazil, India, and Indonesia) report the most cases [32]. Fewer than 200 new cases occur in the U.S. annually and 75% of these occur in immigrants [33].

The bacterium multiplies very slowly (12 days), and is an obligate intracellular organism that cannot be cultured. It has a predilection for cooler parts of the body including the ears and nose. Symptoms usually take 1 to several years (up to 20) to develop [32], so even a remote travel history to an endemic region may offer a clue to diagnosis. Only 5% of the population is susceptible to leprosy, while 95% have natural immunity. Leprosy is not very contagious, but household contacts of an untreated patient are at increased risk for developing leprosy and may also be nasal carriers of *M. leprae* [34]. A respiratory route of transmission is very likely: the bacterium can be found in abundance in nasal secretions of lepromatous leprosy patients. Leprosy affects the skin and peripheral nerves early in disease. The nose is affected early in lepromatous leprosy, as discussed later.

The clinical manifestation of leprosy depends on the patient's immune response to the bacterium: those with a robust immune response to *M. leprae* have limited disease ("tuberculoid" or "paucibacillary"). Skin biopsy in these patients demonstrates well-formed granulomas and very few acid fast bacilli (*M. leprae*). Patients with minimal immunologic response to the bacterium are at the opposite end of the spectrum and have "lepromatous" leprosy ("multibacillary"), characterized by sheets of foamy macrophages laden with acid fast bacilli on histopathology. Borderline categories fall between these extremes. Patients with tuberculoid disease typically have 1–3 skin lesions that are large, hypopigmented (or reddish) macules or "patches" with distinct borders

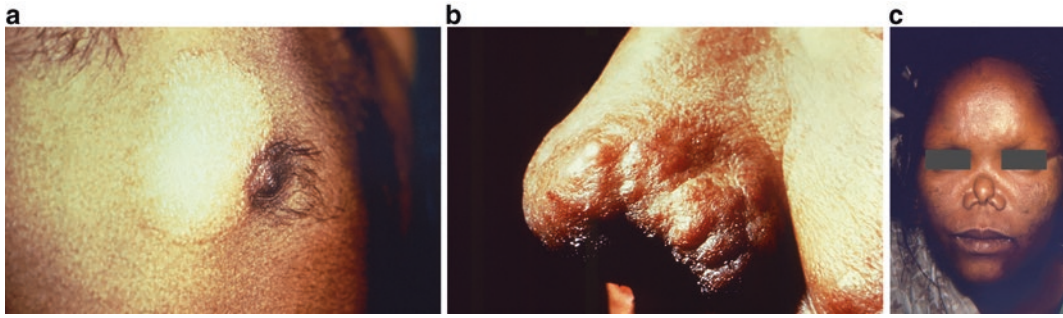

Fig. 16.6 (**a**–**c**) Leprosy. (**a**) Hypopigmented lesion of tuberculoid leprosy; anesthesia within the lesion is typical. (**b**) Lepromatous leprosy with nodules involving the nose. (**c**) Chronic lepromatous leprosy with saddle nose deformity. From the Centers for Disease Control and Prevention (CDC), Public Health Images Library

(Fig. 16.6a). The lesions have decreased or absent sensation, a feature that distinguishes these from other skin lesions. In lepromatous leprosy, there may be diffuse thickened skin or multiple macules and nodules, with the nodules typically involving the earlobes and face (Fig. 16.6b). Hair loss of the outer eyebrows is common. Involvement of peripheral nerves occurs in all types of leprosy, and can lead to nerve enlargement and peripheral neuropathy, with paresthesias of the hands and feet. Chronic infection can lead to "claw hand" and foot drop, and resorption of fingers and toes. The diagnosis of leprosy is made by biopsy of the skin lesion (leading edge), and treatment is with a prolonged course (up to 2 years) of oral dapsone plus rifampin, plus clofazimine in lepromatous cases [33].

Nasal manifestations of leprosy occur in lepromatous leprosy, and nasal discharge in lepromatous disease contains abundant *M. leprae*. Intranasal findings may be the only manifestations of early lepromatous leprosy. Barton and Davey's 1976 description of intranasal findings in 300 leprosy patients remains helpful [35]. In this series, intranasal infection was not seen in patients with tuberculoid leprosy, but was seen in 97% of patients with lepromatous leprosy. These patients usually complained of nasal congestion, crusting, and bleeding; 40% had hyposmia. Early findings included nodular thickening of the nasal mucosa, which often appeared paler than surrounding tissues, or isolated mucosal nodules. The anterior end of the inferior turbinate was the site involved first. Patients with later stage lepromatous leprosy had "gross inflammation of the nasal mucosa and severe obstruction" [35], and some also had perforation of the septal cartilage. With progressive untreated infection, perichondritis and periosteitis of the septum and inferior turbinates develops and leads to the classic saddle nose deformity (Fig. 16.6c). A very rare nasal manifestation of lepromatous leprosy is an intranasal mass, or leproma. This was described recently in a Korean patient who had no other apparent signs of leprosy [36].

Syphilis

The bacterium *Treponema pallidum* causes syphilis, and infection may be transmitted congenitally or acquired sexually. The classic stages of untreated acquired infection include primary syphilis, characterized by a painless chancre at the site of inoculation that resolves spontaneously; secondary syphilis, characterized by a diffuse rash often involving the palms and soles; latent syphilis, defined as having positive serology but no clinical manifestation of syphilis; and tertiary syphilis. Tertiary syphilis, which occurs years or decades after the primary infection, is characterized by cardiovascular, neurologic, or gummatous disease. Gummas are necrotizing granulomatous lesions that most often affect the skin, mucous membranes, and bones but may affect any organ.

In early congenital syphilis, nasal involvement is evident as rhinitis ("snuffles") (Fig. 16.7). A generalized periostitis and perichondritis can also occur in early congenital syphilis and this can

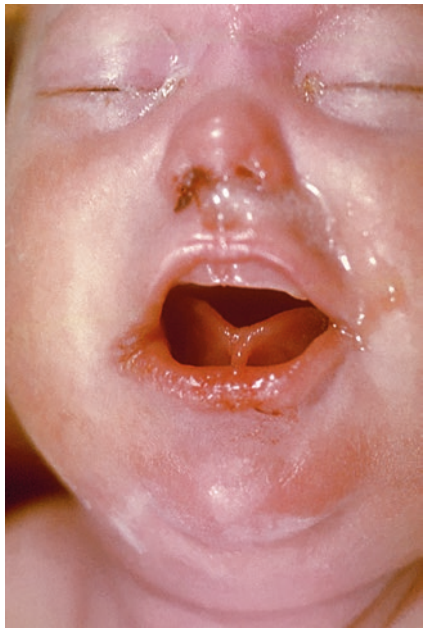

Fig. 16.7 Congenital syphilis; early stage showing infant with "snuffles" from inflammation of the nasal mucosa. From the Centers for Disease Control and Prevention (CDC), Public Health Images Library

involve the nasal septum [37]. The resulting bone and cartilage loss in the nasal septum leads to loss of the structural support in the nose and subsequent saddle nose deformity in "late" (>2 years) congenital syphilis. In a series of 271 patients with late congenital syphilis (average age 29 years old) seen in the 1960s, a saddle nose deformity was common and seen in over 70% of patients [38].

In acquired syphilis, nearly all nasal manifestations are due to gummatous (tertiary) syphilis. The gumma may cause a chronic ulceration inside the nose or of the nose and skin above the upper lip. A case of a slowly destructive midfacial gumma in an HIV-positive patient has been described [39]. The ulcerative mass of a syphilitic gumma may be mistaken for a malignancy until biopsy demonstrates granulomatous changes [40]. *Treponema pallidum* cannot be cultured, and diagnosis of tertiary syphilis is made by serologic studies and histologic findings on biopsy. Nontreponemal tests such as rapid plasma reagin (RPR) spontaneously decline in titer with time and can be negative in up to 50% of tertiary syphilis cases, so treponemal tests such as TPPA (*Treponema pallidum* particle agglutination assay) should be ordered along with the nontreponemal test in any patient who may have a gummatous nasal lesion. Treatment of syphilis with penicillin is curative.

Ozena

Ozena, which means "stench" in Greek, is also called primary atrophic rhinitis. Atrophic rhinitis is characterized by progressive atrophy of the nasal mucosa, crusting, and foul odor. Atrophic rhinitis may be either primary (ozena) or secondary (e.g., resulting from prior sinonasal surgery, trauma, radiation, or various infectious and noninfectious granulomatous conditions). Ozena is very rare outside endemic regions in Africa, the Middle East, and Asia. It may be seen in nonendemic areas in immigrants from endemic regions. Several recent cases have been described in the U.S. and the United Kingdom in immigrants from Nigeria, countries in east Africa, and Saudi Arabia [41, 42]. Patients with ozena complain of excessive crusts, a sensation of nasal obstruction, and thick, often foul-smelling nasal discharge. On examination, there is atrophic nasal mucosa, crusting, and usually an enlarged nasal cavity. There may be resorption or destruction of intranasal bones such as the inferior turbinates. If the mucosa is biopsied, histopathology demonstrates a squamous epithelium rather than the normal respiratory epithelium. Ozena is thought to be idiopathic, although *Klebsiella ozenae* can be cultured in many cases [41–43]. Culture-directed antibiotics are usually given, often for prolonged courses, but without uniform success [41]. Randomized controlled trials to determine optimal treatment have not been performed. A fluoroquinolone has been effective in several cases that were culture-positive for *K. ozena*e [41, 42], and this class of antibiotics may prove to be most effective.

Rhinoscleroma

Rhinoscleroma, or "scleroma," is a chronic granulomatous disease of the nose and upper airways caused by *Klebsiella rhinoscleromatis*. The disease was first described in 1870 by Hans Von

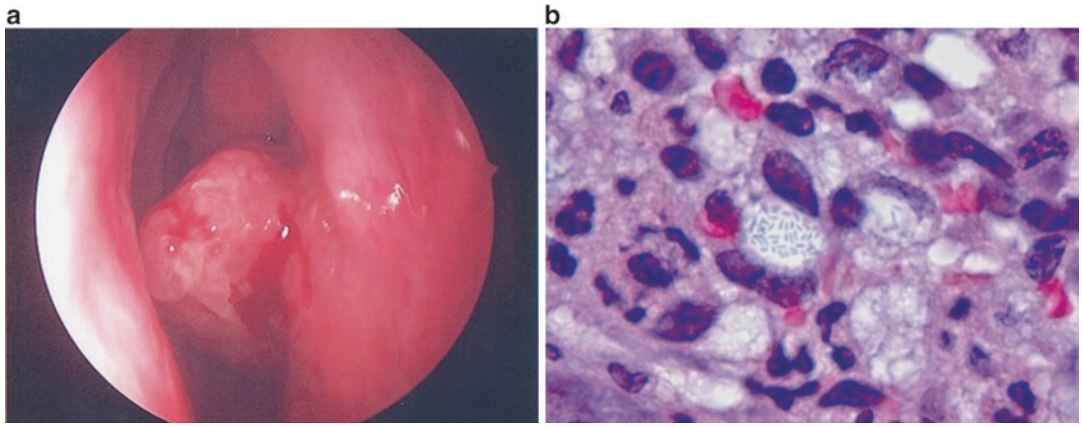

Fig. 16.8 (**a**, **b**) Rhinosclerma. (**a**) Fleshy, friable mass arising from the nasal septum. (**b**) Hematoxylin-eosin stain of laryngeal biopsy (100×) showing the classic Mikulicz cells of rhinoscleroma. These cells are foamy or vacuolated histiocytes, some containing the causative bacterium, *Klebsiella rhinoscleromatis* (note tiny rod-like structures in the central white oval area). Reproduced from Suchanova et al. [47], with permission from Sage Publishing

Hebra in Europe, but it is very rare in Europe now. It is primarily seen in Central and South America, Egypt and several other African nations, and India, Indonesia, Papua-New Guinea, and other areas of southern or southeastern Asia. Occasionally rhinoscleroma is reported in non-endemic areas such as western Europe or the U.S., but then primarily in immigrants from endemic regions [43–47]. The disease is chronic, so immigrants may reside in the non-endemic country for several years prior to diagnosis. For example, one report described an Egyptian man who had lived in Italy for 8 years prior to onset of symptoms due to rhinoscleroma [46].

The disease involves the nose in nearly all cases (90–100%), sometimes with extension to the nasopharynx, larynx, oral cavity, trachea, bronchi, Eustachian tube, and middle ear. Occasionally, the larynx is involved without evidence of nasal disease. Molumi and Dubey reported 134 cases seen in Papua New Guinea 1995–2013 [48]. The nose and nasopharynx were involved in 92%, including cases with extension to other areas, while the remaining 13% of patients had primary involvement of the larynx without nasal involvement. Rhinoscleroma has three stages, catarrhal-atrophic, granulomatous or hypertrophic, and fibrotic. The first stage usually lasts weeks to months, while the second and third stages may last for years before diagnosis and treatment. During the first stage, patients have persistent rhinorrhea or foul-smelling discharge with crusts [43]. During the second stage, there are intranasal nodules, granulomatous tissue, or masses that may be mistaken for malignancy (Fig. 16.8a). The masses may be polypoid and often arise from the anterior septum; nasal deformity from the destruction of cartilage and intranasal masses may occur [43]. In the third stage there is scarring, and a tracheostomy may be necessary if there is laryngeal involvement.

Diagnosis is usually made by biopsy and culture during the granulomatous phase of disease. The classic foamy or vacuolated macrophages ("Mikulicz cells") seen on histology in biopsies of this phase were first described by Mikulicz in 1876; intracellular bacilli can be seen in some cells (Fig. 16.8b). Cultures are positive for the causative organism, *Klebsiella rhinoscleromatis*, in approximately 50% of the cases. The organism is sometimes described in the literature as a subspecies of *K. pneumoniae*, but recent genome analysis suggests it is a separate species [49]. Although other *Klebsiella* species are widely distributed in the environment (water, soil, plants), *K. rhinoscleromatis* has never been found in a non-human host and it has a characteristic somatic: capsular antigenic fingerprint of O2:K3 [45]. Treatment is usually with an antibiotic such as ciprofloxacin or trimethoprim-

sulfamethoxazole for one to several months [45], although the optimal duration has not been defined. Surgery may be required in some cases. Relapses may occur, requiring retreatment.

Fungal Infections

Invasive Aspergillosis and Mucomycosis

These mold infections usually occur in the immunocompromised host and arise from the sinuses. The nose may also be involved occultly, as demonstrated by biopsy of middle turbinate mucosa. Invasive fungal sinus infections are discussed further in Chap. 15.

Histoplasmosis

Histoplasma capsulatum is a fungus that is endemic in many locations worldwide, including the Ohio and Mississippi River valleys in the U.S., parts of Mexico, Central and South America, Africa, Asia, and Australia. It is thermally dimorphic, being a mold in the environment but a yeast in human tissues. The fungus lives in the environment, particularly in soil that contains large amounts of bird or bat droppings. Activities that disturb soil can lead to aerosolization of the microscopic fungal spores and inhalation. Primary infection almost always occurs in the lungs and is usually asymptomatic and self-limited in the immunocompetent host. Infection may remain dormant for years, however. An immunocompromised patient may develop evidence of disseminated infection from either recently or remotely acquired primary infection. A history of even remote residence in an endemic area may be significant. At the time of presentation with extrapulmonary disease, the lungs may be clear. Evidence of disseminated histoplasmosis may occur in immunocompetent hosts but this is rare.

Disseminated histoplasmosis may involve the upper airway, usually oral cavity, pharynx, or larynx. Nasal involvement is very rare and typically presents as an ulcerated intranasal lesion with overlying crusts [50] or as a granulomatous intranasal lesion that may mimic a tumor. Diagnosis is by biopsy and fungal culture. Treatment is with antifungal therapy, usually with an induction course of liposomal amphotericin followed by a very prolonged course of itraconazole. Another endemic fungal infection, blastomycosis (cause by *Blastomyces dermatiditis*), may very rarely cause intranasal lesions [51].

Conidiobolomycosis

This infection is a localized zygomycosis that is also called rhinofacial Entomophthoro-mycosis (order Entomophthoromycosis, class Zygomycetes). The infection, due to the fungus *Conidiobolus coronatus*, is rare and affects immunocompetent hosts, especially those engaged in farming or other outdoor activities. The disease occurs in Africa, Central and South America, and Southeast Asia. It may be seen in non-endemic regions in immigrants [52]. The fungus is present in soil and decaying vegetation, and is probably acquired by inhalation. The clinical presentation is usually chronic and symptoms include nasal obstruction, discharge, or deformity. The nose may develop gradual and painless swelling (Fig. 16.9) [53]. Intranasal exam usually shows masses or nodules [53]. The classic finding on biopsy is short broad hyphae ensheathed by eosinophilic material (Splendore-Hoeppli phenomenon). The organism may grow on fungal culture. Treatment is with antifungal agents.

Parasitic Infections

Leishmaniasis (Mucosal)

Leishmaniasis is a parasitic disease caused by an obligate intracellular protozoan that is transmitted by the bite of the sand fly. The sand fly is one-third (or less) the size of a mosquito. Different species of sand fly transmit different *Leishmania* species so the manifestations of disease vary across the world, and the disease is often categorized as New World (Mexico, Central and South America) or Old World (Asia, Africa, southern Europe). The disease has three main clinical syndromes, cutaneous, mucosal, or visceral, with cutaneous being the most common and mucosal being the type that affects the nose.

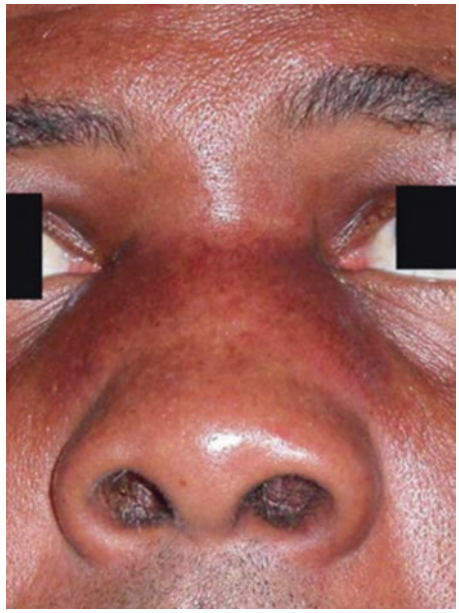

Fig. 16.9 Conidiobolomycosis (rhinofacial Entomophthoromycosis). A Sundanese immigrant to Switzerland complained of 9 months of painless swelling of his nose. Cultures of a nasal biopsy grew *Conidiobolus coronatus*. Reproduced from Fischer et al. [53], with permission from Springer

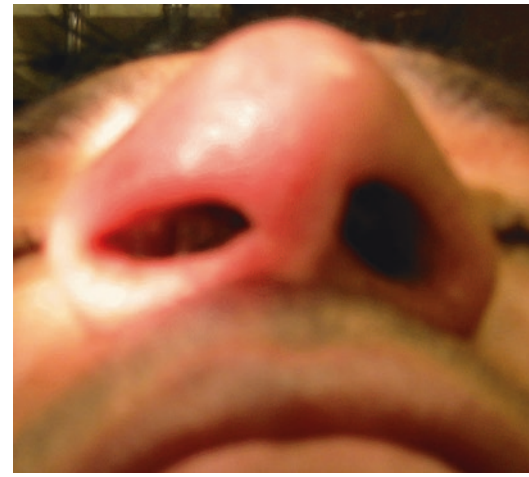

Fig. 16.10 Leishmaniasis (mucosal). A 35-year-old immigrant from Brazil to the U.S. presented with a history of an intranasal ulcer for 6 months and nasal congestion, swelling, and pain for 2 months. The right nostril was partially collapsed and tissue under the rim was thickened. The nasal septal mucosa was inflamed and had a cobblestone appearance. Diagnosis of *Leishmania* (*V.*) *braziliensis* was made by special culture of a biopsy specimen for *Leishmania*. The case is further described in reference [55]. (Photograph courtesy of Dr. Marlene L. Durand)

The mucosal form is found only in New World leishmaniasis. Mucosal leishmaniasis, also called espundia, occurs in parts of Mexico, Central America, and South America except for Chile and Uruguay [54]. Cases are occasionally seen in non-endemic countries, such as the U.S., in immigrants from Mexico and Central and South America [55].

All mucosal leishmaniasis cases result from occult metastatic spread of an earlier cutaneous inoculation of the *Viannia* subgenus of *Leishmania*, especially *L.* (*V.*) *braziliensis* (or less often by *L. amazonensis*). The first manifestation of infection is a painless cutaneous lesion occurring at the site of a sand fly bite but weeks to months later. The skin lesion begins as a papule but becomes an ulcerated plaque, which heals spontaneously over several months. A scar may result. In a small percentage of untreated cases, the patient develops mucosal leishmaniasis one or more years later. The skin lesion may have gone unnoticed. Amato et al. reported a series of 140 patients with mucosal leishmaniasis seen in Brazil and less than half recalled a skin lesion [56]. Rarely, cutaneous and mucosal lesions are present simultaneously (mucocutaneous leishmaniasis). The risk of developing mucosal leishmaniasis after untreated cutaneous leishmaniasis is unknown, but probably less than 5%.

The initial symptoms of mucosal leishmaniasis usually relate to the nose, although some cases may have oral or pharyngeal symptoms first [54]. Nasal congestion, rhinorrhea, and epistaxis are the most common presenting symptoms. Most patients have nasal mucosal disease or septal perforations (87% in the Amato series), while some also (or only) have oral/palatal disease (24%) or laryngeal disease (16%) [56]. Clinical signs in the nose may evolve over time and may include hyperemia and edema, nodules, ulceration, and nasal perforation [57] (Fig. 16.10). Diagnosis of mucosal leishmaniasis is made by biopsy of abnormal areas of mucosa for pathology, culture, and polymerase chain reaction (PCR) testing. The parasite does not grow on routine culture media and the necessary specialized media (e.g.,

Novy-MacNeal-Nicolle) can be obtained from the reference laboratory, ideally prior to biopsy. In the U.S., physicians should contact the Centers for Disease Control and Prevention (CDC) (see the CDC website, http://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf). Mucosal leishmaniasis is treated with liposomal amphotericin, miltefosine, or antimonial compounds. Guidelines for the diagnosis and treatment of leishmaniasis have been published recently by the Infectious Disease Society of America [57].

Rhinosporidiosis

Rhinosporidiosis is a chronic infection that typically causes intranasal masses. It is caused by an unusual organism, *Rhinosporidium seeberi*. The infection occurs in tropical regions worldwide (e.g., South America, Africa, Asia) but is most prevalent in southern India and Sri Lanka [58]. The infection can occur in several animal species in addition to humans. The organism cannot be propagated in the laboratory and classification has been difficult. It was originally thought to be a parasite, then a fungus, and most recently an aquatic protistan parasite. Through phylogenetic analysis, it has been placed in a new clade named Mesomycetozoa that also includes some fish parasites [59]. It is postulated that humans acquire infection during bathing in contaminated water, particularly stagnant bodies of water [58].

Most rhinosporidiosis patients are young to middle-aged, live in rural areas, and work in agriculture [60]. The disease manifests as polypoid masses that most often arise in the nose, with the second most common site being the palpebral conjunctiva; other sites, such as the urethra, may be affected. The intranasal masses may be large and obstruct the nostrils. They may be pedunculated or sessile and are usually pink or red. They may have a "strawberry" appearance because of the presence of white subepithelial dots on the pink/red background of the mass. These white dots represent the thick-walled sporangia of the organism [61]. Diagnosis is based on histology since the organism cannot be cultured. Pathognomonic sporangia are seen in tissue biopsy specimens. These sporangia are 60–450 μm in diameter and contain up to 12,000 endospores each [59]. Treatment is with surgical excision, with electrocautery of the base of the mass after excision. A prolonged course of dapsone is often given postoperatively to prevent disease recurrence.

Conclusion

The nose may be infected by viruses, bacteria, fungi, or parasites. The most common nasal infections are viral, self-limited, and occur as part of the common cold. Minor bacterial infections of the nasal skin or vestibule are usually caused by *S. aureus* and are easily treated. However, any bacterial infection involving the nose should be promptly treated to prevent the rare but life-threatening complication of septic cavernous sinus thrombosis. Rare intranasal infections include those that are mucosal manifestations of a systemic disease with a prolonged latency, such as intranasal TB, leprosy, syphilis, and histoplasmosis, or represent localized inoculation of an unusual pathogen, such as conidiobolomycosis or rhinosporidiosis. Most rare nasal infections are chronic and occur in tropical regions of the world. However, patients with such infections may present to an otolaryngologist in a non-endemic region months or years after visiting or living in an endemic region. Knowledge about rare nasal infections may be helpful to all otolaryngologists, regardless of where they see patients.

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Acute Pharyngitis, Tonsillitis, and Peritonsillar Abscess

17

Molly L. Paras and Miriam B. Barshak

Anatomy and Pathophysiology

The pharynx is a fibromuscular tube extending from the skull base to the lower border of the cricoid cartilage connecting the oral cavity to the esophagus. Portions of the pharynx lie posterior to the nasal cavity (nasopharynx), oral cavity (oropharynx), and larynx (laryngopharynx) (Fig. 17.1a). The muscular components include three pharyngeal constrictor muscles and the stylopharyngeus, salpingopharyngeus, and palatopharyngeus muscles. The circular structure of lymphoid tissue located in the nasopharynx and oropharynx is known as Waldeyer's ring. It is formed by two palatine tonsils (commonly called tonsils) in the lateral walls of the tonsillar fossa, a pharyngeal tonsil (commonly called the adenoid), two tubal tonsils, and the lingual tonsil. The adenoid tonsil is large between ages 3 and 8 and then regresses. The tubal tonsils are located near the Eustachian tube openings. The lingual tonsil is located at the base of the tongue. Peritonsillar abscess refers to infection adjacent to one of the palatine tonsils (Fig. 17.1b).

The tympanic branch of the glossopharyngeal nerve is responsible for referred pain present with tonsillar inflammation. The palatoglossus muscle forms the anterior tonsillar pillar, the palatopharyngeus muscle forms the posterior tonsillar pillar, and the pharyngeal constrictors form the base of the tonsillar fossa. The tonsil capsule attaches to the pharyngeal muscles [1].

When patients present to medical care with a "sore throat" due to an infection, they can be experiencing pharyngitis, tonsillitis, or pharyngotonsillitis. The exact mechanism that leads to pain with inflammation in this region is incompletely understood; however, studies have demonstrated that bradykinin and prostaglandin may play a role in mediating a pain response [2–4].

Epidemiology

Sore throat is a very common complaint, generating 12 million ambulatory visits annually in the U.S. [5]. The highest burden of acute pharyngitis and tonsillitis occurs in children and young adults. A Swedish study found that 66.5% of cases of streptococcal tonsillitis and 65% of

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_17

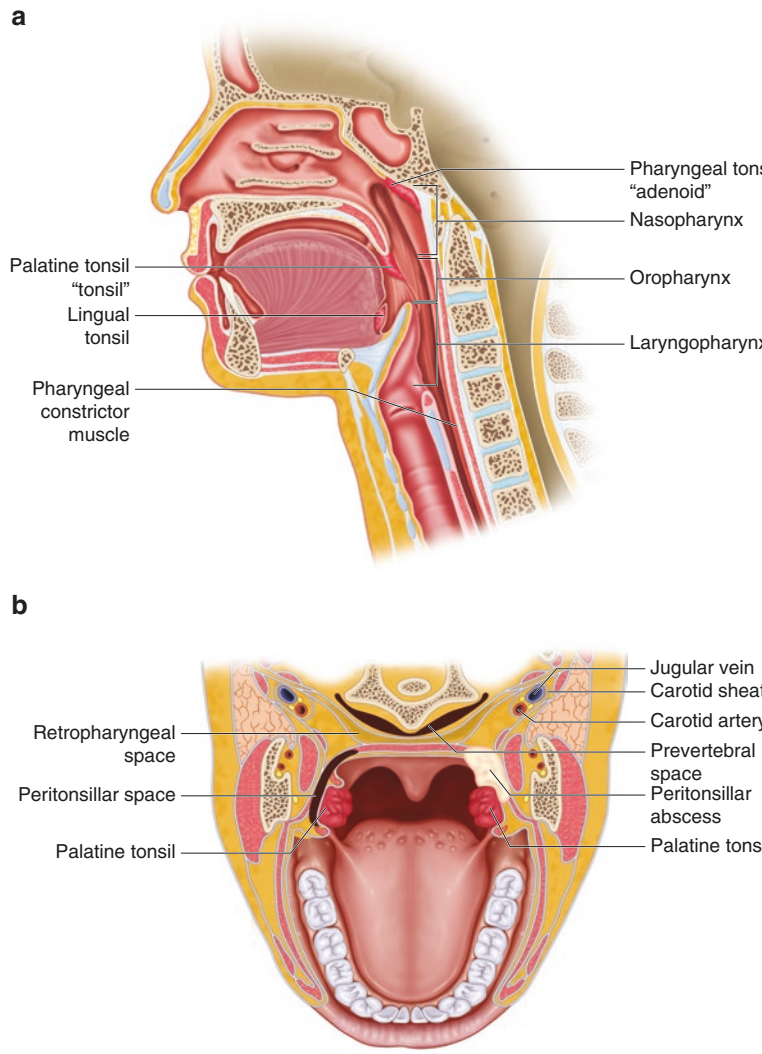

Fig. 17.1 (**a**) Sagittal view of the pharynx. (**b**) Peritonsillar abscess and its relationship to other structures in the throat

acute pharyngitis cases occurred in those aged 5–35 years old, with the 5–14 year olds having the highest burden of disease in this population sampled for both the conditions [6]. Similarly, in a study using national survey data from the U.S., the majority of outpatient pharyngitis visits were by patients under the age of 19 [7]. Viral agents are the most common cause of pharyngitis, and in temperate climates, pharyngotonsillitis tends to be more prevalent in the winter and early spring, corresponding to circulation of these respiratory viruses.

Clinical History

Acute pharyngitis and tonsillitis are clinical diagnoses. Patients with acute pharyngitis and tonsillitis report irritation or pain in the posterolateral oropharynx which tends to be exacerbated by swallowing. Depending on the infectious agent causing their disease, they may also variably report associated fever, rhinorrhea, cough, tender or enlarged lymph nodes, or rash. It is important to inquire about associated symptoms, sick contacts, travel, vaccination history, sexual history,

including history of oral sex, and other risk factors for human immunodeficiency virus (HIV) acquisition. This detailed information may aid the clinician in narrowing the differential diagnosis and allow targeted diagnostic testing (Table 17.1).

Table 17.1 History and physical examination findings suggesting possible pathogens causing pharyngitis or tonsillitis

Historical clues	**Suggestive etiologies**
Epidemic pharyngitis	Adenovirus (water exposure), group G *Streptococcus* (dairy/eggs)
Daycare exposure	Adenovirus, Enterovirus, Parainfluenza virus, Rhinovirus, Respiratory syncytial virus (RSV), group A *Streptococcus* (GAS)
Intravenous drug use	Human immunodeficiency virus (HIV)
High risk sexual behaviors	HIV, Herpes simplex virus (HSV), *Chlamydia trachomatis, Neisseria gonorrhoeae*
Unvaccinated	*Corynebacterium diphtheriae*

Clinical signs/ symptoms	**Suggestive etiologies**
Cough	*C. pneumoniae*, *Mycoplasma pneumoniae*, respiratory viruses
Rhinorrhea	Adenovirus, Parainfluenza virus, Rhinovirus, RSV
Weight loss	HIV
Nausea, abdominal pain	GAS

Physical exam findings	**Suggestive etiologies**
Rash	GAS, *Arcanobacterium haemolyticum*, HIV, Epstein Barr Virus (EBV), Adenovirus, Coxsackievirus, Enterovirus
Conjunctivitis	Adenovirus
Adenopathy	GAS, Adenovirus, EBV (posterior, axillary, inguinal chains), HSV
Palatal petechiae	GAS, EBV
Oral ulcers	Coxsackievirus, Enterovirus, HIV, HSV
Tonsillar exudates	GAS, *Fusobacterium*, group C *Streptococcus, N. gonorrhoeae*, Adenovirus, EBV, HSV; *Corynebacterium diphtheriae* commonly causes pseudomembranes over the tonsils that bleed on scraping
Splenomegaly	EBV

Patients who have developed a peritonsillar abscess as a complication of tonsillitis may report a sore throat that becomes progressively severe and may be unilateral, as well as fever, a change in voice, difficulty with swallowing secretions leading to drooling, and difficulty opening their mouth. It is important to elicit other symptoms that may reflect more severe illness such as lightheadedness or syncope, which may indicate hypotension and sepsis, or difficulty with breathing, which may portend impending respiratory failure.

Examination

The examination of a patient with a sore throat should include measurement of vital signs. A fever is variably present depending on the pathogen. Tachycardia, hypotension, or tachypnea may be clues that the patient is systemically unwell. Examining the nares and nasal mucosa may reveal rhinorrhea or hyperemia, often associated with viral agents causing sore throat, such as rhinovirus, adenovirus, or parainfluenza virus. Pharyngeal edema and erythema is visible with pharyngitis. Tonsillar edema or erythema is present with tonsillitis. Exudates on the posterior pharynx or tonsillar pillars are more commonly seen with group A *Streptococcus* (GAS), Epstein Barr Virus (EBV), *Neisseria gonorrhea*, and diphtheria (see Chap. 19). Petechiae on the soft palate may be seen in GAS. Unilateral peritonsillar swelling with displacement of the tonsil suggests peritonsillar abscess (Fig. 17.2). A rash may be present with certain infections, including GAS, *Arcanobacterium haemolyticum*, HIV, and EBV. Tender adenopathy in the cervical chain is commonly described with pharyngotonsillitis (Table 17.1). Swelling of or difficulty with rotating the neck may suggest a more extensive deep neck space infection (see Chap. 27).

There is considerable overlap between the infectious causes of pharyngitis and tonsillitis. Specific infectious agents and the clinical syndromes they cause will be reviewed here along with diagnostic and therapeutic considerations for each. Viruses are the most common cause of pharyngitis [8–10].

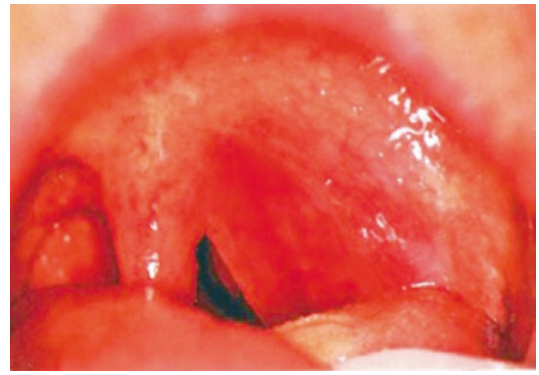

Fig. 17.2 A view of the oropharynx in a patient with a peritonsillar abscess. From: Flint, Paul W. Throat disorders. In: Goldman L, Schafer AI (eds). Goodman-Cecil Medicine, 25th edition. Elsevier, Inc. 2016, with permission

Viral Etiologies of Pharyngitis

Adenovirus

Adenovirus is a common cause of pharyngotonsillitis. In an Italian study, extensive diagnostic testing of children presenting with acute pharyngitis revealed adenovirus to be the most common single viral agent [9]. A retrospective study of children in Spain with positive pharyngeal cultures for adenovirus demonstrated that 88% had tonsillitis and 52% of those had exudates [11]. Cervical lymphadenopathy and a rash may also be present. Pharyngoconjunctival fever syndrome is classically associated with adenovirus serotypes 3 and 7. Patients present with pharyngitis and conjunctivitis in the spring or summer, usually after swimming. This is highly contagious and may spread to up to 50% of close contacts [12]. Direct fluorescent antibody testing of nasopharyngeal swabs can confirm the diagnosis. Treatment is supportive.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV), a member of the *Paramyxoviridae* family, is another common cause of pharyngotonsillitis and tends to be seasonal with outbreaks occurring in the late fall through spring in temperate climates. RSV is spread via respiratory secretions [8, 9]. Rapid antigen assays or polymerase chain reaction of nasopharyngeal swabs can make the diagnosis. Treatment of pharyngitis caused by RSV is supportive.

Enterovirus

Members of the *Enterovirus* family have been implicated in causing pharyngitis, specifically herpangina and hand-foot-mouth disease, which are more common in children than adults. These viruses spread either from gastrointestinal or respiratory shedding. Herpangina, most commonly caused by members of the group A Coxsackievirus family, refers to the clinical syndrome of fever and a painful vesiculo-ulcerative enanthem of the soft palate, posterior pharynx, and tonsils. Hand-foot-mouth disease is most commonly caused by Coxsackievirus A16 and enterovirus A71, although outbreaks attributed to Coxsackie A6 have been described [13, 14]. Hand-foot-mouth disease manifests clinically as herpangina in conjunction with a vesicular rash on the hands, feet, and buttocks [15, 16] (Fig. 17.3). Outbreaks are common in daycare settings. Diagnosis is usually clinical, and treatment is supportive.

Infectious Mononucleosis

Infectious mononucleosis (IM), characterized by fever, sore throat, adenopathy, and malaise, is classically caused by the herpesvirus EBV, although the differential diagnosis includes cytomegalovirus (CMV), human herpes virus 6, and HIV. Epstein Barr Virus is most common among those 5–25 years of age and spreads via contact with virus shed in oral secretions [17]. Clinical signs that point toward a diagnosis of EBV IM

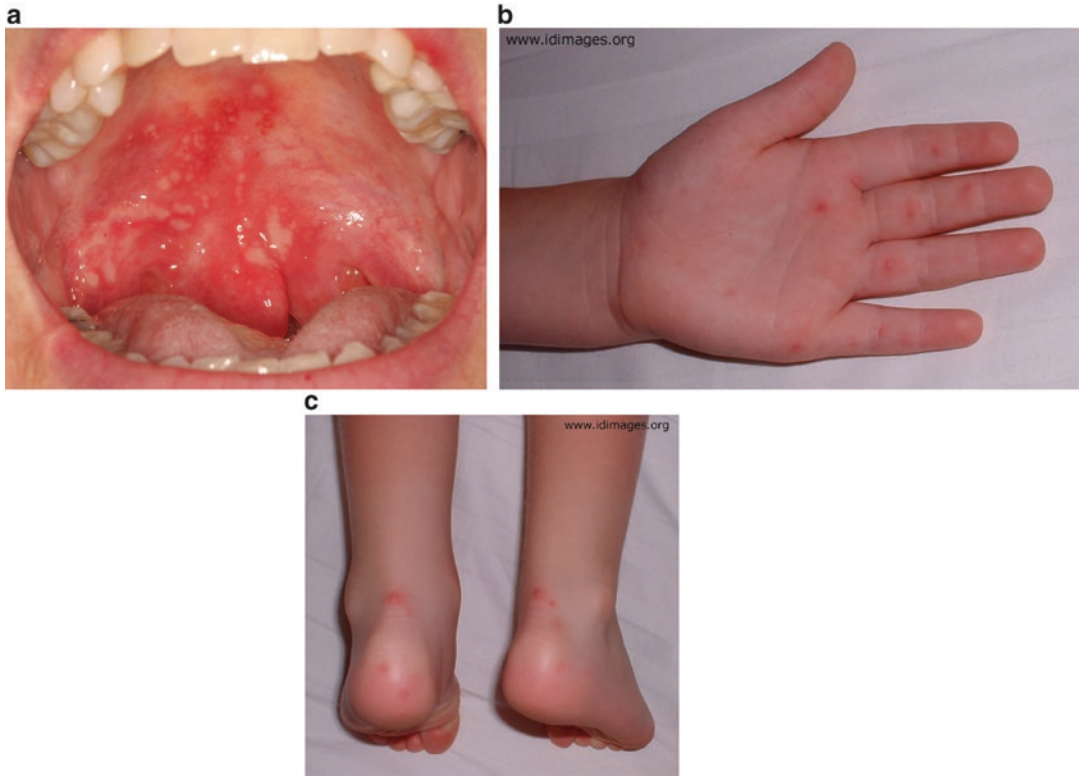

Fig. 17.3 Hand-foot-mouth disease. (**a**) Shallow lesions in the posterior oropharynx (Reproduced from Bruch and Treister [16] with permission from Springer), (**b**) Vesicular rash on the hands and (**c**) feet. (Reprinted with permission from Partners ID Images. Copyright Partners Healthcare System, Inc. All rights reserved) [15]

are palatal petechiae, seen in up to 25% of affected patients, and adenopathy in the posterior cervical, axillary, and inguinal chains [18, 19]. Other exam findings include tonsillar enlargement with or without exudates, splenomegaly, and jaundice. A diffuse maculopapular rash often develops in EBV IM after treatment with amoxicillin, ampicillin, or antibiotics containing these antibiotics such as amoxicillin-clavulanate. The incidence is approximately 30% in children with EBV IM treated with amoxicillin [20]. A rash in EBV IM has been described after treatment with other antibiotics, such as cephalexin [21], azithromycin [22], and quinolones [23], although this is rare—only three cases of azithromycin-related rash have been described, for example. The etiology of the amoxicillin-related rash in mononucleosis is unknown, but may represent a true allergy in some cases [24]. A rash may also accompany the EBV IM infection itself. In a study from Israel of 238 children hospitalized with EBV IM, a rash developed in 33% of children treated with antibiotics versus 23% of untreated children [20].

Lymphocytosis and atypical lymphocytes are also features of EBV IM, although these may also occur in IM due to CMV. A heterophile antibody test, also called monospot, is a latex agglutination assay that may be useful in confirming the diagnosis of EBV-associated IM [25, 26]. There are important limitations for this test. Children <5 years of age do not reliably produce heterophile antibody during acute infection [27]. A false positive heterophile antibody may occur in patients with other conditions such as lymphoma, acute HIV, and systemic lupus erythematosis. False negative heterophile testing is commonly seen when the test is sent early in the course of infection; the sensitivity of heterophile testing for IM reaches 95% sensitivity only after 2 weeks of

EBV infection. If the heterophile antibody is negative, but IM due to EBV is still suspected, then one option is to repeat the heterophile test later in the course of illness, and another is to send EBV-specific serologies. Notably, in Europe, EBV-specific antibodies are routinely used as the primary laboratory test for IM due to EBV whereas in the U.S., the heterophile is most often used, although this test is not recommended by the Centers for Disease Control and Prevention (CDC) for general use [28]. Epstein Barr Virus viral capsid antigen (VCA) IgM and IgG antibodies are sensitive and specific. In acute IM from EBV, the VCA IgM is elevated. Early in the course of infection, the VCA IgG is negative, but later in the course the VCA IgG level rises. VCA IgM levels tend to wane after 3 months, while VCA IgG antibodies persist for life. Nuclear antigen IgG antibodies (EBNA) are detectable 6–12 weeks after infection and persist for life. Early antigen (EA) IgG antibodies are variably expressed in acute illness (Table 17.2). Epstein Barr Virus polymerase chain reaction (PCR) testing should not be used to diagnose IM. Treatment for EBV IM is supportive, and patients should be counseled that they may continue to experience fatigue for months. The authors of a Cochrane review on the use of steroids for symptom control in IM concluded that based on the seven trials, there was insufficient evidence on the efficacy of steroids in this setting [29]. If splenomegaly is present, then contact sports should be avoided to decrease the risk of splenic rupture.

When a patient presents with an IM-like syndrome, acute retroviral syndrome due to HIV should be considered. Risk factors include, but are not limited to, high risk sexual behaviors (men who have sex with men, sex with sex workers, multiple partners), intravenous drug use, or intranasal cocaine use. In a prospective cohort study that identified 40 subjects with primary/early HIV infections, the symptoms most strongly associated with primary HIV infection were fever and rash [30]. In this population, the sensitivity of pharyngitis occurring in primary HIV infection was 44% and specificity 77%. Other symptoms associated with acute HIV infection include oral ulcers, weight loss, arthralgias, and anorexia. When acute HIV is suspected, typically a combination of HIV antigen/antibody immunoassay and an HIV viral load is obtained [31]. In acute infection, the antibody test is often negative, and the viral load is often very high. Patients with acute HIV should be referred urgently to providers with clinical experience in treating HIV.

Table 17.2 Epstein Barr virus serology interpretation

EBV status	VCA IgM	VCA IgG	EBNA	EA IgG
No exposure	–	–	–	–
Acute infection	+	+/–	–	+/–
Remote infection	+/–	+	+	+
Indeterminate	–	+	–	+

EA early antigen, *EBNA* nuclear antigen IgG, *VCA* viral capsid antigen

Herpes Simplex Virus

Herpes simplex virus (HSV) is another cause of pharyngitis and/or tonsillitis, especially in adolescents and young adults. In a study of college students presenting with "upper respiratory symptoms" who underwent a throat swab, 5.7% had cultures positive for HSV, with 17% of those having concomitant infections with GAS, *Mycoplasma pneumonia*, and EBV [32]. In this study 94% of the isolates were HSV type 1, although HSV type 2 causing pharyngotonsillitis has been described in sexually active patients [32, 33]. Symptoms of HSV pharyngotonsillitis include fever, pharyngeal erythema, tonsillar exudates, and enlarged, tender, cervical adenopathy. In the college campus study, only 17% of those with HSV had ulcerative lesions present on physical exam, highlighting the need to maintain a high clinical suspicion for this viral etiology as the culprit for pharyngotonsillitis [32]. Another possible explanation for the findings of this study is that HSV can reactivate in the setting of inflammation due to another etiology. Herpes simplex virus is diagnosed by viral culture of a throat swab, although a special type of swab (calcium alginate) and viral transport media are required. Valacyclovir, acyclovir, or famciclovir can be used for the treatment of HSV pharyngotonsillitis (Table 17.3).

Table 17.3 Recommended targeted therapy in older adolescents and adults for specific pathogens causing pharyngitis or tonsillitis

Pathogen	Recommended treatment for tonsillopharyngitis	Alternative treatment	Comments
Arcanobacterium haemolyticum	Macrolide (e.g., azithromycin, erythromycin)	Amoxicillin, cefuroxime, doxycycline, clindamycin	Trimethoprim-sulfamethoxazole resistance is common. Penicillin treatment failures have been reported
Chlamydia pneumoniae	Treatment is generally recommended only if there is concurrent pneumonia (see the text)	See adjacent comment	See adjacent comment
Chlamydia trachomatis	Azithromycin 1 g PO × 1	Doxycycline[a] 100 mg PO twice daily × 10 days	
Fusobacterium necrophorum	Penicillin VK 500 mg PO four times daily or Penicillin plus metronidazole 500 mg PO three times daily or Amoxicillin-clavulanate 875 mg PO twice daily[b]	Clindamycin 300–450 mg PO four times daily[c]	Macrolides lack activity against *Fusobacterium* spp. Parenteral therapy recommended for serious infections Metronidazole is drug of choice for *Fusobacterium* infections but does not cover GAS so should be combined with a GAS-active agent
Group A *Streptococcus* (GAS)	Penicillin V 250 mg PO four times daily or 500 mg PO twice daily × 10 days or Amoxicillin 1000 mg PO daily or 500 mg PO twice daily × 10 days Or Benzathine penicillin G 1,200,000 U ×1 IM Doses are for usual adult weight patients (at least 27 kg). See footnote for pediatric dosing information[c]	Cephalosporins Or Clindamycin 300 mg PO three times daily Or Clarithromycin 250 mg PO twice daily × 10 days Or Azithromycin 500 mg PO day 1 followed by 250 mg PO days 2 through 5 (use pediatric dosing for weights less than 40kg)[c]	Alternative therapy should be reserved for those truly penicillin allergic; because macrolides do not cover *Fusobacterium,* empiric macrolide treatment of pharyngitis is not recommended especially in the adolescent/young adult population
Group C/G *Streptococcus* (GCS/GGS)	Same as GAS		Treatment is controversial as GCS/GGS have not been linked to rheumatic fever
Herpes simplex virus (HSV)	Valacyclovir 1 g PO twice daily × 7–10 days	Famciclovir 250 mg PO three times daily × 7–10 days or Acyclovir 400 mg PO three times daily × 7-10 days	Treatment of first episode of HSV pharyngitis
Mycoplasma pneumoniae	Treatment is generally recommended only if there is concurrent pneumonia (see text)	See adjacent comment	See adjacent comment
Neisseria gonorrhoeae	Ceftriaxone 250 mg IM ×1 *and* Azithromycin 1 g	Gentamicin 240 mg IM and azithromycin 2 g PO ×1	Dual therapy (same day) is required for *N. gonorrhoeae*

IM intramuscular, *kg* kilogram, *mg* milligram, *PO* oral

[a]Off label use

[b]*Fusobacterium necrophorum* isolates may be resistant to penicillins (up to 10% of isolates) and clindamycin (up to 10% of isolates). Nearly all are susceptible to metronidazole and to a beta-lactam/beta-lactamase inhibitor combination such as amoxicillin-clavulanate

[c]Pediatric dosing for GAS is given in reference 34. Summary:Penicillin non-allergic: Penicillin 250 mg twice daily or three times daily x10 days, or amoxicillin 50 mg/kg daily (maximum 1000 mg) or 25 mg/kg PO twice daily (maximum 500 mg per dose) or penicillin G 600,000 units IM for patients weighing less than 27 kg, use adult dose for weight ≥ 27 kg. Penicillin-allergic: cephalosporins (if not allergic), clindamycin, azithromycin, clarithromycin (see reference [34] for dosing).

Bacterial Etiologies of Pharyngitis

Group A *Streptococcus* (*Streptococcus pyogenes*)

Group A *Streptococcus* (GAS), or *Streptococcus pyogenes*, is a leading bacterial cause of pharyngotonsillitis in children and adults and predominates in school-aged children [34, 35]. Typical symptoms include the sudden onset of sore throat, odynophagia, fever, headache, nausea with or without vomiting and abdominal pain. On exam, erythema with or without exudates on the pharynx and tonsillar pillars is generally present (Fig. 17.4a) and there may be petechiae on the soft palate, anterior cervical adenopathy, or a scarlatiniform rash. The rash is often described as a confluent, sandpaper rash that starts on the trunk and spreads to the extremities, sparing the palms and soles [35–37] (Fig. 17.4b). These symptoms/signs may be less sensitive and specific in younger children [35, 36]. Several prediction rules, based on clinical features and epidemiology, have been developed to aid the clinician in determining the likelihood of GAS pharyngitis (Table 17.4). The best-known prediction criteria are the Centor Criteria, derived from clinical and culture data obtained from 286 adults at a single emergency department [38]. This scoring system gives a point for each of the following: tonsillar exudates, cervical adenopathy, fever and absence of a cough. In a validation study, 7% of patients with one Centor criterion, 21% of patients with two Centor criteria, 38% of patients with three Centor criteria, and 57% of patients with four Centor criteria were confirmed to have GAS with either a rapid antigen detection test (RADT) or throat culture if the RADT was negative [39] (Table 17.5). These results highlight the fact that the Centor Criteria are more helpful for their negative predictive value than for positive predictive value. Specifically, the presence of three or four criteria has a positive predictive value of 40–60%, while the presence of two or fewer criteria has a negative predictive value of 80% for GAS infection. The McIsaac score, more

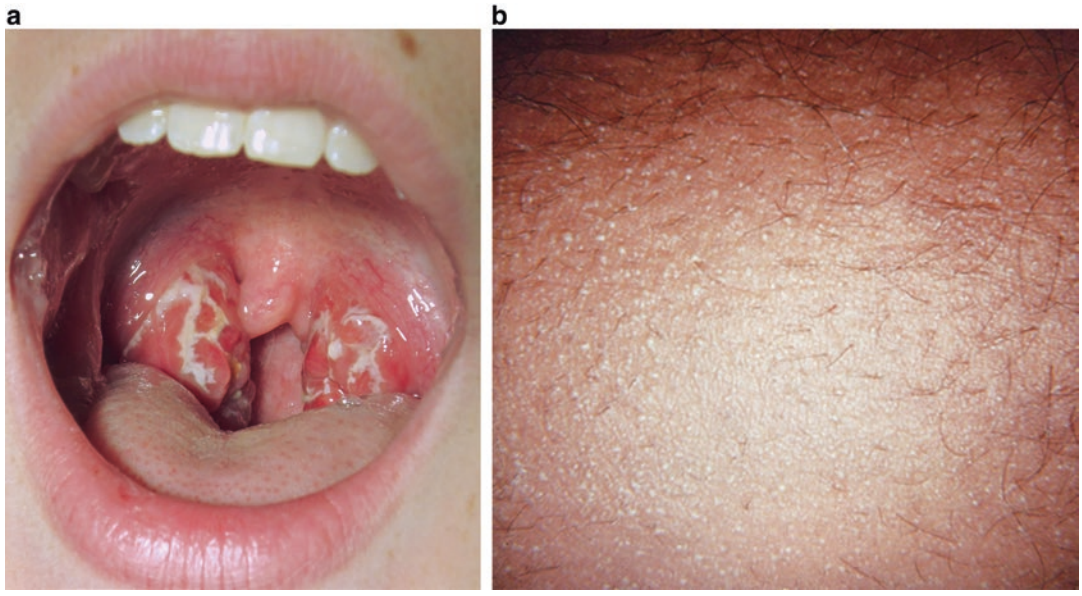

Fig. 17.4 (**a**) Erythema with exudates on the tonsillar pillars in a patient with culture positive Group A *Streptococcus* (Published under a Creative Commons Atrribution-Share Alike 3.0 Unported License. By James Heilman, MD—Own work, CC BY-SA 3.0 and GNU Free Documentation License, Version 2.1 https://commons.wikimedia.org/w/index.php?curid=11596322). (**b**) Sandpaper rash in a patient with scarlet fever secondary to Group A *Streptococcus*. (Reprinted with permission from Partners ID Images Copyright Partners Healthcare System, Inc. All rights reserved.) [37]

Table 17.4 Centor and McIsaac scores

Clinical criteria	Point
Centor score [30]	
Fever	1
Tonsillar exudates	1
Tender anterior cervical adenopathy	1
Absence of cough	1
McIsaac Score [32]	
Fever >38 °C	1
No cough	1
Tender anterior cervical adenopathy	1
Tonsillar swelling or exudate	1
Age 3–14 years	1
Age 15–44 years	0
Age ≥ 45 years	-1

C Celsius, *GAS* Group A *Streptococcus*

Table 17.5 Predictive value of Centor and McIsaac scores for pharyngitis due to group A *Streptococcus*

Score	Percent of patients testing GAS positive by Centor score, %	Percent of patients testing GAS positive by McIsaac score, %
0	3	3
1	7	5
2	17	11
3	34	28
≥4	56	53

commonly used for pediatric patients, adjusts the Centor score based on the patient's age, as children ages 3–14 are more likely to have GAS compared to adults over the age of 45, who are unlikely to have GAS pharyngitis [40]. More specifically, the likelihood of GAS as the etiology of pharyngitis in an adult patient is about 10% [41].

The Infectious Diseases Society of America (IDSA) has published guidelines on the diagnosis and management of GAS pharyngitis. When a patient presents with pharyngotonsillitis, unless rhinorrhea, cough, oral ulcers, and/or hoarseness are present to support a viral etiology, obtaining a throat swab for RADT and/or culture is recommended [34]. To obtain a throat swab, the tongue should be pressed down, and the swab should be rubbed over both tonsils and the posterior pharyngeal wall with caution to avoid touching any other intraoral mucosa or saliva [42]. Rapid antigen detection tests are either optic immunoassays, enzyme-linked immunoadsorbent assay (ELISA), or latex agglutination based on the Lancefield streptococcal group antigen A and have a sensitivity range of 65–96% and specificity of 68–99% [42]. Notably, the group C and G streptococcal antigens are not detected by RADTs. The IDSA guidelines recommend that for children and adolescents a negative RADT should be followed up by a throat culture, but a positive RADT does not require confirmatory testing [34]. For adults, the IDSA guidelines state that a negative RADT does not usually require a confirmatory culture. Anti-streptococcal antibody titers are not recommended in the diagnosis of acute pharyngitis. Post-treatment RADT or throat cultures are also not routinely recommended [34].

Group A *Streptococcus* remains 100% susceptible to penicillin, although some isolates are resistant to clindamycin, doxycycline, or macrolides [43]. A ten-day course of penicillin or amoxicillin is recommended as first-line treatment for GAS pharyngotonsillitis (Table 17.3). An alternative for patients who may have difficulty adhering to 10 days of treatment is to administer one dose of benzathine penicillin intramuscularly (1.2 million units). For those with true but non-life-threatening allergies to penicillins, alternatives include first-generation cephalosporins (for those not allergic) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days. It is worth noting that there is significant resistance to macrolides among GAS in some areas of the world and that macrolides do not cover *Fusobacterium* species, which are important pathogens to consider especially in adolescents and young adults, as discussed later. For this and other reasons, it is worth exploring the penicillin allergy history thoroughly. If patients who report penicillin allergy say they have subsequently tolerated amoxicillin, amoxicillin-clavulanate, cephalexin, or other cephalosporin drugs, those agents are preferred over non-beta lactams for treating GAS pharyngitis.

The goals of GAS pharyngitis treatment are to prevent complications, shorten the duration of illness, and decrease infectivity [35]. Complications or infections that may accompany GAS pharyngitis include peritonsillar abscess (discussed

later), retropharyngeal abscess (Chap. 27), sinusitis (Chap. 11), otitis media (Chap. 4), mastoiditis (Chap. 6), and cervical lymphadenitis (Chap. 26) [35]. Streptococcal toxic shock syndrome is another potential complication of GAS pharyngitis and is associated with shock and organ failure. Nonsuppurative complications include acute rheumatic fever, which is thought to be driven at least in part by molecular mimicry leading to tissue injury, and acute glomerulonephritis. Patients with acute rheumatic fever present with varied clinical manifestations, including arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Late manifestations of acute rheumatic fever include rheumatic heart disease with severe calcification of the mitral valve leading to mitral stenosis. Acute rheumatic fever is rare in the U.S. but remains common in other areas of the world such as Africa and in aboriginal populations in Australia and New Zealand, perhaps due to differences among commonly circulating GAS strains in those areas. Acute glomerulonephritis is a delayed complication of GAS infection with clinical presentations ranging from asymptomatic hematuria to acute nephritic syndrome.

Groups C and G *Streptococcus*

While they can be normal colonizers of the oropharynx, both group C and group G *Streptococcus* have been identified as causes of acute pharyngotonsillitis. In a study of college students presenting with acute sore throat, group C or G *Streptococcus* was detected in 9% [41]. Group C *Streptococcus* has been linked to endemic cases of pharyngitis. In a cohort study evaluating throat swabs from college students presenting with exudative pharyngitis compared to controls, symptomatic subjects were more likely than controls to have group C *Streptococcus* cultured from their swabs [44]. Patients with group C *Streptococcus* pharyngitis tend to present like GAS with fevers and exudative tonsillitis [45]. Group G *Streptococcus* has been implicated as the causative agent of several epidemics of pharyngitis in the community and has been linked to ingesting contaminated foods, particularly dairy and egg products [46, 47]. There is no known association between pharyngitis with group C or G streptococci and acute rheumatic fever.

Fusobacterium necrophorum

Fusobacterium necrophorum, an obligate anaerobic Gram-negative bacillus, is another common cause of pharyngitis, particularly in adolescents and young adults [48, 49]. In a recent study of 312 college students presenting to a student health clinic, *F. necrophorum* was detected in 20.5% of symptomatic cases, whereas GAS was detected in only 10.3% of cases [41]. Co-infection with beta-hemolytic streptococci has been implicated in recurrent episodes of pharyngitis as well [41, 50]. *Fusobacterium necrophorum* is a primary cause of peritonsillar abscess and Lemierre's syndrome, a suppurative internal jugular thrombophlebitis that can cause septic pulmonary emboli. Numerous virulence factors, including leucotoxin, proteolytic enzymes, and haemagluttinin, are felt to contribute to invasive disease [48, 51]. *Fusobacterium necrophorum* is not detected on rapid streptococcal testing methods or on routine throat cultures. *Fusobacterium necrophorum* is usually susceptible to penicillins but some strains are resistant due to the presence of a beta-lactamase; these are susceptible to beta-lactam/beta-lactamase inhibitor combinations such as amoxicillin-clavulanate. Fusobacteria are also susceptible to clindamycin or metronidazole, although metronidazole does not treat group A streptococci. Robert Centor recently reviewed the data for *F. necrophorum* and group A streptococcal pharyngitis and noted that in patients ages 15–24, each of these organisms causes approximately 10% of pharyngitis cases, but that one in 400 cases due to *Fusobacterium* would likely result in Lemierre's syndrome if not treated appropriately [52]. Given the severity of illness associated with this pathogen, consideration should be given for treating of adolescents and young adults who have streptococcus-negative pharyngitis with penicillin plus metronidazole, amoxicillin-clavulanate, or clindamycin. Macrolides lack activity against *F. necrophorum* so should not be used unless combined with

metronidazole, if *Fusobacterium* infection is a consideration [52]. The diagnosis and management of Lemierre syndrome is reviewed in Chap.18.

Arcanobacterium haemolyticum

Arcanobacterium haemolyticum is isolated most commonly in adolescents and young adults. It is a facultative anaerobic Gram-positive bacillus that grows slowly; cultures discarded early may miss isolating the bacteria. Clinically it presents similarly to GAS pharyngitis, although a rash develops in up to 50% approximately 1–4 days after the sore throat begins and may be the predominant clinical manifestation [53]. The rash is a scarlatiniform, maculopapular rash that starts on the extremities and progresses to the trunk, sparing the palms, soles, and face [54]. Macrolides are considered drugs of choice for pharyngitis caused by *A. haemolyticum* [55, 56] (Table 17.3). The optimal dosing and duration, however, is unknown as no prospective clinical trials have been performed. In vitro studies demonstrate susceptibility to beta-lactams, although treatment failures with penicillin have been reported. The organism is also susceptible to clindamycin and doxycycline.

Mycoplasma and *Chlamydia pneumoniae*

"Atypical" bacteria including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* can cause pharyngitis [8, 9]. These are often associated with a cough which may be prolonged (weeks). Diagnosis is difficult due to limited testing options and the fact that the organisms will not grow on routine culture. Some labs may be able to perform PCR, whereas others rely on serologic testing. A review of the laboratory diagnosis of *C. pneumoniae* infections highlights that throat swabs are suitable for specimen testing [57]. In this review, the sensitivity of the various PCR protocols was comparable and PCR had a sensitivity of 10–100 elementary bodies. Based on seroprevalence studies demonstrating that 50–70% of adults have *C. pneumoniae* IgG antibodies, it is thought that reinfection is common and this may limit the ability of serologic testing to make conclusive diagnoses in the setting of acute pharyngitis [57]. Patients with pharyngitis due to *Mycoplasma* or *C. pneumoniae* generally are not treated unless there is concurrent pneumonia. Pneumonia due to these organisms is treated with a macrolide, fluoroquinolone, or doxycycline.

Sexually Transmitted Infections: *Gonorrhea* and *Chlamydia trachomatis*

Neisseria gonorrhoeae and *Chlamydia trachomatis*, both classically sexually transmitted urogenital organisms, are increasingly being isolated from the oropharynx due to oral sex. Pharyngeal infections are generally asymptomatic, but tonsillar exudates have been described. Fever and adenopathy are often absent. In a report from Japan, 225 heterosexual patients with acute tonsillitis, acute pharyngitis, or abnormal pharyngeal sensation underwent a throat swab. Five cases (2.2%) of *N. gonorrhoeae* and two cases (0.9%) of *C. trachomatis* were identified; none of the seven cases had genitourinary symptoms [58]. In a German study of men who have sex with men, the authors found on pharyngeal testing a prevalence of 1.5% for *C. trachomatis* and 5.5% for *N. gonorrhoeae,* but pharyngeal symptoms were reported in only 5% of the cases where one of the two pathogens was detected, highlighting the importance of screening high risk individuals as a public health intervention [59]. Nucleic acid amplification tests (NAATs) are recommended for the detection of *N. gonorrhoeae* in urogenital but not extragenital sites, because NAAT is not approved by the Food and Drug Administration (FDA) for testing oropharyngeal or conjunctival sites [60, 61]. Culture should be performed for pharyngeal infections. Treatment for *N. gonorrhoeae* pharyngitis consists of a single intramuscular dose of ceftriaxone 250 mg, combined with a single dose oral dose of azithromycin 1 g [62]. Treatment of *C. trachomatis* pharyngitis consists of either a single dose of 1 g azithromycin or a course of doxycycline for 7 days [62] (Table 17.3).

Diphtheria

Diphtheria, caused by *Corynebacterium diphtheriae,* is rare in developed countries due to vaccination but is a cause of severe pharyngitis in non-immune persons and can be spread person to person. Diphtheria is discussed in Chap. 19.

Recurrent Tonsillitis and Tonsillectomy

Experts recommend defining "recurrent acute tonsillitis" as >2 distinct episodes in 12 months and chronic tonsillitis as symptoms persisting for >3 months [63]. It is important to consider viral infection with concurrent GAS colonization in patients who present with recurrent tonsillitis complaints and have repeatedly positive swab studies for GAS, since about 15% of the population is colonized with GAS. These colonized patients lack elevated antistreptococcal antibody titers or other evidence of inflammatory response to GAS, and are not thought to be suffering ill consequences from GAS carriage or to be contagious.

Surgical management of recurrent bacterial tonsillitis has historically included tonsillectomy, although this is not performed during an episode of tonsillitis or peritonsillar abscess (the latter sometimes called a "quinsy" tonsillectomy). Both extracapsular (removal of the entire palatine tonsils) and intracapsular (reducing the volume of tonsils without exposing the tonsillar capsule) tonsillectomy have been performed. The effect of tonsillectomy in children is most clearly seen in the reduction of sore throat episodes, particularly in the first year after the procedure [63]. The long-term effect of tonsillectomy in adults is not clear [63, 64]. European guidelines recommend consideration of tonsillectomy only if more than six episodes of tonsillitis have occurred [64]. Clinical practice guidelines in the U.S. from the American Academy of Otolaryngology-Head and Neck Surgery include the following statement regarding tonsillectomy in children ages 1–18 years old: "The panel offered *options* to recommend tonsillectomy for recurrent sore throat infection with a frequency of at least 7 episodes in the past year or at least 5 episodes per year in the past 2 years or at least 3 episodes per year in the past 3 years with documentation in the medical record of each episode of sore throat and 1 or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for group A beta-hemolytic streptococcus" [65].

Peritonsillar Abscess

Peritonsillar abscess, a complication of tonsillitis, occurs when pus collects between the capsule of the palatine tonsil and the pharyngeal muscle [66] (Fig. 17.1b). It has been described as an extreme end of the spectrum of tonsillitis—ranging from tonsillitis to peritonsillar cellulitis to peritonsillar abscess [67].

Clinical Presentation and Epidemiology

Patients present with fever, severe often unilateral sore throat, a muffled "hot potato" voice, drooling, trismus, and ipsilateral ear pain. A course of antibiotics for pharyngitis does not preclude progression to a peritonsillar abscess in some cases. In a large series from Denmark, 73% of cases occurred in patients who were 8–30 years old, and the median duration of symptoms was 5 days [68]. Nearly 40% of patients had taken antibiotics prior to admission, and this was a penicillin-type antibiotic in 94%. On examination, there may be unilateral peritonsillar swelling with displacement of the tonsil (Fig. 17.4).

Peritonsillar abscess is the most common deep neck space infection in children and adults and may be life threatening as it can cause septic shock, airway compromise, necrosis leading to carotid sheath hemorrhage or extension into the deep neck space of the posterior mediastinum [67, 69, 70]. The peak incidence occurs in the teen years, although studies have shown that *F. necrophorum* peritonsillar abscess is more age-dependent than GAS peritonsillar abscess [71].

Studies have also shown an association with smoking in young adults. A retrospective Danish cohort study, with enrolled subjects having a median age of 21, found an odds ratio of 2.5 for the development of peritonsillar abscess in smokers [72].

Microbiology

Group A *Streptococcus* is commonly regarded as the primary peritonsillar abscess pathogen, but normal oral flora are the only organisms cultured in nearly half of peritonsillar abscess cases and *F. necrophorum* appears to be more common than GAS in series that culture for *Fusobacterium* species [66–68]. In a study of 760 patients cultured for peritonsillar abscess in Denmark 2001–2006, 47% of cultures grew only mixed oral flora, 25% grew *F. necrophorum*, and 19% grew GAS [68]. Most of the *Fusobacterium* cases (87%) and group A streptococcal cases (90%) grew in pure culture, although mixtures of these two organisms or other pathogens occurred. Other specific etiologies were uncommon: group C/G streptococci (5%), *Staphylococcus aureus* (2%), and *Haemophilus influenzae* (1%) [68]. Patients with *Fusobacterium* peritonsillar abscess were younger than patients with group A streptococcal peritonsillar abscess, although not by much (median age 18 versus 23, respectively).

Evaluation and Treatment

Patients with uncomplicated peritonsillar abscess may be managed as an outpatient, but many providers recommend an inpatient stay. In the United Kingdom for a first episode of uncomplicated peritonsillar abscess in an immunocompetent host, imaging and cultures are not generally recommended [67]. Intraoral ultrasound can be used to confirm the diagnosis and assist in determining drainage strategies. Computerized axial tomography scan or magnetic resonance imaging can be reserved for cases where there is concern for spread of infection beyond the peritonsillar space [67].

Treatment strategies range from medical management to abscess tonsillectomy. In a retrospective cohort study of patients with a peritonsillar abscess in the U.S., 33% received initial medical management, which included antibiotics in all cases and corticosteroids in 78% [69]. The remaining 67% of patients who received initial surgical management also all received antibiotics but additionally underwent incision and drainage (77%), needle aspiration (22%), or tonsillectomy (2%). Those with larger abscess size, muffled voice, drooling, peritonsillar bulge, trismus, and dysphagia were more likely to receive initial surgical therapy. Patients managed surgically were more likely to receive corticosteroids. Patients treated medically were more likely to be admitted to the hospital, but there was no difference in complication rates, return visits, or failure rates. While there were limitations to the study, including a lack of randomization and limited statistical power due to low failure rates in both groups, the authors argue that for smaller, less advanced abscesses, initial medical therapy may be considered. Medical management includes analgesia, rehydration, and antibiotic therapy—often with empiric penicillin based therapy targeting GAS and broader anaerobic coverage with metronidazole. In a meta-analysis that included 153 combined subjects, steroids were associated with improvement in trismus, reduction in fever and length of stay and percent of patients swallowing water sooner, but there was no difference in eating a normal diet at 7 days [73]. Guidelines suggest that steroids may be useful, but more evidence is needed to make a recommendation [67, 70].

Surgical interventions include aspiration, incision and drainage (I&D), and abscess tonsillectomy. Treatment should be individualized. Aspiration and I&D have a similar failure rate of approximately 10%. Although I&D may relieve pain faster and will drain most of the accumulated pus in one setting, it is a more painful procedure. Needle aspiration management requires the use of a large bore needle to adequately aspirate thick material and often employs three aspirations to achieve acceptable decompression. Similarly, repeat aspiration may be required. In a

review of the literature comparing needle aspiration to I&D, Johnson et al. found that I&D had an initial success rate of 93.7% versus 91.6% for needle aspiration, but this would mean that 48 patients would need to undergo I&D to save one patient an initial treatment failure using aspiration [70]. Unfortunately, the management protocols for both aspiration treatment patients and I&D treatment were variable among the reviewed studies, so there was not uniformity in the post-procedure care including the plans for inpatient versus outpatient treatment, intravenous vs. oral antibiotics, etc. Both needle aspiration and I&D require patient cooperation to be successfully completed in the non-operating room setting. If managed as an outpatient, patients should be seen again within 24–48 h to assure appropriate treatment response. In some cases, I&D is completed under general anesthesia.

Abscess tonsillectomy, which is removal of the tonsil with a peritonsillar abscess ("quinsy tonsillectomy"), has traditionally been preferred if there are complications or if alternative therapy has failed [42]. The tonsillectomy is usually only performed on the abscessed site, because surgery of the inflamed contralateral tonsil can lead to increased complications such as bleeding. Intubation for tonsillectomy may be more challenging in the setting of peritonsillar abscess but may be required for children who may not be able to cooperate with an awake procedure [42]. The procedure itself is done in the fashion of standard extracapsular tonsillectomy, with the bulk of the dissection work already having been accomplished by the accumulation of pus between the tonsil and the superior constrictor. Care must be taken not to dissect through the constrictor muscles into the parapharyngeal space and associated neurovascular structures. Interval tonsillectomy, performed after the peritonsillar abscess has resolved with the goal of preventing recurrence, may be more challenging than abscess tonsillectomy given scarring/fibrosis that develops after the infection. Interval tonsillectomy generally is reserved for those at high risk for recurrence (prior peritonsillar abscess, age <40) [67]. It is important to consider that abscess tonsillectomy has been shown to be as safe as interval tonsillectomy and only one recovery period is necessary for abscess tonsillectomy compared to two with interval tonsillectomy [70]. Yet, with interval tonsillectomy, both tonsils may safely be removed.

Summary

Pharyngitis and tonsillitis are common in both adults and children. Most infectious pharyngitis is viral, especially in adults, but distinguishing viral from bacterial infections clinically is challenging. Guidelines currently recommend using a combination of clinical features to guide the decision to test for GAS, which is more common in children than in adults. Patients who are very likely to have viral pharyngitis based on clinical criteria such as the Centor or McIsaac Criteria should not undergo testing or treatment for GAS. Eliciting a social history is important in patients with pharyngitis, as sexually transmitted infections including HIV, HSV, gonorrhea, and *Chlamydia* are rare but important causes of pharyngitis in patients with epidemiologic risk factors. *Fusobacterium necrophorum* is an important cause of pharyngitis, especially in adolescents and young adults where it may be a more common etiology than GAS. *Fusobacterium* is not treated by macrolides, which are often prescribed for penicillin-allergic patients with pharyngitis, but is susceptible to amoxicillin-clavulanate, penicillin plus metronidazole, or clindamycin. Most isolates are susceptible to penicillin but some strains have a beta-lactamase. Pharyngeal colonization with GAS must be considered in patients who frequently have GAS in throat samples. Peritonsillar abscess may complicate *Fusobacterium* or GAS pharyngitis, but in many cases, cultures grow only oral flora. Treatment usually includes drainage of the abscess plus antibiotic therapy. Antibiotics should be broad-spectrum and include coverage of GAS, oral anaerobes including *Fusobacterium*, *S. aureus*, and *H. influenzae.*

Acknowledgments The authors would like to acknowledge Ramy Elshaboury PharmD., B.C.P.S.-A.Q. I.D. for his review of Table 17.3.

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Lemierre's Syndrome

18

Marios Stavrakas, Petros D. Karkos, and Christos D. Karkos

Introduction

Lemierre's syndrome, sometimes called necrobacillosis or postanginal septicaemia, was first described as a clinical entity by Courmont and Cade in 1900 [1], but was named after André Lemierre, who reported 20 patients with anaerobic "septicaemia" in 1936 [2]. He divided his patients into six groups, based on the source of infection. His first group included infection of the pharynx, particularly tonsillar and peritonsillar abscesses, and he described it as "anaerobic postanginal septicaemia" ("angina" was the old term for sore throat). No formal definition for Lemierre's syndrome exits so there is confusion in the literature as to the case criteria. Most series include only those cases that have a history of recent oropharyngeal infection (pharyngotonsillitis or peritonsillar abscess), clinical or radiological evidence of internal jugular vein thrombosis, and isolation of anaerobic pathogens, mainly *Fusobacterium necrophorum*, from the blood or other sterile sites (Table 18.1) [3]. However, some authors also include cases of septic jugular thrombophlebitis arising from the ear, teeth, or other non-pharyngeal locations [4] or cases due to organisms other than anaerobes (e.g., group A streptococci) [4, 5]. Other series include only those cases that have evidence of septic emboli, in addition to meeting other criteria [5]. In this chapter, the case criteria used will be those in Table 18.1 unless otherwise noted.

Epidemiology

Following the introduction of penicillin in the 1940s and its widespread use for oropharyngeal infections, the incidence of Lemierre's syndrome decreased significantly. No cases of Lemierre's syndrome were reported in the 1950s and 1960s [6], and it was believed to be a "forgotten disease" in the 1980s and 1990s. Since the 1990s, however, there has been an increase in the number of reported cases of Lemierre's syndrome. The reason is unknown but may be related to the more judicious use of antibiotics in recent years for common oropharyngeal infections, or to a wider awareness of Lemierre's syndrome [3, 7]. The use of macrolides to treat patients with pharyngitis who are penicillin-allergic may contribute to the incidence of Lemierre's syndrome, as *F.*

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https://doi.org/10.1007/978-3-319-74835-1_18

Table 18.1 Characteristics typical of Lemierre's syndrome [3]

1. Oropharyngeal infection[a]
2. Clinical or radiological evidence of internal jugular vein thrombosis
3. Isolation of anaerobic pathogens, mainly *Fusobacterium necrophorum*[a]

[a]Some authors include as Lemierre's syndrome cases of septic jugular venous thrombophlebitis that have another source of infection or that are caused by non-anaerobic pathogens

necrophorum is resistant to macrolides. A review by Riodan of 222 cases of Lemierre's syndrome found that 30% of the patients had received antibiotics prior to admission, but half of these patients had received macrolides [5].

Lemierre's syndrome is rare, with an estimated annual incidence of 3.6 cases per one million population [8]. The male-to-female ratio is nearly equal (1:1.2) [3]. While patients' ages have ranged from 2 months to 78 years (median 22 years) [3], most cases occur in previously healthy adolescents or young adults. A review of nearly 60 years of published cases of Lemierre's disease found that 51% of the patients presented during adolescence, 20% presented in their 20's, and 18% presented during the first decade of life [3]. The above figures indicate that Lemierre's syndrome is predominantly a disease of young patients, but without sparing any age group [3]. The reason for the predominance of Lemierre's syndrome in adolescents and young adults may relate to the high frequency of sore throat due to *F. necrophorum* in this age group, in whom this organism may cause more cases of pharyngitis than group A *Streptococcus*. This is discussed further in Chap. 17.

Lemierre's syndrome has a significant mortality rate. According to Lemierre's study in 1936, 18 of the 20 patients that he described subsequently died [2]. This was in the pre-penicillin era, however. The current overall mortality rate is 5%, which is slightly lower compared with rates of 6–22% previously reported in the antibiotic era [3, 9].

Microbiology

The most common pathogen isolated in Lemierre's syndrome is *F. necrophorum,* a Gram-negative anaerobe. Routine throat cultures will fail to detect this organism because it is an obligate anaerobe. Cultures of any abscess should include both anaerobic and aerobic cultures. *Fusobacterium* bacteremia can be detected in blood cultures, as these include both aerobic and anaerobic bottles.

The contribution of *F. necrophorum* to Lemierre's syndrome has been assessed by several studies. Chirinos et al., in a study that included Lemierre's syndrome cases due to any organism, found that of 81.7% of the cases were due to *F. necrophorum*, including 10.1% due to *F. necrophorum* in combination with other organisms, 5.5% were due to other organisms and 12.8% had negative cultures [4]. The other organisms included several types of anaerobes (e.g., various *Bacteroides* species, *Peptostreptococcus*, *Eikenella corrodens*), *Lactobacillus* species, groups A, B, or C *Streptococcus*, viridans streptococci (e.g., *Streptococcus oralis*), and occasional unexpected organisms such as enterococci, *Proteus*, *Candida*. Which of these non-fusobacterial organisms comprised the 5.5% of cases due to "other organisms" alone was not reported. It is not unusual to find *F. necrophorum* alone as the etiology of Lemierre's syndrome [3–5, 10, 11]. Karkos et al. reviewed all cases of Lemierre's syndrome that had positive cultures for anaerobes and found that *F. necrophorum* (57% of cases), *Fusobacterium* species not further identified (30%), and *F. nucleatum* (3%) accounted for 90% of cases, while other anaerobes comprised 10% of cases [3]. The reason that *F. necrophorum* is the major cause of Lemierre's syndrome is due to the organism's virulence factors. *Fusobacterium necrophorum* possesses a lipopolysaccharide endotoxin that is lethal in animal models [12]. The inflammatory response in *F. necrophorum* infections depends on the production of a leukocidin and exotoxin [13]. *Fusobacterium necrophorum* produces more leukocidin and exotoxin than other *Fusobacterium* species and thus *F. necrophorum* is the only *Fusobacterium* species that aggregates human platelets [14].

Of interest, *F. necrophorum* is a much more common pathogen in animals than in humans. There are two subspecies of *F. necrophorum*, *F. necrophorum* subspecies *necrophorum* (seen in animal infections), and *F. necrophorum* subspecies *funduliforme* (seen in human infections) [15, 16]. Both subspecies can produce an extracellular leukotoxin [15]. *Fusobacterium necrophorum* has

been considered as being part of the normal oral flora of humans, but some recent studies question this and postulate that the organism is acquired prior to the onset of pharyngitis symptoms [16].

Pathophysiology

The parapharyngeal space anatomy and its relation with the adjacent vascular structures plays an important role in the pathophysiology of Lemierre's. The parapharyngeal space resembles an inverted cone, extending from the hyoid bone (tip of the cone) to the skull base (base of the cone). Medially lies the buccopharyngeal fascia on the superior constrictor muscle while laterally lies the internal pterygoid muscle, the parotid gland and the mandible. The parapharyngeal space is divided by the styloid process in an anterior (muscular) and a posterior (neurovascular) compartment; the latter contains the carotid artery, internal jugular vein and vagus nerve. Spread of an infection to the posterior compartment can involve the carotid artery or the internal jugular vein, leading to serious systemic complications.

Infection of the parapharyngeal space can be caused by spread of tonsillitis, pharyngitis, parotitis, otitis, mastoiditis, or dental infection. If the infection remains untreated, internal jugular vein thrombosis can occur due to compression or extension of thrombophlebitis of the peritonsillar veins into the jugular vein [10, 12, 17]. More specifically, the progress of the disease has been described in several stages: (1) primary infection (e.g., pharyngitis, tonsillitis), (2) local invasion of the parapharyngeal space (mainly via lymphatic vessels) and internal jugular vein thrombosis, and (3) metastatic complications [4].

Internal jugular vein thrombophlebitis is usually caused by virulence factors of *F. necrophorum.* These factors have been proven to trigger human platelet aggregation both in vitro and in animal models [10, 18, 19].

Clinical Presentation

> *Be not deceived by a comparatively innocent appearing pharynx as the veins of the tonsil may be carrying the death sentence of your patient.*
> *C. Hall, 1939* [20]

Table 18.2 Typical clinical presentations of Lemierre's syndrome [3]

Sore throat	33%[a]
Neck mass	23%
Neck pain	20%
Bone/joint pain	8%
Otalgia and/or otorrhoea	8%
Dental pain	5%
Orbital pain	1%
Gastrointestinal symptoms	1%
Limb weakness	1%

[a]Some authors report a much higher frequency of sore throat [4], [9], and note that dyspnea (24%) and pleuritic chest pain (31%) are common [4].

Clinical presentation is closely associated with the primary site of infection or its sequelae. Most patients have an antecedent pharyngeal infection, but rarely, other sources of infection have been described (e.g., middle ear, larynx, teeth, paranasal sinuses, and orbit) [3]. The most common initial symptom in patients with Lemierre's syndrome is sore throat, followed by neck mass and neck pain (Table 18.2) [3]. Other presenting symptoms can be otalgia, dental pain, pleuritic chest pain, dyspnea, cough, haemoptysis, joint pain, and abdominal pain [7]. Sore throat usually precedes all other symptoms by 4–5 days. The interval can be up to 12 days [14, 16]. In some cases, there is complete resolution of sore throat before the internal jugular vein becomes thrombosed. The neck pain is usually unilateral and may be aggravated, due to irritation of the sternocleidomastoid muscle, on turning the head away from the involved side. A neck mass may be palpable at the angle of the jaw or along the anterior border of the sternocleidomastoid. Patients with Lemierre's syndrome may also have cervical lymphadenitis which can either be unilateral or bilateral. Local complications may be present, such as peritonsillar abscess, parapharyngeal abscess, or paratracheal abscess [4, 21, 22].

Pulmonary symptoms are common in patients with Lemierre's syndrome, usually due to septic pulmonary emboli. One-quarter of patients have dyspnea and one-third have pleuritic chest pain on presentation [4]. The clinician may hear localized crackles and pleural rub on examination. Hemoptysis may be present [2, 4]. Pleural effusions may progress to empyema (10–15%) [8]. Progression to acute respiratory distress syn-

drome, requiring mechanical ventilation, is rare but occurs in some patients (<10%). Septic arthritis has been reported to occur in 13–27% of the patients, with the hip most commonly involved [5]. Osteomyelitis, however, is rare (3%). Abdominal wall abscess is very rare, and one case of pyomyositis has been reported [23]. Abdominal pain is common but intra-abdominal infection (abscess of the liver or spleen, peritonitis) is rare [8]. Retrograde extension of internal jugular vein thrombophlebitis into the cavernous or sigmoid sinus is a life-threatening complication of Lemierre's syndrome [5, 24, 25]. Meningitis or intracerebral abscess has been very rarely described. Other rare complications include cardiac (endocarditis, pericarditis, septic shock) [5, 22, 26], renal (abscess, acute renal failure, hemolytic uremic syndrome) [14, 27–29], and hematologic (thrombocytopenia, disseminated intravascular coagulation, subsequent peripheral ischemia and gangrene) [5, 30, 31].

Diagnosis

> *The appearance and repetition several days after the onset of sore throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible.*
> *A. Lemierre, 1936* [2]

To diagnose Lemierre's syndrome, the clinician should be aware of the existence of the syndrome and its manifestations, both localized and systemic. Clinical suspicion plays a paramount role in early diagnosis of the disease [32] (Table 18.3). It is essential to highlight that doctors rarely encounter patients with Lemierre's syndrome so there is quite frequently a significant delay in diagnosis. According to Alvarez et al., this delay may be on average 5 days from presentation [33]. Isolation of *F. necrophorum* in blood cultures should strongly suggest the diagnosis. A chest x-ray is often the first study performed (92% of cases) and demonstrates pathological findings in 75%, although it may be reported as normal in 10% [3]. In the presence of septic pulmonary emboli, the chest x-ray may reveal multiple peripheral round and wedge-shaped opacities that rapidly progress to cavitation [34].

Table 18.3 Signs and symptoms that increase the clinician's suspicion for Lemierre's syndrome [31]

Increasing suspicion for Lemierre's syndrome
• Pharyngitis that does not resolve in 3–5 days
• Pharyngitis followed by systemic or respiratory symptoms such as fevers, chills, rigors, or dyspnea
• Pharyngitis associated with lateral cervical pain and dysphagia
• Pharyngitis followed by sepsis or multiple pulmonary abscesses

The most commonly requested scan is computed tomography (CT) of the neck and chest (55%), and many authors favor contrast-enhanced CT as the imaging modality of choice (Figs. 18.1 and 18.2). Contrast-enhanced CT is superior to non-contrast CT in identifying additional pathologies, soft tissue abscesses, osteomyelitis, and septic arthritis [35–38]. The CT findings in Lemierre's syndrome include distended veins with enhancing walls, low attenuation intraluminal filling defects, and localized tissue edema [17, 39]. High resolution CT provides higher sensitivity and can contribute significantly in establishing the diagnosis [40].

Doppler ultrasound is another commonly used imaging modality. It is frequently the first step in terms of imaging as it can demonstrate internal jugular vein thrombosis and it is quick, relatively inexpensive, and does not involve exposure to radiation. However, ultrasound provides poor imaging beneath the clavicle and under the mandible and may miss a fresh thrombus because of low echogenicity. Magnetic resonance imaging (MRI) has been suggested as the imaging method of choice because of its high sensitivity, greater soft tissue contrast, and avoidance of radiation [41]. It has not yet been established as superior to CT, mainly because of the higher cost. Other radiological studies that are rarely used now include conventional retrograde angiography, gallium scan, and scintigraphic venography with Technetium (Tc) 99 [14, 42].

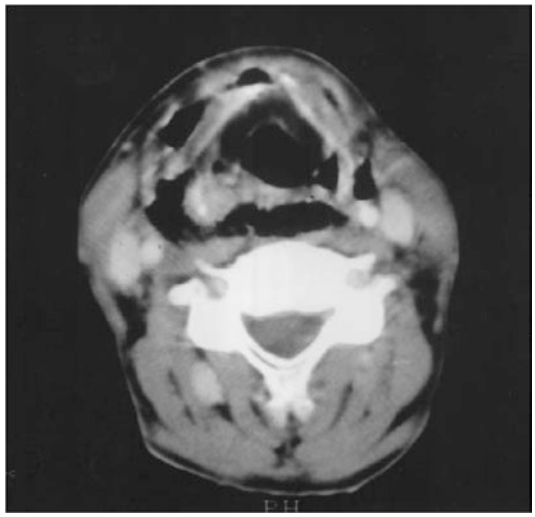

Fig. 18.1 Contrast-enhanced computed tomography scan of the neck in patient with Lemierre's syndrome. Gas is present within the anterior neck compatible with infection with gas-forming organisms. There is also a retropharyngeal space abscess. (Reproduced from Karkos PD, Karkanevatos A, Panagea S, Dingle A, Davies JE. Lemierre's syndrome: how a sore throat can end in disaster. Eur J Emerg Med 2004;11:228–30 [39], with permission from Wolters Kluwer Health)

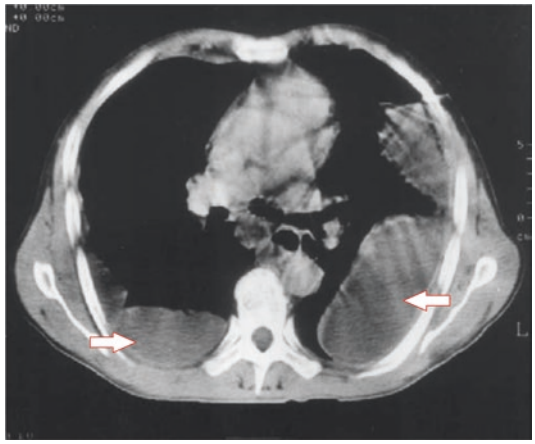

Fig. 18.2 Contrast-enhanced computed tomography scan of the chest. Bilateral empyemas are evident (arrows), and there is also gas in the mediastinum. (From Karkos PD, Karkanevatos A, Panagea S, Dingle A, Davies JE. Lemierre's syndrome: how a sore throat can end in disaster. Eur J Emerg Med 2004;11:228–30 [39], with permission from Wolters Kluwer Health)

Differential Diagnosis

Careful clinical examination, evaluation of the history and presenting symptoms, isolation of *F. necrophorum* in blood cultures, and radiological evidence of the disease can lead to the diagnosis. All the above can also help differentiate Lemierre's syndrome from other infections such as viral pharyngitis, infectious mononucleosis, and pneumonia [5].

Treatment

Antibiotic treatment is the first-line treatment for Lemierre's syndrome. *Fusobacterium necrophorum* is usually susceptible to penicillin, clindamycin, metronidazole, and chloramphenicol. There is a variable response to second and third-generation cephalosporins, and the organism is resistant to macrolides. Penicillin treatment can potentially fail due to β-lactamase production of the infecting microorganism, so a beta-lactam, beta-lactamase combination (e.g., ampicillin-sulbactam), or penicillin plus metronidazole should be prescribed, rather than penicillin alone. Based on the literature, metronidazole is associated with the most rapid response [3, 43], and the addition of metronidazole to any antibiotic regimen should be considered even in cases being treated with a beta-lactam, beta-lactamase combination (e.g., ampicillin-sulbactam). Although clindamycin has activity against most *Fusobacterium* species, up to 10% of isolates may be resistant (see Chap. 2). In addition, many cases of Lemierre's syndrome are due to mixed bacterial infections that include mouth flora streptococci that also may be resistant to clindamycin. Therefore, monotherapy with clindamycin is not recommended. Monotherapy with metronidazole is also inadvisable because of the possibility of a mixed infection; metronidazole will treat only Gram-negative anaerobes. A combination of penicillin and metronidazole is usually recommended [27, 44]. An alternative therapy for penicillin-allergic patients is a carbapenem (e.g., meropenem).

There are no available guidelines regarding the optimal duration of antibiotic treatment, but all patients should receive initial intravenous therapy. Therapy is usually given for a total of 4–6 weeks. Armstrong et al. in their literature review demonstrated that antibiotic treatment duration ranges from 7 to 84 days, with a median of 42 days of therapy [10]. Antibiotics are usually given as initial intravenous therapy (minimum 2 weeks) followed by several weeks of oral antibiotics. However, the optimal course should be individualized for each patient because there is significant variability in the severity of illness and the location and severity of any metastatic infection. Input from an infectious disease specialist in determining the optimal antibiotic choice and duration of treatment is recommended.

The role of anticoagulation in Lemierre's syndrome remains controversial. Although only a minority of patients receives anticoagulation (21%), most patients eventually do well and recover [10]. The risk of thrombosis progression or recurrence is low and this must be weighed against the risk of bleeding from anticoagulation [45]. Anticoagulation should probably be reserved for patients with evidence of retrograde progression of the internal jugular vein thrombus (e.g., to the cavernous sinus). Anticoagulation is usually continued for 3 months, once started [10].

Surgical intervention plays a significant role in the treatment of Lemierre's syndrome. Drainage of any accessible abscesses is essential. That may include neck, parapharyngeal space and peritonsillar abscesses, and distant septic complications, such as lung empyema, septic arthritis, or cerebral abscess [14, 17]. Ligation or resection of the internal jugular vein is a last resort and rarely required: it may be indicated in patients with persistent septic embolization despite aggressive antibiotic therapy [46].

Morbidity and Mortality

The mortality rate in Lemierre's report, published during the pre-penicillin era, was 90% (18 of the 20 patients included in the study group subsequently died) [2]. In more recent studies, mortality is estimated around 5%. Lemierre's syndrome leads to significant morbidity, resulting in prolonged in-hospital and/or intensive care unit stay in about 52% of the cases [3].

Conclusion

Lemierre's syndrome is rare and usually consists of the triad of recent oropharyngeal infection (e.g., pharyngitis, tonsillitis, peritonsillar abscess), septic jugular venous thrombophlebitis, and cultures of blood or abscesses positive for *F. necrophorum*. Many cases have septic pulmonary emboli and patients may present with respiratory symptoms such as dyspnea and pleuritic chest pain. Metronidazole has excellent activity against *F. necrophorum* but does not treat other organisms that may be present in a mixed infection, so an antibiotic combination such as intravenous penicillin plus metronidazole is usually given. Lemierre's syndrome has a 5% mortality even in the antibiotic era, so early diagnosis and appropriate treatment are essential.

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Diphtheria

19

Alakes Kumar Kole and Dalia Chanda Kole

Introduction

Diphtheria, a contagious disease first recognized by Hippocrates in the fifth century BCE, is caused by the Gram-positive bacillus, *Corynebacterium diphtheriae*. The word "diphtheria" comes from the Greek word for leather and refers to the membrane that develops in the throat of an infected person. Klebs was the first to identify the organism (1883) and Loeffler the first to cultivate the organism (1884). The bacterium has been called the "Klebs-Loeffler" bacillus as a consequence. Roux and Yersin first demonstrated that the organism produced a toxin (1888), and von Behring and Kitasato (1890) demonstrated that administering an "anti-serum" or "antitoxin," the antibody-containing serum produced in animals infected with an attenuated strain, would prevent mortality. The first successful treatment of a child with diphtheria using the antitoxin occurred in Germany in 1891. The antitoxin was produced in horses and soon became commercially available. The mortality rate, which had been 50%, fell dramatically as a consequence. It became quickly evident, however, that the antitoxin had to be administered soon after the onset of symptoms in order to be effective.

Large scale vaccination programs began after Ramon and others demonstrated in the 1920s that diphtheria toxin could be rendered safe for vaccination by exposure to heat and formalin, producing a "toxoid." Because of widespread vaccination since then, diphtheria is rarely seen in developed countries today although the disease is still endemic in many developing countries (e.g., India, Nepal, Bangladesh, and Myanmar). Modern vaccination schedules include a 3-dose "primary" vaccine series before age 1, a fourth dose ("booster") during the second year of life, a fifth dose (booster) in early childhood (age 4–7 years), and another booster dose either in adolescence (age 9–15 years) or early adulthood [1, 2]. Booster doses are also recommended every 10 years during adulthood.

Bacteriology

Corynebacterium diphtheriae bacilli are Gram-positive, unencapsulated, non-sporulating, rod-like organisms with a tendency to club at one or both ends (Fig. 19.1). The genus name comes from the Greek "koryne," or club. Diphtheria may be either toxigenic (toxin-producing) or non-toxigenic. Non-toxigenic strains usually

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_19

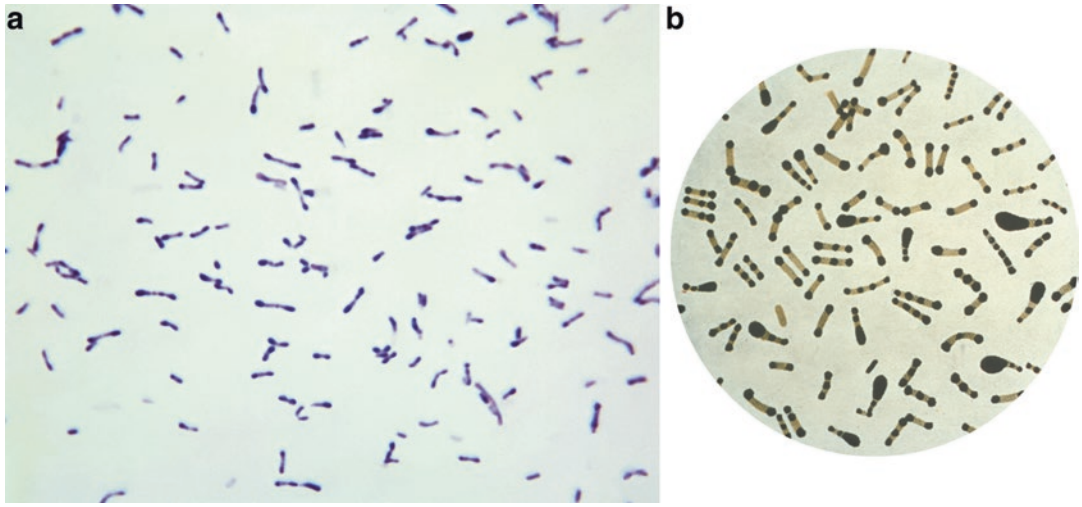

Fig. 19.1 Stains of *Corynebacterium diphtheriae*, after growth on culture media. (**a**) Gram stain, demonstrating that it is a Gram-positive bacillus with "clubbed" ends. (**b**) Albert's stain, taken from an 18-h culture. The clubbed ends are easily seen. From the U.S. Centers for Disease Control and Prevention (CDC) Public Health Image Library, photograph (**a**) attributed to CDC, Dr. Graham Heid, 1965, photograph (**b**) attributed to CDC, 1979

cause a mild form of disease without any major organ damage. Toxigenic strains produce a powerful exotoxin that causes severe disease with both local tissue damage and remote organ dysfunction. Toxin production only occurs by bacteria that have been infected ("lysogenized") by a virus carrying the tox gene. Production of the toxin by the bacterium occurs following depletion of local extracellular iron stores, as high iron concentrations cause a bacterial suppressor gene to be activated that suppresses toxin production.

Diphtheria has four biotypes, gravis, intermedius, mitis, and belfanti, and any may produce toxin [3]. Historically, biotype gravis has been associated with severe illness and a high case fatality rate while mitis has been associated with milder disease. However, mortality may occur from any biotype. In an outbreak of diphtheria in Krygystan in 1995, the mitis biovar caused two-thirds of culture-positive cases and over 40% of the deaths [4].

Corynebacterium diphtheriae will grow on blood agar plates but it is difficult to detect on throat cultures without use of special media. The microbiology laboratory must be alerted to the possibility of diphtheria when throat cultures are sent, as selective media can be used to detect the organism. The throat culture swabs must be transported to the laboratory quickly and media inoculated promptly to optimize growth. Loeffler's media will grow the organism rapidly, but the tellurite-containing Tinsdale media is used more often. Tinsdale media inhibits normal oral flora and *C. diphtheriae* colonies appear black with brown halos (Fig. 19.2). Once there is growth of *C. diphtheriae*, a test for toxin production, such as the modified Elek test, should be performed.

Rarely, another stain of *Corynebacterium*, *C. ulcerans*, may produce diphtheria toxin and produce a respiratory illness identical to diphtheria [5]. Culture methods are similar.

Epidemiology

Humans are the only known reservoir for diphtheria, and cases are spread by contact with respiratory droplets, exudate from skin lesions, or fomites [3]. Diphtheria is highly contagious and patients remain contagious for 48–72 h after starting antibiotic therapy. In untreated or partially treated respiratory cases, patients may be contagious for 2–6 weeks. Humans can be

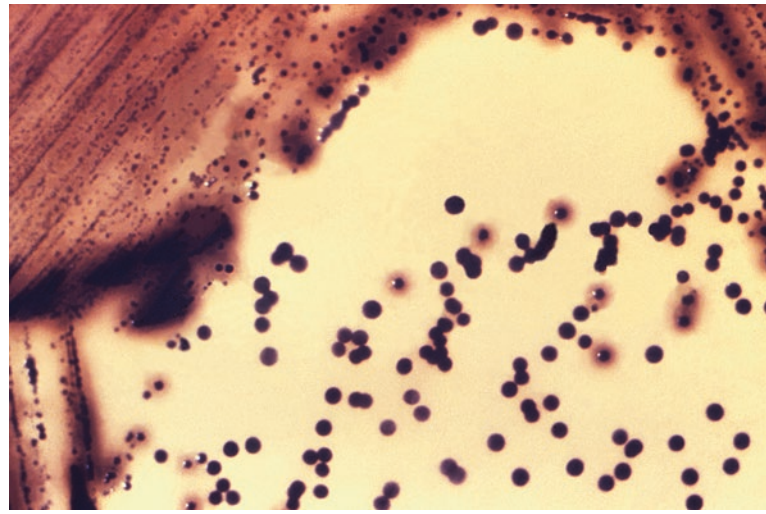

Fig. 19.2 Culture of *Corynebacterium diphtheriae* growing on Tinsdale agar. Colonies are black with brown haloes. From the U.S. Centers for Disease Control and Prevention (CDC) Public Health Image Library, photograph attributed to Dr. Theo Hawkins, 1979

asymptomatic carriers of toxigenic or non-toxigenic diphtheria strains, and these chronic carriers may be contagious for 6 months or more. Immunity in the individual, either natural or from vaccination, does not prevent asymptomatic carriage. Patients with cutaneous diphtheria may contribute to the transmission of diphtheria in a population, as skin lesions are often chronic and *C. diphtheriae* may be transmitted by contact with the exudate.

Diphtheria may occur throughout the year although in temperate climates, the disease occurs mostly in the colder months. This may be due to the increased risk of transmission in crowded indoor conditions.

Diphtheria occurs globally and remains a health threat, particularly in developing nations. The disease is endemic in many developing countries, primarily due to incomplete childhood vaccinations including booster doses. Children have been the major victims of diphtheria historically [6]. Several recent series also reported that the majority of cases (60–85%) occurred in children ages 0–10 years old [7–9]. In contrast, an outbreak during the 1990s in the New Independent States of the former Soviet Union included a large number of adults, with 70% of cases occurring in patients older than 15 [10, 11]. Table 19.1 compares the epidemiology of diphtheria reported by six representative studies from different countries and decades [4, 6–9, 12].

Many adults remain susceptible to diphtheria, primarily due to waning immunity and failure to get the recommended booster doses [13]. A study from the United Kingdom found that only 31% of adults in 1995 were fully immune (titer >0.1 IU/ml) while 39% lacked any detectable antibodies (titer <0.01 IU/ml) [14]. Over 50% of adults age 50–59 lacked immunity in that study. A study from the United States that evaluated immunity in adults 1988–1994 found that only 30% of 70-year-olds were fully immune [15]. A report from Brazil in 2003 found that only 31% of adults age 18–61 had adequate immunity [16].

A decline in vaccination rates in the countries of the former Soviet Union contributed to the largest epidemic of diphtheria in the past 50 years. This epidemic began in 1990 in Russia (Russian Federation), spread to the Ukraine in 1991, then to 12 of the 13 remaining New Independent States (e.g., Baltic states, central Asian nations) during 1993–1994 [11]. The epidemic peaked in 1995 and ultimately resulted in 157,000 cases and 5000 deaths [17]. More than 40% of cases occurred in adults older than 40. The epidemic was controlled by mass immunizations along with early detection and management of cases and close contacts. As a result, new cases in the affected regions decreased by over 95% between 2000 and 2009, from 1.82 to 0.07 cases per million population [18]. By 2009, only Latvia still had an incidence of over one case per million

Table 19.1 Clinical and epidemiologic features of respiratory diphtheria

Study	Naiditch [6]	Kadirova[a] [4]	Pantukosit [7]	Kole [8]	Santos [12]	Jain [9]
Country	United States	Kyrgystan	Thailand	India	Brazil	India
Years	1940–1950	1995	1996	2009–2011	2010	2011–2014
Total number of cases	1433	676	31	200	27	180
No. vaccinations	NR	NR[a]	16%	15%	4%	54%
Partial vaccination (1–2 doses)	NR	NR[a]	65%	10%	59%	21%
Age ≤ 10 years[a]	58%	19%	78%	60%	48% < 7 years old	85%
Age ≤ 20 years[a]	72%	48%	97%	68%	96%	100%
Age 20–40 years	19%	42%	3%	32% > 20 years	4%	0
Age ≥ 40 years	9%	10%	0	15% >30 years	0	0
Presenting features						
– Pseudomembrane	97%	76%[a]	100%	NR	93%	100%
– Sore throat	NR	69%	90%	74%	NR	58%
– Fever	NR	79%	100%[a]	56%	NR	98%
– Dysphagia	NR	35%	3%	24%	NR	90%
– Bull neck	12%	8%	0	16%	52%	34%
– Nasal regurgitation	NR	NR	NR	10%	NR	NR
– Shortness of breath	NR	5%	NR	8%	NR	35%
– Hoarseness	NR	15%	10%	4%	NR	13%
– Bleeding	NR	NR	3%	1%	NR	6%
Complications						
– Airway compromise	NR	NR	10%	7%	NR	NR
– Cardiac	9%	22%	10%	68%[a]	NR	30%
– Neurologic	6%	5%	0	15%	15%	10%
Death	10%	3%	0	2.5%	11%	24%

NR not reported

[a]Notes: In various studies, age group cut-off points were either <10 years old or ≤10 years old. In the Kadirova study, 68% of pediatric patients (age 0–19) received <3 doses vaccine, 24% "pre-membranous" patients may have included carriers (see the text), rates for some clinical features are based on a graph. In the Pantukosit study, all patients had fever but 69% of patients had low-grade fever (<38 °C = 100.4 °F). In the Kole study, only 4% of patients had symptomatic cardiac complications

population, the WHO target incidence, but Latvia's rate had fallen dramatically from 111 cases per million in 2000 to 2.67 per million in 2009 [18]. The major age groups affected in the epidemic were adolescents and adults, many of whom had been at least partially vaccinated, but deaths occurred primarily in unvaccinated adults and infants. Biovar gravis caused 60–80% of cases overall and 99% of cases in Latvia [18].

In Western Europe and the U.S., rates of diphtheria have been low in the vaccine era. In the U.S., widespread vaccination programs that began in the 1920s led to a dramatic decrease in the incidence of diphtheria, from 200,000 cases in 1921 to 0–2 cases annually since 2000. A study of U.S. cases 1971–1981 found that only 5% of all U.S. counties reported any cases of non-cutaneous diphtheria during that decade, nearly all from western states, and Native Americans (22.6 cases per million) and children age 14 and younger (0.8 cases per million) had the highest rates [19]. The mortality rate in unvaccinated patients was tenfold higher than in fully vaccinated patients (13.4% versus 1.3%). The diphtheria incidence declined over the decade, and there were only two cases in the U.S. in 1980 (0.01 cases per million population) [19]. The incidence has decreased even further since then, and only

two cases of diphtheria have occurred in the U.S. 2004–2015 [20]. This reflects the high U.S. DTP3 (three doses of diphtheria, tetanus, pertussis vaccine) vaccination rate [21]. However, vigilance for diphtheria must be maintained even in countries with low rates of diphtheria, as imported cases in visitors and returned travelers may occur. One such case occurred in Massachusetts in 2004 when a 60-year-old woman of unknown vaccination status developed a sore throat (positive on culture for toxigenic *C. diphtheriae*) following a trip to a diphtheria-endemic Caribbean island [22]. A family member who accompanied her on the trip was found to be a carrier.

Worldwide, approximately 5000–8000 cases of diphtheria have been reported to the WHO annually over the past decade. Diphtheria is still endemic in several tropical countries, with the greatest number of cases reported to the WHO most recently (2015) from India (2365 cases), Madagascar (1627 cases), and Lao People's Democratic Republic (194 cases) [21]. Considering the populations of those countries, the incidence in 2015 was highest in Madagascar (67 cases per million population), followed by Loa People's Democratic Republic (29 cases per million) and India (1.8 cases per million). The true incidence of worldwide diphtheria may be higher, as cases in rural areas may be underreported. The main cause of the persistence of diphtheria in developing countries is incomplete childhood vaccination including booster vaccinations. However, significant progress has been made over the past decade. According to a WHO report, in 2005 only 65% of the population in India and 49% in Madagascar had received DPT3 but this rate increased to 87% and 89%, respectively, in 2015 [21]. As a consequence, diphtheria cases in India and elsewhere are gradually declining [23].

A recent concern has been inadequate immunologic response to vaccination in infants and children in some countries. Diphtheria-containing vaccines usually produce protective immunity in over 90% of children who have received three doses. However, a recent study found that only 56% of 1100 children in Lao People's Democratic Republic had protective diphtheria antibody levels after three doses of vaccine although 90% had detectable levels [24]. The authors of that study hypothesized that various factors, such as freezing of the vaccine during transportation (vaccine should be refrigerated not frozen), inaccurate record-keeping, suboptimal timing of vaccine administration, and childhood malnutrition, may have contributed to the low vaccine response rate.

Pathogenesis

In a susceptible host, *C. diphtheriae* colonizes the mucosa of respiratory tract and within the first few days, toxigenic strains produce a potent exotoxin that causes local tissue inflammation and necrosis resulting in the formation of dense pseudomembrane (exudate, inflammatory cells, necrotic tissue, and organisms). Toxin is also absorbed into systemic circulation causing dysfunction of various organs (heart, nervous system, kidneys). The exotoxin has two protein fragments (A and B), of which the B fragment binds to cell receptors enabling fragment A to enter the cell cytosol and inhibit protein synthesis.

Non-toxigenic strains usually cause mild to moderate pharyngitis and do not form the typical pseudomembrane. Non-toxigenic strains very rarely become toxigenic (by lysogenic conversion). Occasionally non-toxigenic strains cause invasive infections such as bacteremia, endocarditis, mycotic aneurysms, septic arthritis, and osteomyelitis [25].

Clinical Manifestations

Respiratory Diphtheria

Classic or "Faucial" Diphtheria

This is the most common form of diphtheria, and symptoms typically begin after an incubation period of 2–5 days (range 1–10 days). Patients initially complain of sore throat (approximately 80%), malaise, pain with swallowing, and mild fever (usually less than 101 °F). In a study from Thailand, 100% of patients had fever but this was less than 100.4 °F in nearly 70% of cases [7]. Pharyngeal injection and cervical lymphadenop-

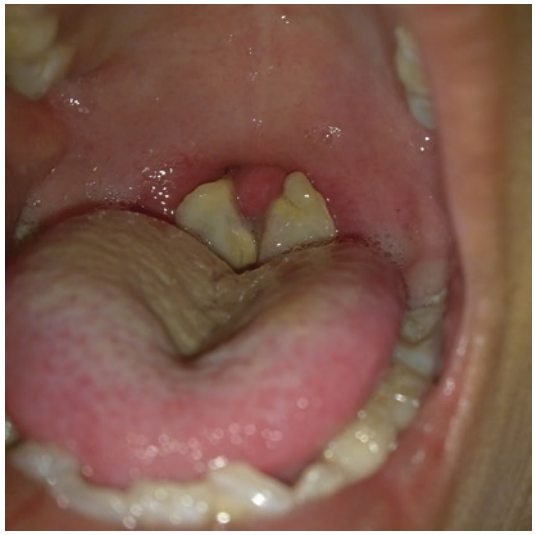

Fig. 19.3 Faucial diphtheria

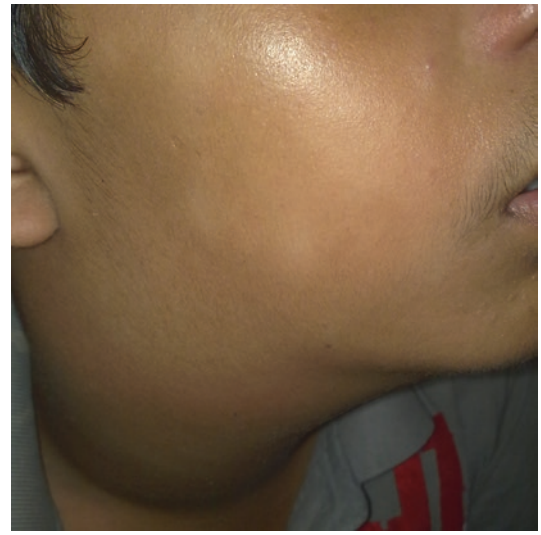

Fig. 19.4 "Bull neck" manifestation of diphtheria

athy may be present. After 2–3 days, a bluish-white membrane develops covering one or both tonsils. This membrane sometimes extends to the soft palate, pharynx, or even larynx. The membrane gradually becomes grayish or even black (in the presence of bleeding) (Fig. 19.3). The membrane is adherent to the underlying tissues and attempts to remove it resulting in bleeding. This extensive pseudomembrane formation along with tissue edema or associated local bleeding may result in airway obstruction, which may lead to wheezing, a choking sensation, or development of stridor. The clinical features reported by several series are noted in Table 19.1.

In an undiagnosed or very severe case, there may be marked enlargement of cervical lymph nodes and this, along with soft tissue swelling, produces a characteristic "bull neck" appearance (Fig. 19.4). In such cases more toxin is absorbed into the circulation causing severe prostration, tachycardia, hypotension, stupor, coma, or even death despite adequate medical treatment. A bull neck presentation is associated with a high mortality rate (>50%).

The severity of infection on presentation usually correlates with the extent of the pseudomembrane. In 1954, Naiditch and Bower reported clinical features of 1433 cases of diphtheria treated in the 1940s in Los Angeles, California, and the 61% of cases with tonsillopharyngeal involvement alone had a mortality of 1.8%, while cases with extension to other areas (e.g., larynx, tracheobronchial tree) had a mortality of 24%, [6]. Bull neck cases had a mortality of 33%.

A pseudomembrane is a major clinical feature of diphtheria but may be absent in rare cases. A pseudomembrane was reported as absent in 2.6% of cases in the Naiditch study but mortality was still 5% in these patients [6]. In most series, a pseudomembrane is present in over 95% of diphtheria cases. However, in diphtheria outbreaks in which patients with sore throat are routinely screened for diphtheria, a higher percentage of cases lack a pseudomembrane. These patients may represent either diphtheria carriers (sore throat not due to diphtheria) or "pre-membranous" diphtheria. In the 1995 Kyrgystan outbreak, 24% of cases with positive diphtheria cultures presented without a pseudomembrane, but all patients with sore throat were screened for diphtheria during that outbreak so carriers would be included in that number [4].

Nasal Diphtheria

Primary nasal diphtheria is a mild form of diphtheria seen mainly in infants and young children. Patients present with catarrhal symptoms, unilateral nasal discharge (mostly blood stained), and

excoriation of nostril. After careful examination, a grayish-white pseudomembrane is usually seen on the nasal septum that bleeds on attempts to dislodge it. Only 1.9% of cases in the 1954 Los Angeles study had primary nasal diphtheria: 22% were younger than 12 months old, 44% were 1–5 years old, and none died [6].

Laryngeal or Tracheobronchial Diphtheria

Isolated primary laryngeal diphtheria is very rare, comprising 1.4% of diphtheria cases in one study [6]. Most cases with laryngeal involvement are due to faucial diphtheria with secondary extension to the larynx. Cases of primary laryngeal diphtheria are diagnosed only by an otolaryngologist when a patient is referred with history of low grade fever, barking cough, and early development of hoarse voice and dyspnea. The main danger of laryngeal diphtheria is the development of sudden and early airway obstruction requiring either urgent endoscopic removal of pseudomembrane or tracheotomy, or both.

Tracheobronchial diphtheria occurs as a downward extension of faucial or laryngeal diphtheria. In the 1954 Los Angeles study, the tracheobronchial tree was involved in 6.7% of cases and had a mortality of 67% [6]. Urgent intubation or tracheostomy, allowing removal of diphtheria membranes, may be life-saving.

"Malignant" Diphtheria (Diphtheria Gravis)

This is an older term but still used occasionally today. Patients with malignant diphtheria present with high fever, severe sore throat, diffuse swelling of the neck (bull neck), tachycardia, hypotension, stridor, or cyanosis. The typical patient is unvaccinated or only partially vaccinated, malnourished, and has a history of presenting late to clinical care, or of significant delay in the correct diagnosis of diphtheria. Early myocardial involvement with advanced conduction abnormalities and severe bleeding from local sites contribute to a high mortality (>50%). A 1943 study by Frobisher reported similar features of malignant diphtheria, emphasizing the sudden onset, high fever, bull neck, and frequent cardiac toxicity seen in these cases [26]. Frobisher noted that tonsils are usually very large but that pseudomembrane formation may be "slight."

Complications of Respiratory Diphtheria

Airway Complications

Airway complications may arise in respiratory tract diphtheria as a result of local obstruction by the pseudomembrane or by secondary aspiration pneumonia. Acute airway obstruction is a potentially lethal complication and requires urgent laryngoscopic removal of membrane and/or tracheostomy. The causes are either extension or aspiration of pseudomembrane into the larynx, laryngospasm, edema, or bleeding.

Cardiac Toxicity

Evidence of cardiac toxicity occurs in up to two-thirds of patients but many cases are subclinical [27]. A vaccination history does not preclude cardiac toxicity. In a series from India involving 200 diphtheria cases treated from 2009 to 2011, 75% of patients had a vaccination history but evidence of cardiac involvement developed in 68% [8]. In most of these cases, myocarditis was subclinical and detected by electrocardiographic screening. In another study from India involving 180 pediatric patients (ages 0–20 years old), cardiac complications occurred in 30% and were associated with a 52% mortality [9]. Over half of the patients in that study lacked immunity.

Diphtheria myocarditis with clinical manifestations is associated with a high mortality (60–70%). Myocarditis typically develops at the end of the first week of illness, but may develop 2–3 weeks after onset [28]. Risk factors include extensive pseudomembrane formation, presence of a bull neck, and delayed initiation of treatment [29–31]. Diphtheria toxin is directly cardiotoxic, causing DNA fragmentation, cytolysis that leads to hyaline degeneration, and necrosis of the myocardium [32]. The majority of patients with cardiac involvement from diphtheria remain asymptomatic and have only electrocardiogram (ECG) changes and/or elevation of aspartate

tranaminase (AST). But symptomatic patients develop shortness of breath, disproportionate tachycardia, and in severe cases, features of cardiac failure. The transient nonspecific ECG abnormalities (e.g., repolarization abnormality, abnormal Q wave, QTc prolongation, T wave inversion, ST segment elevation) are frequent but "sickle-like sagging" of the ST segment is more specific. First degree heart block may occur and progress to more severe forms of block, such as hemiblock, bundle branch block, atrioventricular (A-V) dissociation, or complete heart block. In a study from Chile of 167 patients with diphtheria 1976–1986, 27% developed myocarditis including 11% with severe forms of heart block [33]. Several patients died within 48 h of pacemaker insertion due to cardiogenic shock or ventricular fibrillation. In a more recent study from Vietnam, 21% of the 154 children with diphtheria 1995–1996 had cardiac involvement: this developed 2–20 days after onset of diphtheria [34]. Mortality in children with cardiac involvement was 38%, and ischemic changes and complete heart block on initial ECG were risk factors for mortality. The severity of diphtheria myocarditis usually parallels the elevation of AST so AST levels may be helpful in monitoring cases [27]. Survivors of diphtheritic myocarditis eventually recover normal cardiac function. In the Vietnam study, 15 survivors of myocarditis returned for 1 month follow-up and all had normal ECGs [34].

Neurologic Toxicity

Neuropathy in diphtheria is due to toxin-mediated demyelination of nerves and occurs in 5–15% of cases ([4, 6, 9, 12]). The incidence is directly related to the severity of local disease; mild disease rarely produces neuropathy [27, 35], while up to 75% of patients with severe disease may develop neuropathy. The initial features, which usually relate to local effects of the toxin, include palatal paralysis, perioral numbness, and bulbar findings. Patients complain of numbness in the lips, tongue, or gums [36]. Paralysis of the soft palate and posterior pharynx may cause regurgitation of swallowed fluids through the nose [27]. Dysphonia (nasal voice) and dysphagia occur due to involvement of the ninth and tenth cranial nerves (bulbar involvement). Involvement of the third cranial nerve may occur, causing diplopia, ptosis, and anisocoria. The seventh cranial nerve may be affected and lead to facial palsy. Involvement of the third and seventh cranial nerves occurred in 30% and 10% of patients, respectively, in one series of patients with neurologic complications of diphtheria [37].

Neurologic involvement usually develops at the end of the second week of illness but may occur weeks to months later. Logina and Donaghy reported clinical features of 50 patients from Latvia with diphtheria neuropathy [37]. The first neurologic symptoms were bulbar in 98% of patients and began a median of 10 days (range 2–50) after onset of respiratory diphtheria. Limb symptoms also occurred in most (90%) patients, developing at a median of 37 days (range 12–63) after onset of diphtheria. Limb symptoms followed bulbar symptoms in all but one patient, and developed as bulbar symptoms were improving in 30% of cases. Peak severity of neurologic symptoms occurred at a median of 49 days and improvement began at a median of 73 days.

Peripheral nerve involvement usually develops 10 days to 3 months later [27]. Weakness begins in the proximal muscles of the extremities and extends distally. Rarely the presentation may be as acute flaccid paralysis, mimicking poliomyelitis. In many countries (e.g., India) the existing surveillance for acute flaccid paralysis identifies a small portion of diphtheria cases with neurological involvement [35]. Severe motor involvement may occur and patients may develop either quadriparesis or quadriplegia with hypotonia, areflexia, and rarely diaphragmatic paralysis. This presentation may mimic acute demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), although the much higher prevalence of bulbar involvement and the descending pattern indicate diphtheria polyneuropathy [37]. Peripheral sensory involvement is common. In Logina and Donaghy's study, 38% of patients had mild and 46% moderate sensory involvement [37]. The involvement may be in a stocking-glove pattern.

Various combinations of autonomic disturbances (sympathetic and parasympathetic) may develop and may cause sudden death as a result of fulminant autonomic dysfunctions.

Rarely, neurological involvement may be biphasic, with secondary worsening of bulbar symptoms occurring after initial recovery [38, 39]. Eventually, however, most patients with diphtheria neuropathy recover full neurologic function although recovery may be very slow. Logina and Donaghy reported that 97% of patients still had some neurologic symptoms at one year follow-up, but these symptoms were mild in nearly all cases (mild numbness, paresthesias, or weakness) [37]. Only 6% of patients required a cane or other walking aids.

Renal and Other Complications

Renal injury usually occurs either from hypotension or from a toxin-mediated effect on the renal tubules. The incidence varies from less than 1% to 16% [6, 9]. Serum sickness occurs in a few cases following antitoxin therapy and is often manifested as mild, urticaria-like localized cutaneous lesions that persist for a few hours or days. Bacteremia may occur from toxigenic or nontoxigenic diphtheria. Diphtheria may also produce encephalitis.

Cutaneous Diphtheria

Cutaneous diphtheria is usually caused by nontoxigenic strains but may be caused by toxigenic strains. This type of diphtheria is more common than respiratory diphtheria in many developing countries, but the incidence has decreased following socioeconomic improvement in these countries. Cases may also be seen in developed countries with a very low incidence of diphtheria. From 1995 to 2000, 17 cases of cutaneous diphtheria caused by toxigenic strains were detected in the United Kingdom, and all were imported cases [40].

The disease manifests as a scaling rash or a nonhealing, ulcerated lesion with an elevated margin (Fig. 19.5). Epidemiologically, cutaneous diphtheria is important primarily because of its role in the spread of diphtheria strains. Cutaneous diphtheria can be more contagious than the respiratory type. Skin lesions typically follow an indolent course, persisting for weeks to months, and rarely cause respiratory diphtheria [41, 42].

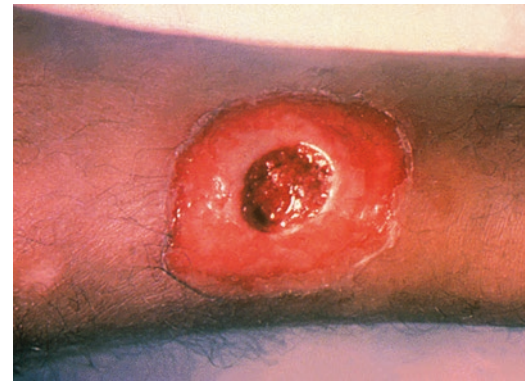

Fig. 19.5 Cutaneous diphtheria involving the leg. From the U.S. Centers for Disease Control and Prevention (CDC), Public Health Image Library

Diagnosis is usually suspected on the basis of clinical features and epidemiology, particularly if there is a history of travel to a diphtheria-endemic regions, and is confirmed by bacterial culture.

Cutaneous diphtheria is treated with erythromycin or penicillin. Antitoxin is not routinely indicated because toxigenic complications are rare and most cases are caused by nontoxigenic strains. Following treatment, lesions usually heal within 12 weeks but sometimes require more than a year [13, 25, 43].

Non-respiratory, Non-cutaneous Diphtheria

Rarely diphtheria may involve other mucous surfaces such as the conjunctiva (purulent ulcerative conjunctivitis) and vulvo-vagina (ulcerative vulvovaginitis), or may involve the external auditory canal (recurrent otitis externa). The incidence of these manifestations is very rare. The 1433 cases reported in the 1954 Los Angeles study included only three cases involving the eye, five involving the ear, and 1 involving the vagina [6].

Diagnosis

Diphtheria is diagnosed on the basis of the clinical presentation, with confirmation by culture of the organism. Treatment with antitoxin and anti-

biotics should not be delayed in a suspected case of respiratory diphtheria, because urgent therapy is necessary to avoid fatal complications. Cultures may require 72 h or more to turn positive, and fail to grow in some cases (e.g., prior antibiotic therapy). In developed countries, early diagnosis may be difficult because of atypical presentations and because the disease is very rare. Routine laboratory tests are usually nonspecific and the white blood count is usually only moderately elevated. A checklist may be helpful for physicians who rarely see cases of diphtheria (Table 19.2) [44].

An accurate bacteriological diagnosis is crucial for therapy and epidemiological purposes. A culture should be obtained from the nose and throat, including beneath the membrane if possible. Culture swabs must be transported to the microbiology laboratory quickly for prompt inoculation on appropriate media. The laboratory should be alerted about the possibility of diphtheria and the need for special media. The throat swabs should be inoculated on both tellurite media such as Tinsdale agar (for selective growth of *C. diphtheriae*) and blood agar (for routine throat culture). In cases of prior antibiotic therapy, the culture may be negative and in such cases, a positive polymerase chain reaction (diphtheria tox gene) or isolation of the organism from close contacts is helpful for diagnosis. Once *C. diphtheriae* bacilli are isolated, they must be tested for toxin production either by polymerase chain reaction assay or Elek's immunoprecipitation test [45].

The differential diagnosis of diphtheria includes other causes of acute pharyngitis (see Chap. 17). Table 19.3 lists some of the features of various types of pharyngitis and tonsillitis. The distinctive feature of diphtheria is the pseudomembrane, although this may be missing or patchy in some patients with early diphtheria.

It is worth noting that *Corynebacterium ulcerans*, a species usually associated with animal infections, may produce diphtheria toxin and cause a disease in humans identical to that caused by *C. diphtheriae*. Any throat culture that grows *C. ulcerans* should be tested for toxin production [46].

Table 19.2 Checklist for assessing a patient with suspected diphtheria

	Symptom or event	Yes/no
1. Suspect case	Pharyngitis, naso-pharyngitis, tonsillitis, laryngitis, tracheitis, or a combination of these. Absent or low-grade fever	
	Grayish, adherent pseudomembrane present	
	Membrane bleeds if manipulated	
2. Probable case	Suspect case above plus 1 or more of the following	
	• Stridor	
	• Bull neck (cervical edema)	
	• Toxic circulatory collapse	
	• Acute renal insufficiency	
	• Submucosal or subcutaneous peterchiae	
	• Myocarditis	
	• Death	
	Recently returned (<2 weeks) from travel to area with endemic diphtheria?	
	Recent contact (<2 weeks) with confirmed diphtheria case or carrier?	
	Recent contact (<2 weeks) with visitor from area with endemic diphtheria?	
	Recent contact with dairy or farm animals?	
	Immunization status: never immunized or incompletely immunized, or not up-to-date with booster vaccinations containing diphtheria vaccine (e.g., any DTaP/DT/Tdap/Td shot within the past 10 years?)	
3. Laboratory confirmed case	Positive culture of *C. diphtheriae* (or *C. ulcerans*) AND positive Elek Test OR positive PCR for tox gene (positive for subunit A and B)	

Adapted from the Centers for Disease Control and Prevention [44]

Treatment of Respiratory Diphtheria

In a suspected case of diphtheria, the patient should be assessed carefully with special attention to airway patency and any cardiovascular instability (hypotension or conduction abnor-

Table 19.3 The differential diagnosis of respiratory diphtheria

Infection[a]	Microbiology[a]	Clinical features[a]
Diphtheria	*Corynebacterium diphtheria*	Sore throat, adherent pseudomembrane on tonsils and/or pharynx that bleeds with attempts at removal, low-grade fever, pain or difficulty swallowing, bull neck
Bacterial pharyngitis (see Chap. 17)	Group A *Streptococcus*, Group C/G *Streptococcus*, *Fusobacterium necrophorum*, others (see Chap. 17)	Sore throat, tonsillopharyngeal erythema and edema, exudate may be present but no pseudomembrane; fever may be present, tender anterior cervical lymphadenopathy. In Group A streptococcal pharyngitis, a rash (scarletiniform) or red tongue papillae (strawberry tongue) may be present
Infectious mononucleosis (see Chap. 17)	Epstein-Barr virus	Sore throat, tonsillopharyngeal erythema, cervical lymphadenopathy; in some cases, generalized maculopapular skin rash, palatal petechiae; positive heterophile antibody test usually but may be negative in early cases
Acute epiglottis	Hemophilus influenzae type b, Group A or C *Streptococcus*, *Streptococcus pneumoniae*	Severe sore throat, dysphagia, muffled voice, pain on gentle palpation over larynx; swollen epiglottis on endoscopic examination
Acute peritonsillar abscess (see Chap. 17)	Normal oral flora, Group A *Streptococcus*, *Fusobacterium necrophorum*	Sore throat, severe on one side, Trismus may be present, unilateral swelling and redness of peritonsillar area, asymmetry of soft palate, contralateral shifting of uvula
Oropharyngeal and/or esophageal candidiasis	*Candida albicans*, other *Candida* species	Sore throat (may be mild), creamy white spots or patches on tongue or mucous membranes, pain with swallowing; patient usually immunosuppressed (thrush is common in healthy infants, however)
Vincent's angina	*Borrelia vincentii* and *Bacillus fusiformis*	Severe throat pain but mostly localized in the gums, gum necrosis with occasional bleeding, cervical lymphadenopathy
Acute retropharyngeal abscess (see Chap. 27)	Aerobes (e.g., *Staphylococcus aureus*, Group A *Streptococcus*, *Haemophilus influenzae*) plus anaerobes	Fever (often high), sore throat, pain with swallowing, retropharyngeal bulge, neck stiffness

[a]Not all-inclusive

mality). The patient should be referred urgently to a hospital where specialists are available (e.g., infectious disease physicians, otolaryngologists, cardiologists, and anesthesiologists), along with a skilled nursing staff and the facility for barrier nursing care. Most importantly, diphtheria antitoxin must be obtained on an emergency basis and administered as soon as possible.

All suspected diphtheria cases should be isolated immediately in the emergency department and hospital and treated with droplet precautions and contact precautions. Of note, the CDC recommends only droplet precautions for respiratory diphtheria [47], although it notes that fomite transmission is possible. Therefore, it seems prudent to use both droplet and contact precautions until the patient is no longer contagious (two negative cultures obtained 24 h apart).

Patients should be evaluated promptly, including evaluation for severity of symptoms, overall clinical status, vital signs, and development of any stridor. A throat swab should be collected, from the pseudomembrane if possible, by a physician or other trained healthcare professional. The throat swab should be sent without delay to the laboratory for stains (Gram stain and Albert's stain) plus culture (routine blood agar plus specialized media for *C. diphtheriae* such as Loeffler's slant and/or Tinsdale agar). The laboratory should be alerted about the potential case of diphtheria.

Treatment with diphtheria antitoxin and antibiotics should be started immediately in cases that are clinically compatible with diphtheria, without waiting for results of cultures. All patients should be monitored closely for the development of any respiratory or cardiac complication. Severe cases having a toxic appearance require continuous monitoring, and may require resuscitative measures (e.g., tracheos-

tomy or temporary cardiac pacing). In cases with airway compromise, immediate action should be taken (e.g., tracheostomy, intubation, clearing of pseudomembrane endoscopically by an otolaryngologist).

Diphtheria Antitoxin

Diphtheria antitoxin, the mainstay of therapy, is a specific agent used to neutralize unbound toxin, thus preventing further progression of organ damage (Fig. 19.6). Since the antitoxin is prepared from horse serum, every patient must be first tested for hypersensitivity by a skin test. Patients with positive or equivocal skin tests will require a desensitization protocol to receive the antitoxin safely. A skin test protocol is listed in the CDC website [48]. Informed consent is mandatory (parents or legal guardian in cases of minors), unless the patient cannot give consent, no next-of-kin or legal guardian is available, the illness is life-threatening and therapy with antitoxin cannot be delayed [48]. The physician should enquire about an atopic history (asthma, allergic rhinitis, urticaria), or allergy to horse serum: the CDC recommends using a desensitization protocol for these patients as well, regardless of the result of the skin test [48]. A negative skin test does not always preclude the chance of a severe allergic reaction. In addition, patients who have received antihistamines within the previous 24 h or more (depending on the antihistamine) may have falsely negative skin test results. The CDC notes that "possibly other drugs such as tricyclic antidepressants" may interfere with the skin test [48]. The recommended desensitization protocol may vary by manufacturer; the protocol recommended by the CDC involves administering an increasing dose of dilute antitoxin every 15 min over a 3-h period, beginning with 0.1 ml of a 1:1000 dilution [48]. Trained personnel and necessary medications and equipment (e.g., epinephrine, intubation kit) should be readily available to treat any severe allergic reactions such as anaphylaxis.

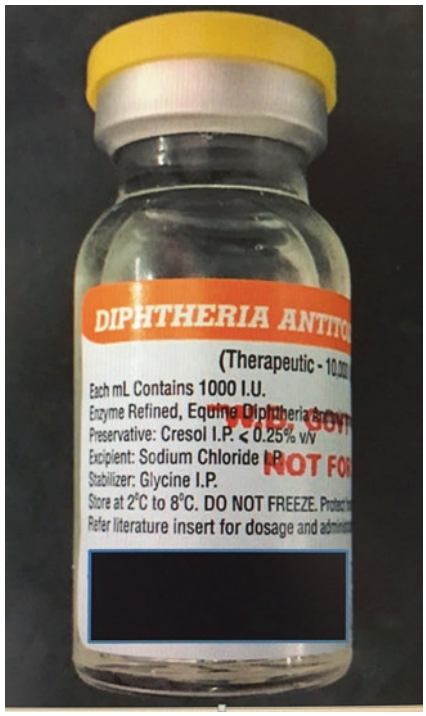

Fig. 19.6 Diphtheria antitoxin

The recommended dose of antitoxin depends mainly on the time elapsed since the onset of the first symptoms of diphtheria, sites of involvement, and the presence or absence of a bull neck. The recommended doses are:

- Systemic disease manifestations of three or more days' duration, or patients with bull neck: 80,000–100,000 units
- Nasopharyngeal disease: 40,000–60,000 units
- Pharyngeal or laryngeal disease of two days duration: 20,000–40,000 units

The dose of antitoxin is the same for all the ages. Antitoxin must be warmed to 32–34 °C before administration [48]. The preferred route is intravenous but intramuscular route may be used only in mild to moderate cases. The dose of antitoxin should be mixed with 250–500 ml of normal saline and infused over 2–4 h. Pregnancy is not a contraindication to antitoxin administration. Repeat doses of antitoxin are not recommended because of serious allergic reactions as a result of antibody formation. The possible adverse reactions following antitoxin administra-

tion include anaphylactic reactions, febrile reactions, serum sickness (skin rash, arthralgia, angioedema), and injection site pain.

Antibiotics

Antibiotics are necessary to kill the organism, limiting further toxin production that will hasten early recovery and also reduce spreading the disease to others. Procaine penicillin G is the preferred antibiotic and should be administered for a period of 14 days. In cases of penicillin allergy, erythromycin is given for the same duration. The doses recommended by the CDC are: procaine penicillin G daily, intramuscularly (300,000 units every 12 h for those weighing 10 kg or less, and 600,000 units every 12 h for those weighing more than 10 kg) for 14 days, or erythromycin orally or by injection (40 mg/kg/day; maximum, 2 g/day) for 14 days [20]. The disease usually becomes non-contagious 48 h following antibiotic therapy, but for epidemiological purposes, two consecutive negative cultures (24 h apart) are required to demonstrate elimination of the organism.

Isolates should be tested for susceptibility. Reduced susceptibility to penicillin for both toxigenic and non-toxigenic strains has been reported [12, 49].

Monitoring

All diphtheria patients need close monitoring with respect to any abnormalities in pulse (rate, rhythm), changes in blood pressure (hypotension), respiratory rate, development of stridor or cyanosis, any bleeding, or serum sickness-like illness.

Specialists' consultations are required in certain emergency situations and these must be available around the clock in the referral hospital.

- ENT specialist: in difficult cases for airway protection, for the removal of a pseudomembrane endoscopically. Tracheostomy may be required.
- Cardiologist: in cases of advanced cardiac conduction abnormality due to severe myocarditis requiring temporary pacing.
- Pulmonologist and anesthesiologist: in cases of severe laryngeal obstruction by a pseudomembrane with associated aspiration pneumonia and cyanosis. Intubation may be required.
- Infectious disease specialist: in cases of atypical presentation of diphtheria or any unusual disease complications.

Follow-Up Vaccination

Respiratory diphtheria does not produce immunity and patients should be vaccinated against diphtheria as appropriate for their age.

Management of Close Contacts and Carriers

All household contacts require a throat swab for culture and should receive chemoprophylaxis regardless of age or immunization status. Confirmation of eradication of carriage state following treatment is necessary for those found to be culture positive [3]. Chemoprophylaxis of household contacts should be with either oral erythromycin (40 mg/kg per day for children and 1 g per day for adults) for 7–10 days, or if compliance is uncertain, with a dose of intramuscular benzathine penicillin (600,000 units for children under age 6 and 1.2 million units for patients age 6 and older) [20]. In addition, all contacts require close supervision and should be treated with antitoxin at the earliest signs of illness. Carriers require treatment with the same antibiotics as contacts, and should also be kept under strict surveillance for any signs of the disease. Both contacts and carriers should be vaccinated as appropriate for their age.

Prognosis

The case fatality rate of diphtheria has been unchanged for several decades, remaining at 5–10% in most series. The mortality rate may be

higher (60–90%) in unvaccinated or partially vaccinated patients, patients with clinical evidence of myocardial involvement, age less than 5 years or above 40 years, and those who received the antitoxin very late. Patients with bull neck are also at higher risk of death. The most important predictors for mortality are the time interval of antitoxin administration from the onset of first respiratory symptom and vaccination status of the affected individuals.

Prevention

The only way to control diphtheria effectively is through immunization. The goal should be to immunize all infants before they lose their maternal antibody, and then give booster doses to enhance and maintain immunity. Diphtheria vaccine has been combined with pertussis and tetanus vaccines since the 1940s as DTP. Pertussis vaccines are now designated as "whole cell" (the original vaccine) or "acellular" (introduced in the 1980s) so the combination may be written as DTwP (whole cell pertussis) or DTaP (acellular pertussis), although the WHO uses DTP to designate either. Acellular pertussis-containing vaccines are preferred by most countries and are the only pertussis-containing vaccines recommended in patients age 7 years and older [1].

There are pediatric formulations, DTaP and DT, given to infants and children younger than 7, and "adult" formulations, Tdap and Td, given to patients age 7 and older. The pediatric formulations contain a similar amount of tetanus toxoid as the adult formulations but several times as much diphtheria toxoid. Adults and all children age 7 and older, including those who missed the usual vaccine schedule, should be prescribed the adult formulations. Diphtheria toxoid is highly efficacious and the protective antibody (>0.1 IU of anti-toxin/mL) is produced in more than 95% of cases following complete vaccination. Immunosuppression is not a contraindication to vaccination, although it may reduce the immune response to vaccination. Pregnancy is also not a contraindication.

The World Health Organization (WHO) recommends that all children receive a 3-dose "primary" series of DTP before age 1 (starting as early as 6 weeks old), a 4th DTP dose ("booster") at age 12–23 months, and Td booster doses at ages 4–7 years and ages 9–15 years [1]. The Centers for Disease Control and Prevention (CDC) recommends five doses of DTaP given at ages 2 months, 4 months, 6 months, 12–15 months, and 4–6 years [2]. Adults age 19 and older should receive booster doses of Td every 10 years. Recommendations for interrupted or delayed vaccinations are given in the WHO and CDC websites [1, 2]. Diphtheria toxoid-containing vaccines should be stored in the refrigerator (at 2–8 °C) but should not be frozen; most manufacturers state that frozen vaccines should be discarded.

Conclusion

Diphtheria is still with us and causes a high mortality, despite the availability of an effective vaccine. The main cause of the persistence of diphtheria is inadequate immunization coverage, including booster shots, in developing countries. In developed countries, where the disease is very rare, diphtheria must be considered in the differential diagnosis of patients presenting with membranous pharyngitis, especially if there is a history of recent travel to an endemic country or recent close contact with such a traveler. Early diagnosis, effective therapy, and close monitoring are all essential to reducing mortality.

Acknowledgement The authors would like to thank Dr. Sumit Chakrabarty for his critical review of the manuscript and Mr. Asish Sikder for his technical support.

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Epiglottitis, Acute Laryngitis, and Croup

20

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Introduction

Epiglottitis, acute laryngitis, and croup are infections of the upper airway, affecting the epiglottis, larynx, and larynx and trachea, respectively. Croup may also involve the bronchi. Epiglottitis is a bacterial infection, while acute laryngitis and croup are primarily viral infections.

Epiglottitis was known to the ancient world. The infection was probably described by Hippocrates 2400 years ago when he wrote: "There is fever, chill, pain in the head, the underpart of the jaw is swollen: the patient swallows with difficulties his saliva. The patient cannot spit, he cannot tolerate to lie down, and if he stays in this position he chokes" [1]. In 1791, the first clear description of acute epiglottitis was published, and the term "epiglottitis" was coined in 1830 [2]. Invention of the laryngoscope in the 1850s allowed direct visualization of the swollen epiglottis, and soon thereafter the mirror examination of the hypopharynx and larynx became widely practiced. In the early twentieth century, the term "acute epiglottitis" became part of standard medical terminology and the role of bacteria in the pathogenesis of the disease became clear. The prognosis of the disease improved in some cases with tracheotomy, tracheostomy, or intubation. George Washington, the first president of the United States, died in 1799 of an acute infection that was probably epiglottitis [3]. A tracheotomy (a new procedure then) was proposed by one of his physicians but not performed. The major advance in treatment of epiglottitis occurred following the introduction of antibiotics in the mid-twentieth century. The introduction of the *Haemophilus influenzae* type b (Hib) vaccine in 1985 dramatically decreased the incidence of epiglottitis, especially in the pediatric population. The vaccine was improved (conjugated vaccine) in 1987 and 1990 so that efficacy extended to children younger than 18 months.

Croup, an old term meaning "to cry hoarsely," was originally applied to cases with croup-like symptoms (inspiratory stridor, hoarseness, and a barking cough) due to diphtheria. However, diphtheritic "croup" was subsequently distinguished from viral croup by the twentieth century. Croup now refers to acute viral laryngotracheobronchitis or laryngotracheitis.

Acute Epiglottitis (Supraglottitis)

Epiglottitis, also called supraglottitis, is an acute infection of epiglottis and surrounding supraglottic tissues that can rapidly lead to life-threatening

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_20

airway obstruction. Supraglottitis is a more accurate term because in many cases, several supraglottic structures are involved (e.g., aryepiglottic folds, arytenoids). Prior to the introduction of the Hib vaccine 30 years ago, *H. influenzae* type b caused most cases of epiglottitis and the disease primarily affected children younger than 5 years old. Now, invasive *H. influenzae* type b infections are very rare in children and the incidence of epiglottitis is higher in adults than in children.

Epidemiology

Before the Hib vaccine, the incidence of epiglottitis in children under age 5 years was as high as 15 cases per 100,000 population. The peak incidence occurred in children under age 3. Since the introduction of the Hib vaccine in 1985, the incidence in children has decreased to 0.5–0.7 cases per 100,000. In Finland, 50–60 cases per year of epiglottitis were seen throughout the country in 1985–1986, and this decreased to only two cases in 1992, reflecting the widespread use of the Hib vaccine [4]. In Sweden, the incidence of epiglottitis in children under age 5 decreased from 21 to 0.9 cases per 100, 000 following Hib vaccination [5]. The median age of children affected by epiglottitis has also increased in the Hib vaccine era. At one center, the median age of children with epiglottitis before 1989 was 36 months and 81 months (nearly 7 years) after 1990 [6].

The incidence of epiglottitis in adults has remained stable or has increased since the introduction of the Hib vaccine [7, 8]. In Finland, the annual incidence of epiglottitis in adults increased from 1.88 (1990–1999) to 4.7 (2000–2009) per 100,000 [8]. In Denmark, the annual incidence in adults has been stable at 1.9 cases per 100,000 [9]. Most cases of epiglottitis now occur in adults. A study from Australia found that 84% of patients hospitalized for epiglottitis in the vaccine era have been adults [10]. The average age of adults with epiglottitis is mid-40s, but the range in one series was wide (age 18–92 years) [8].

Epiglottitis usually occurs in previously healthy children or adults. There is no clear seasonal variation. Slightly more males than females are affects, with a ratio of 1.4:1–1.7:1 in most series [8].

Pathophysiology

The epiglottis is a leaf shaped elastic cartilage with overlying loose connective tissue and a thin mucosa. The laryngeal airway in children is narrow. A comparatively minor swelling of the mucosa may cause significant airway narrowing. Acute epiglottitis usually starts with swelling of the lingual surface of the epiglottis, and then spreads to the laryngeal surface and the aryepiglottic folds. Bacterial invasion of the mucosa leads to fulminant infection. Especially in children, the epiglottis is the primary focus of infection and other parts of larynx may not be swollen. An epiglottic abscess can develop in either adults or children.

Microbiology

As noted above, *H. influenzae* type b caused most cases of epiglottitis in the pre-vaccine era. This was determined from blood cultures (positive in many children with *H. influenzae* epiglottitis), and some throat cultures. The true etiology of epiglottitis is now difficult to determine in most cases, because adults comprise the majority of cases and only 10% are bacteremic [8]. Throat cultures are contaminated by oral flora so may not demonstrate the true pathogen. In a series of 34 adults, only one had a positive blood culture (*H. influenzae*), while eight with throat cultures grew oral flora organisms in seven and *H. influenzae* in one [11].

Streptococci such as *Streptococcus pneumoniae* and Group A *Streptococcus* are the predominant causes of epiglottitis in most series in the vaccine era [8, 9, 12]. *Staphylococcus aureus* causes some cases, and cases due to methicillin-resistant *S. aureus* (MRSA) have been described [13]. A large series of epiglottitis in adults

reported positive blood cultures in 16 (10% of those in whom blood cultures were obtained) [8]. Of these 16 cases, cultures grew streptococci (including *S. pneumoniae*, Group A *Streptococcus*, *Streptococcus milleri*) in 11 (69%), *S. aureus* in two (13%), and Gram-negative bacilli in two (13%) including a case due to *Pseudomonas* [8]. Only one patient in that study had a culture positive for *H. influenzae*, and that grew on a throat culture.

The microbiology of epiglottitis in children is similar to that in adults. The Hib vaccine effectiveness is approximately 98%, so cases of epiglottitis due to *H. influenzae type b* are rare but do still occur. In one series of 19 children admitted in the vaccine era, *H. influenzae* type b was the etiology of six cases; streptococci accounted for another six cases (*S. pneumoniae*, Group A *Streptococcus*, other beta-hemolytic streptococci) [14]. In immunocompromised patients, *Pseudomonas* and *Candida* have caused some cases of epiglottitis [15–17].

Clinical Presentation

Children

Children with epiglottitis typically present with a high fever, inspiratory stridor, restlessness, and drooling. Breathing difficulties may cause a toxic and anxious appearance. The child usually presents sitting forward in a "tripod" or "sniffing" position and does not want to lie down. The child's head is hyperextended to maintain a patent airway. The child has pain with swallowing and may have a sore throat. The voice is often muffled, described as a "hot potato voice." Symptoms arise very quickly, in most cases within 12–24 h including symptoms of any antecedent upper respiratory tract infection. Unlike croup, cough is uncommon. Children with epiglottitis are often systemically unwell and the situation is considered an otolaryngologic emergency.

The differential diagnosis in children may include croup (acute laryngotracheobronchitis), discussed later. However, children with croup have a barking cough and are less likely to have drooling or to insist on sitting forward in the "sniffing" position. Children with croup usually appear less toxic than children with epiglottitis.

Adults

Symptoms of acute epiglottitis usually develop more slowly in adults than in children. The most common symptom, seen in nearly all the cases, is sore throat. In a study from Finland of 308 adults admitted with epiglottitis 1989–2009, the mean duration of symptoms prior to presentation was 3.7 days, and 94% of patients complained of sore throat [8]. Other symptoms included odynophagia or dysphagia (80%), fever (60%), dyspnea (38%), hoarseness (30%), muffled voice (12%), drooling (11%), cough (8%), and stridor (7%) [8]. Patients with epiglottitis find breathing in the supine position difficult or impossible and prefer to sit, leaning forward with a hyperextended neck. The patient may cough although infrequently, to clear secretions in the hypopharynx. An epiglottic abscess may be present and this is a risk factor for requiring airway intervention [7]. The differential diagnosis of epiglottitis in adults includes other causes of acute sore throat and severe odynophagia. In epiglottitis, however, the sore throat is more severe than expected based on the findings of the oropharynx examination.

Diagnosis and Evaluation

Children

The extent of physical examination performed prior to securing the airway should be individualized, depending on the severity of the child's illness and the likelihood that their illness is epiglottitis. Rare cases of cardiopulmonary arrest have occurred with attempts at visualization of the epiglottis. Similarly, asking the child to lie supine may be dangerous and respiratory arrest has been reported in this position. When acute epiglottitis is suspected, arrangements to secure the airway should be made immediately. The help of a pediatric otolaryngologist or anesthesiologist is often necessary.

Supplemental humidified oxygen should be given. In children who are not in any respiratory distress, clinical examination may be cautiously performed as long as airway rescue is readily available. The classic red epiglottis may be visualized by gently depressing the anterior tongue with a tongue depressor. Similarly, plain neck x-rays can be obtained in the non-acute setting as the patient can remain in the seated position. The lateral view will indicate thickening of the epiglottis, similarly the anterior view will evaluate for subglottic finding which may be associated with other diagnoses in the differential such as croup. All children suspected of having epiglottitis who are undergoing x-ray evaluation should be closely monitored and observed during the entire period while these films are obtained. In more severe cases, the child should be transported to the operating room where the airway can be secured, by controlled intubation or tracheotomy, and diagnostic endoscopy can be performed.

Diagnostic tests such as blood cultures and routine laboratory tests (e.g., complete blood count with differential) should be performed only after the airway is secured. Throat or epiglottic cultures should be obtained only after the airway is secured. If a deep neck infection or epiglottic abscess is suspected, computed tomography (CT) with contrast can be considered after the airway is secured.

Adults

If acute epiglottitis is suspected, patients should be kept in the sitting position and not asked to lie down. In severe cases with impending airway obstruction, the airway should be secured prior to any attempt at examination. In most cases of adult epiglottitis, there is less risk to performing a direct examination than in children. However, a specialist such as an anesthesiologist or otolaryngologist should be on hand, as the patient can deteriorate rapidly. Indirect laryngoscopy with mirror examination can usually be performed in adults to diagnose epiglottitis, although nasolaryngeal endoscopy with a flexible fiberoptic may be safer and more easily done. The diagnosis of epiglottitis is made by noting a swollen and red epiglottis, although in adults the primary site of swelling may be in other supraglottic structures. One study found swelling of the epiglottis in 73% of adults with epiglottitis but swelling of the epiglottis alone occurred in only 17% [8].

After confirming the diagnosis, the airway should be secured if necessary. An intervention (intubation or tracheotomy) may not be necessary in adults with epiglottitis. In a study of 61 patients in the vaccine era (60 adults, 1 child), only 21% required airway intervention (11 intubations, 2 tracheotomies) [12]. In a study of 308 adults with epiglottitis, 15% required airway intervention (two-thirds intubation, one-third tracheotomy) [8]. Factors associated with the need for airway intervention include a rapid onset of symptoms, stridor, drooling, and tachypnea [8, 12]. Diagnostic tests should be done once the airway is secured, or once it has been determined that the airway is sufficiently patent so as to not require immediate intervention. If there is a suspicion of deep neck infection or an epiglottic abscess, a CT with contrast should be considered once the airway is secure.

Treatment

Medical Treatment

Empiric antibiotic treatment of acute epiglottitis in children or adults should cover *H. influenzae*, *S. pneumoniae* (including penicillin-resistant strains), Group A *Streptococcus*, and *S. aureus* (including MRSA). Intravenous vancomycin plus ceftriaxone will cover these organisms. Even in regions where MRSA is rare, the addition of vancomycin to ceftriaxone is usually recommended because some *S. pneumoniae* isolates are not susceptible to ceftriaxone, and vancomycin will provide additional staphylococcal coverage. In immunocompromised patients, an antibiotic regimen that will also treat *Pseudomonas* should be considered (e.g., intravenous vancomycin plus either meropenem or imipenem). Antibiotics can be tailored once results of blood and throat cultures are known.

Airway Management

Managing the airway is the utmost importance in epiglottitis. Even in patients who appear stable, clinical deterioration can occur at any point. Acute loss of the airway is the primary cause of death in epiglottitis.

Securing the airway by intubation usually can be performed safely, but requires experienced and expert anesthesiologists or otolaryngologists. Preparations for obtaining a surgical airway, such as tracheotomy, should always coincide with any attempt at intubation, as acute airway obstruction can occur with a failed intubation attempt as discussed later. Awake fiberoptic intubation can be attempted in the cooperative patient as an initial attempt to secure the airway. Direct and video-assisted laryngoscopy may be attempted, but the necessary sedation requires rapid access to airway and associated swelling and secretions can limit visualization. If an emergency surgical airway is required, the type depends on the age of the patient. Needle cricothyrotomy can be performed on patients of any age, but this is the preferred surgical technique in children under age 12. Needle cricothyrotomy is easier to perform and less likely to damage the larynx in young children than surgical cricothyrotomy. Needle cricothyrotomy provides stabilization of the patient allowing a formal surgical airway such as a cricothyrotomy or tracheotomy to be performed in a controlled manner. Should immediate airway access be required, then emergent cricothyrotomy such be undertaken, with potential conversion to a standard tracheotomy if warranted.

In adults with epiglottitis, the airway can be maintained without intubation in most patients (80 to 85%) [8, 12]. Severe airway distress is possible in adults but less common than in children, since adults have larger airways. Humidified oxygen and close monitoring (usually in an intensive care unit) may be sufficient for airway management in many adults. Intravenous corticosteroids are often used in an effort to reduce supraglottic inflammation, although randomized controlled trials have not been performed to assess benefit. For adults with moderate to severe respiratory distress, more active intervention is necessary. Tracheotomy is not the first choice but should be chosen if expertise in difficult intubations is limited. Endotracheal intubation should be attempted only by an experienced anesthesiologist (or otolaryngologist) and always with readiness for immediate cricothyroidotomy. A failed endotracheal intubation attempt can result in immediate and total airway distress. There is no time to waste in providing an artificial airway in these cases. In cases with severe airway distress, awake tracheotomy with local anesthesia is the most secure and safe way to provide an airway. The transtracheal intubation should be also left to the most experienced airway specialists.

Epiglottic Abscess

In 10–20% of adults with epiglottitis, there is a concomitant abscess in the epiglottis. The abscess is associated with more severe symptoms and airway distress [7]. In these cases, surgical drainage of the abscess in indicated after the airway is secured. A tracheostomy is often indicated and opening of the abscess is carried out under direct laryngoscopy.

Acute Laryngitis

Clinical Presentation

Acute laryngitis is a common inflammatory disorder of the larynx. Typical symptoms include hoarseness, loss of voice, sore throat, and other nonspecific symptoms of upper respiratory tract infection. Fever and tender cervical lymphadenopathy may be present. Nearly all cases are due to upper respiratory viruses and are self-limited. Patients with laryngitis caused by infection may also have fever and swollen lymph nodes. The symptoms last less than 2 weeks.

Epidemiology

Acute laryngitis is the most common disease of the larynx. The true prevalence in the adult population is difficult to determine, because most

patients do not seek medical attention. A study conducted by the Royal College of General Practitioners in the United Kingdom estimated an incidence of nearly seven cases per 100,000 population per week [18].

Pathophysiology

Inflammation of the larynx may involve any area of the larynx, including the supraglottic, glottic, and subglottic areas [19]. Edema of the vocal cords leads to dysphonia.

An upper respiratory tract infection is the most common cause of acute laryngitis and nearly all cases are viral. The viruses involved are presumed to be those that cause other common upper respiratory infections, such as rhinovirus, influenza, parainfluenza, and adenovirus [19]. Rare cases of acute laryngitis are due to bacteria, or are initially viral but develop bacterial superinfection. Bacterial causes include the usual respiratory bacterial pathogens (Group A *Streptococcus*, *S. pneumoniae, H. influenzae*, *M. catarrhalis*) [19]. A rare case of MRSA membranous laryngitis has been reported in a child with concurrent influenza [20]. Evidence of a bacterial infection elsewhere (e.g., pneumonia, streptococcal pharyngitis) supports a bacterial etiology.

Noninfectious causes of laryngitis include gastroesophageal reflux, fungal infections of the larynx due to inhaled corticosteroids, and irritation from inhalers used for asthma. In most cases, symptoms develop subacutely rather than acutely, and are not accompanied by other symptoms of upper respiratory infection. In many cases of laryngitis due to noninfectious etiologies, the symptoms are chronic by the time the patient presents to the otolaryngologist.

In patients whose duration of symptoms is greater than three weeks, direct visualization of the larynx should be undertaken with the consideration of a possible malignant etiology. This is especially true in patients with a significant smoking history.

Treatment

Because most acute laryngitis cases are due to viruses, treatment is conservative and includes voice rest. A brief course of inhaled or oral corticosteroids can help reduce vocal cord inflammation, but this treatment should only be used in patients who have an urgent need to use their voice. One study found that inhaled versus oral corticosteroids reduced laryngeal hyperemia and edema to a similar degree [21]. Antibiotics should not be used unless there is evidence of bacterial superinfection. A Cochrane review of the literature found no benefit to the use of antibiotics for acute laryngitis [22].

Croup (Acute Laryngotracheobronchitis)

Croup is a clinical diagnosis referring to symptoms of acute viral laryngotracheobronchitis or laryngotracheitis, the latter description preferred by some authors [23]. The clinical presentation is due to acute laryngeal and subglottic swelling and is characterized by the abrupt onset of a barky cough, typically accompanied by hoarseness, inspiratory stridor, and respiratory distress [24]. The term "spasmodic croup" is sometimes used to refer to afebrile episodes of croup that may be recurrent [25].

Epidemiology

Croup is one of the most common causes of respiratory distress in young children, affecting approximately 5% of children during the second year of life [23]. Children between the ages of 6 months and 3 years old are most often affected, although some cases occur in children as young as 3 months and rare cases occur in adolescents [24]. Boys are affected approximately 1.4 times more often than girls [24].

Croup occurs most often in autumn (September to December) in temperate climates [24], but

cases may occur at any point throughout the year. Parainfluenza virus type 1 is the most common cause of croup and this virus produces epidemics of respiratory illness, including croup, in the fall every other year [25–27]. In North America, odd-numbered years have an increased incidence of croup compared with even-numbered years, as a consequence [24].

Microbiology

In a study of 144 children presenting to an emergency department in Helsinki with respiratory stridor, parainfluenza viruses accounted for over 40% of cases with parainfluenza virus type 1 the most common virus identified [28]. Other major causes of croup include parainfluenza virus types 2 and 3, while less common etiologies include influenza A and B and respiratory syncytial virus [25]. Human metapneumovirus, adenovirus, and coronavirus cause some cases.

Pathophysiology

Croup is a viral infection that leads to edema of the larynx and trachea; the bronchi may also be involved. This is most critically manifested by edema within the cricoid ring, which has a fixed circumference as well as being the narrowest region of the pediatric airway. Significant narrowing in this region can lead to life-threatening airway compromise. The narrowed subglottic region leads to the typical barky cough. The subglottic region of a young child is narrower and more pliable than in older individuals, and the narrowing that occurs with inspiration may be exaggerated in a young child with croup [25].

Clinical Features

Croup usually begins with nonspecific upper respiratory tract symptoms (coryza, nasal congestion), but then 12–48 h later there is the abrupt onset of a barky cough. The onset of this cough is usually late at night. Stridor, hoarseness, and fever are other features of the infection. Fever may be high (39.4–40 °C, or 103–104 °F), especially in cases due to influenza or parainfluenza virus [25]. Respiratory distress occurs in varying degrees, depending on the severity of the airway obstruction. In mild cases of croup, stridor is absent at rest but may be present when the child is upset or crying. Cases classified as moderate to severe croup are associated with stridor at rest and an increasing degree of chest wall retractions (although retractions may decrease in severe croup with impending airway failure). In severe croup, the child is agitated or lethargic.

Lateral and anteroposterior (AP) plain film x-rays can be obtained in stable patients, while maintaining close observation. The AP film can demonstrate subglottic airway narrowing, the classic "steeple sign" supporting the diagnosis of laryngotracheobronchitis. Similarly, the lateral film can assist in evaluating for finding associated with alternative diagnoses, such as supraglottis.

Treatment

Most cases of croup are mild, and treatment consists of symptomatic treatment plus a single dose of corticosteroid (0.15–0.6 mg/kg, maximum 10 mg) [24]. A single dose of oral dexamethasone was shown to be beneficial in mild croup in a randomized controlled trial [29]. Humidified air has a long history of use in treating croup, but there is evidence that it is not effective and should not be used [24].

Children with moderate to severe croup require evaluation in an emergency department. Care must be taken to keep the child calm (e.g., the child can sit on the parent's lap), as agitation can worsen symptoms. Treatment of moderate croup is with a single dose of dexamethasone and oxygen as needed [24]. Very brief courses of corticosteroids are well tolerated and safe in children [30].

Treatment of severe croup includes blow-by oxygen (optional unless cyanosis is present), corticosteroids, and nebulized epinephrine. The ben-

efit of nebulized epinephrine in respiratory distress is rapid but short term. Onset of the effect starts within 10 min and lasts from 1 to 2 h [4]. Retreatment with nebulized epinephrine may be required. Children with severe croup may require admission to a pediatric intensive care unit, and intubation is required in some children (<3%). The diagnosis of bacterial tracheitis should be considered in children with a high fever and a toxic appearance; this diagnosis requires treatment with antibiotics.

Conclusion

Epiglottitis, acute laryngitis, and croup (acute laryngotracheobronchitis) are infections of the upper airway, affecting the epiglottis, larynx, and larynx and trachea, respectively. Epiglottitis is a bacterial infection, while viruses cause nearly all cases of acute laryngitis and croup. Acute laryngitis in adults is usually self-limited. Epiglottitis, which used to be prevalent in children under age 5, is now seen more often in adults than in children. This decline in childhood epiglottitis is due to the *Haemophilus influenzae* type b (Hib) vaccine. Streptococci, including *Streptococcus pneumoniae*, are now important causes of epiglottitis. Croup is a viral infection, usually due to parainfluenza virus, that primarily affects children ages 6 months to 3 years old. Epiglottitis and croup can cause sudden and life-threatening loss of the airway, and misdiagnosis or mismanagement can result in fatalities. With appropriate management, however, death from these infections is very rare.

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Chronic Sore Throat

21

Marlene L. Durand

Introduction

There are no published criteria for determining what constitutes a "chronic" sore throat. Chronic sore throat will be defined here as the persistence of symptoms for at least 3 weeks. When evaluating a patient with chronic sore throat, the clinician should distinguish this entity from recurrent episodes of acute sore throat, and from acute pharyngitis with a biphasic pattern (i.e., improves then worsens). The latter suggests a viral followed by a bacterial etiology, or acute bacterial pharyngitis followed by a complication such as peritonsillar abscess or Lemierre's syndrome. However, patients with acute pharyngitis or acute pharyngitis followed by a bacterial complication nearly always present with less than 3 weeks of symptoms. Acute pharyngitis and peritonsillar abscess are discussed in Chap. 17, and Lemierre's syndrome is discussed in Chap. 18.

Most cases of chronic sore throat have non-infectious etiologies. Infectious etiologies include tuberculosis and various fungi. Table 21.1 lists several infectious and non-infectious causes of chronic sore throat.

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Non-infectious Etiologies

Gastric Acid Irritation

Chronic sore throat without a known cause, such as infection or malignancy, is a common reason for referral to an otolaryngologist [1]. Some of these patients may have laryngopharyngeal reflux [1]. Patients with reflux often present with hoarseness, but many also have sore throat [1–3]. Most are unaware of the presence of reflux and lack symptoms of heartburn or regurgitation [3]. Examination usually shows nonspecific signs of laryngeal irritation such as erythema, edema, and vocal cord thickening. These are often concentrated in the posterior larynx. Reinke's edema, or vocal cord swelling from fluid accumulation in the superficial lamina propria, may be present. A recent study of patients with Reinke's edema found a correlation between frequency and duration of acidic laryngopharyngeal reflux events and chronic pharyngitis [4].

Conditions that lead to repeated episodes of vomiting, such as bulimia, may also cause chronic sore throat as well as tonsillar hypertrophy [5]. A rare cause of repeated episodes of emesis and reflux in adults is congenital intestinal malrotation [6].

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_21

Table 21.1 Etiologies of chronic sore throat or hoarseness

Category	Etiology
Non-infectious	Gastric acid irritation from laryngopharyngeal reflux (or, very rarely, from repeated vomiting secondary to bulimia or untreated intestinal malrotation)
	Exposure to irritants
	Autoimmune (pemphigus vulgaris, mucous membrane pemphigoid)
	Aphthous ulcers
	Malignancy (e.g., squamous cell carcinoma)
Infectious	Mycobacterium tuberculosis (TB)
	Fungi (*Candida*, *Cryptococcus*, *Histoplasma*, *Blastomyces*, *Coccidioides*, *Paracoccidioides*)

Exposure to Irritants

Chronic exposure to irritants such as cigarette smoke, air pollutants, or industrial chemicals may lead to persistent sore throat [7]. Irritation from smoking is a common etiology of Reinke's edema. A single exposure to a disaster that releases large amounts of particulate matter and fumes may also cause persistent sore throat. During the first year after the destruction of the World Trade Center in 2001, 62% of exposed fire fighters reported frequent sore throats versus 3% before that exposure [8].

Autoimmune Diseases

Pemphigus vulgaris and mucous membrane pemphigoid are two autoimmune diseases that commonly affect the oral mucosa and can cause chronic throat pain. Pemphigus vulgaris usually presents in middle age and affects men and women equally. The disease is an intraepithelial blistering disease affecting the skin and mucous membranes. The site of immune attack is the keratinocyte cell surface, particularly a specific surface antigen, desmoglein 3. This immune attack leads to loss of cell-to-cell adhesion, or acantholysis. In most patients, the initial manifestation is the development of multiple small blisters in the oral mucosa. These rupture easily, resulting in painful erosions. Any part of the oral cavity may be affected, but the most common sites are cheek mucosa, palate, tongue, lower lip, and gums. These lesions usually develop over several months before spreading to the pharynx, larynx, esophagus, genital mucosa, or skin. A biopsy and direct immunofluorescence study confirms the diagnosis by demonstrating immunoglobulin deposits in the epithelial intercellular spaces. A variant of pemphigus vulgaris is paraneoplastic pemphigus, in which the pemphigus lesions are secondary to an underlying malignancy. Non-Hodgkin's lymphoma and chronic lymphocytic leukemia account for 70% of cases [9]. The diagnosis of malignancy is unknown at the time of appearance of oral lesions in one-third of paraneoplastic pemphigus cases [10].

Mucous membrane pemphigoid is a subepithelial bullous disease that primarily affects mucous membranes. It is characterized by deposition of IgG, IgA, or C3 along the epithelial basement membrane. The skin occasionally may be affected. The reason for the development of this autoimmune condition is unknown. Rare cases of mucous membrane pemphigoid are paraneoplastic [11]. Patients usually present in their 60s and women are affected more often than men. The oral cavity is affected in 85% of patients [12]. Other sites include the conjunctiva, nose, pharynx, skin, anogenital area, esophagus, and larynx [13]. Most patients with throat involvement present with persistent sore throat and odynophagia. On examination, there are vesicles or bullae on the oral mucosa, many of which have ruptured leaving shallow ulcerations with irregular margins. Superficial pseudomembranes may be seen, which may desquamate. The lesions may be anywhere on the oral mucosa but most often involve the gingiva [14]. The diagnosis is made by biopsy of the edge of the ulcer, rather than the center. The diagnosis can be missed if the specimen is placed in formalin and processed routinely. Rather, the specimen should be placed in special transport media or frozen in liquid nitrogen, and processed immediately [15]. Pathology will show a subepithelial cleft at the level of the basement membrane, and immunofluorescence will demonstrate antibodies against the basement membrane.

Aphthous Ulcers

Aphthous ulcers are ulcerations of the oral mucosa of unknown etiology. The ulcers may cause throat pain and are categorized as minor (<1 cm diameter), herpetiform (clusters of small ulcers not caused by herpes simplex virus), or major (>1 cm) [16, 17]. Most are minor and resolve in 1–2 weeks, but major ulcers may persist for several weeks and leave a scar. The etiology is unknown. The term "aphthous-like ulcers" is used for ulcerations associated with systemic disease, and these are identical in appearance to idiopathic aphthous ulcers. Some rheumatologic conditions (e.g., Behcet's disease, lupus erythematosis, Crohn's disease, Reiter's syndrome) and immunocompromising illnesses (e.g., HIV, cyclic neutropenia) may be associated with recurrent aphthous ulcerations. Drugs may also cause chronic oral ulcers, but these ulcers are usually single and located on the side of the tongue [18].

Malignancy

Cancers involving the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx may cause throat pain or hoarseness. The majority of these cancers are squamous cell carcinoma. Smoking and alcohol consumption are risk factors. Human papillomavirus infection is a major risk factor for oropharyngeal cancer, as discussed in Chap. 28. Any patient with chronic sore throat or hoarseness should be evaluated by an otolaryngologist to exclude malignancy. Referred otalgia may also be present and should raise suspicion for a possible malignancy.

Infectious Etiologies

Herpes Simplex and Herpes Zoster

Herpes simplex and herpes zoster almost always cause acute rather than chronic symptoms. Primary or recurrent herpes simplex virus can be severe in immunocompromised patients and involve the oral cavity, pharynx, and larynx [19, 20]. Lesions may be bilateral and consist of painful vesicles or shallow ulcerations. Herpes zoster, which results from reactivation of latent varicella zoster virus, may rarely involve the throat and larynx [21–27]. Lesions resemble those of herpes simplex but are unilateral (Fig. 21.1). Many patients with intraoral or laryngeal zoster have an ipsilateral facial rash (second and thirrd divisions of cranial nerve 5), but some do not. Accompanying cranial nerve palsies are common, most often involving cranial nerves 9 and 10 but sometimes 7, 8, or 11. Patients with Ramsay Hunt syndrome (vesicles in the ear canal and facial palsy) sometimes develop ipsilateral lesions in the throat and involvement of cranial nerves 9 and 10. Mass lesions of the larynx caused by varicella zoster virus are very rare and have been described in case reports [28, 29]. Diagnosis of oral herpes simplex or zoster is accomplished by scraping the base of a lesion and submitting this sample for viral culture or for studies to detect viral antigens (direct fluorescent antibody, polymerase chain reaction testing). Treatment with an antiviral (e.g., acyclovir, valacyclovir, famciclovir) is indicated in immunocompromised patients with herpes simplex and for all patients with herpes zoster.

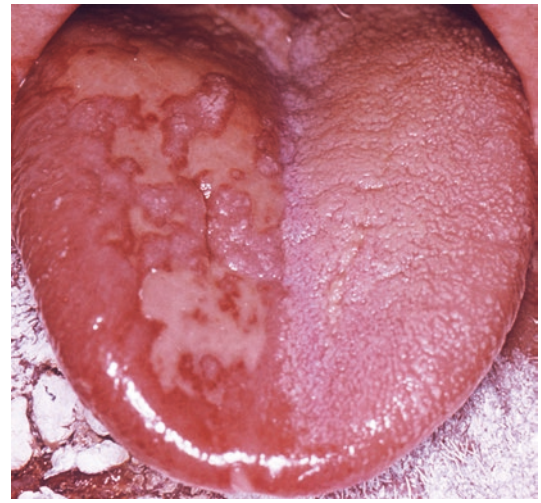

Fig. 21.1 Herpes zoster affecting the right half of patient's tongue and chin. Herpetic lesions involving the throat usually produce acute rather than chronic throat pain. Courtesy of Centers for Disease Control and Prevention (CDC), Public Health Image Library

Tuberculosis

Mycobacterium tuberculosis (TB) usually affects the lungs but may have extrapulmonary manifestations. Extrapulmonary TB involving the throat is uncommon and usually involves only the larynx. Laryngeal TB often presents with hoarseness and a laryngeal mass mimicking cancer. There may or may not be concomitant pulmonary infection. One series of laryngeal TB found that over 50% of patients had a clear chest x-ray [30]. Oropharyngeal TB is very rare (Fig. 21.2). Two recent case reports have described this infection in patients receiving an anti-tumor necrosis factor alpha (TNF-α) agent for rheumatoid arthritis [31, 32]. Tuberculosis involved the tonsil in one patient and the soft palate and uvula in the other; the chest x-ray was clear in one. The use of biologic immunomodulating agents such as TNF-α antagonists is a major risk factor for reactivation TB, and especially for extrapulmonary TB [33–35]. These agents are also risk factors for reactivation of latent endemic fungal infections, as discussed later.

Diagnosis of oropharyngeal or laryngeal TB may be suspected by histopathology findings of granulomas, and special tissue stains for acid fast bacilli (AFB) may show the characteristic red-staining mycobacteria. However, a specimen will be required for microbiology studies as well, and these studies should include AFB stain, culture for mycobacteria, and susceptibility testing.

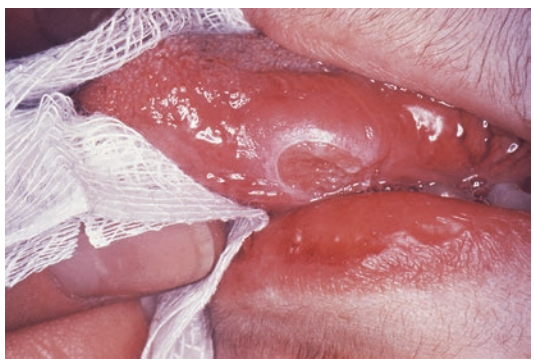

Fig. 21.2 Tuberculosis involving the left side of tongue, causing an ulceration. Courtesy of Centers for Disease Control and Prevention (CDC), Public Health Image Library

All patients found to have extrapulmonary TB should also be evaluated for pulmonary TB. Isolation precautions (airborne isolation) are required for oropharyngeal, laryngeal, or pulmonary TB until the patient is determined to be no longer contagious. This determination can be complicated and is usually made with the help of hospital infectious disease specialists or local governmental epidemiologists. Treatment is with multidrug therapy for TB, given for many months. Tuberculous head and neck infections are further discussed in Chap. 25.

Fungal Infections

Fungi that can cause chronic sore throat or hoarseness include *Candida*, *Cryptococcus*, and endemic fungi. Endemic fungi, so called because they live in the environment in certain geographic areas, include *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Paracoccidioides brasiliensis*. Endemic fungi live as molds in the soil but as yeasts in the human body.

Candida can cause oropharyngeal candidiasis (thrush) which may present as chronic sore throat. Extension to the esophagus may also cause pain with swallowing. Although *Candida* is part of the normal oral flora, the appearance of thrush in the mouth of an adult usually signifies an immunocompromising condition. Other causes of thrush include chronic use of oral or inhaled corticosteroids, other immunosuppressing medications, chemotherapy, radiation therapy of the head and neck, and a recent course of antibiotics. The usual appearance of oropharyngeal candidiasis is "pseudomembranous," with white plaques most often on the tongue, buccal mucosa, and palate (Fig. 21.3a). These plaques can be easily wiped away to reveal an erythematous base. Another common manifestation is "atrophic" or "erythematous" thrush (Fig. 21.3b). This usually affects the tongue and palate, which can appear red and raw. The tongue often appears abnormally smooth due to loss of papillae. White plaques are usually absent. A third presentation is chronic hyperplastic candidiasis which presents

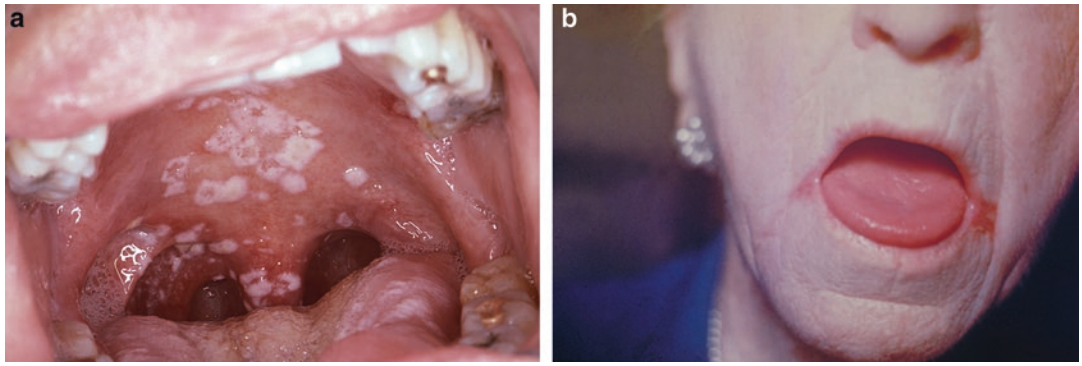

Fig. 21.3 *Candida* causing (**a**) pseudomembranous thrush, and (**b**) atrophic (or erythematous) thrush. Angular cheilitis (irritation at the corners of the mouth) due to thrush may be present as well, as in (**b**). Courtesy of Centers for Disease Control and Prevention (CDC), Public Health Image Library

with a white patch on the oral commissure. However, patients with chronic hyperplastic candidiasis are usually asymptomatic.

The diagnosis of oral candidiasis is usually by clinical appearance, but fungal culture may be required in cases with an atypical appearance or that fail to respond to therapy. Standard initial therapy includes topical or oral anti-fungal agents such as nystatin (topical) or fluconazole (oral). Persistence of oral candidiasis despite therapy may indicate a resistant *Candida* isolate, and culture and susceptibility testing should be requested. *Candida* species, particularly non-*albicans* species, have shown increasing resistance to anti-fungal agents such as fluconazole. Clinical practice guidelines from the Infectious Diseases Society of America can help guide therapy in these cases [36].

Cryptococcus is a yeast found in the soil worldwide. *Cryptococcus* is best known for causing meningitis in immunocompromised hosts, particularly patients with AIDS, although rarely normal hosts can be affected. Cryptococcal laryngitis has been described (fewer than 20 cases) in immunocompromised hosts or in patients using inhaled steroids for asthma [37]. Patients present with chronic hoarseness but may also have chronic sore throat (Fig. 21.4). Examination of the larynx may reveal edema, erythema, leukoplakia, vocal cord thickening or irregularity, or vocal cord masses [37]. Laryngeal lesions can mimic cancer, but biopsy and culture reveal the fungi. Patients should be evaluated for an underlying immunocompromising condition, but the only predisposing factor in some patients is their chronic use of inhaled corticosteroids. Treatment of cryptococcal laryngitis is with a prolonged course of fluconazole.

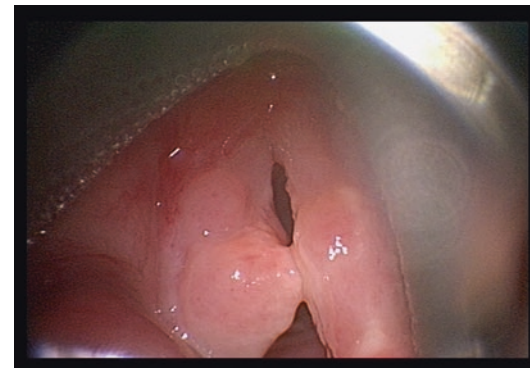

Fig. 21.4 Cryptococcal laryngitis in an 82-year-old patient who had received several years of inhaled corticosteroids for asthma. The vocal cords, pictured here, had masses bilaterally. Biopsy showed fungi on pathology and grew *Cryptococcus neoformans* on culture. Photograph courtesy of Dr. Steven M. Zeitels

Histoplasma capsulatum is a fungus found worldwide. It may very rarely cause oral or laryngeal involvement, with resulting chronic sore throat or hoarseness. *Histoplasma* is the most common of the endemic fungi and it is found in various locations worldwide: the U.S., parts of Central and South America, Africa, Asia, and Australia [38]. In the U.S., histoplasmosis is most common in the Mississippi and Ohio River valley states, although 12% of histoplasmosis cases

occur in non-endemic regions such as New England [39]. The initial infection is usually asymptomatic or produces a mild acute respiratory illness that resolves. In 1 in 2000 to 1 in 5000 patients with the acute infection, it will disseminate either soon after the initial infection (acute disseminated), or reactivate later and disseminate. The latter may occur years after acquiring the acute infection. Immunocompromised patients, including those receiving TNFα inhibitors such as infliximab, are at particular risk for disseminated disease or reactivation of latent histoplasmosis. Oral or laryngeal lesions are a manifestation of disseminated disease, but may be the only manifestation. Only one-third of such patients have fever, and the patient's only complaint may be chronic sore throat [40]. The throat lesions are usually solitary, ulcerated, and indurated with heaped up margins. The lesions may mimic cancer. The most common sites of involvement are the buccal mucosa, tongue, palate, and larynx, but the gingiva may be involved (Fig. 21.5). Oral and laryngeal lesions are often present simultaneously [41]. A biopsy may demonstrate the *Histoplasma* yeasts on pathology. The organism will grow on fungal culture. Treatment is with a prolonged course of itraconazole. It is important to consider this diagnosis because delay in diagnosis and treatment of disseminated histoplasmosis may be lethal in immunocompromised patients.

Blastomyces dermatitidis lives in the environment, particularly in wooded areas with moist soil. It is found in the U.S. along the Mississippi and Ohio River valleys, around the Great Lakes, and along the Saint Lawrence River. The fungus is also found in Canada in the Great Lakes region, and rare cases have been described in Africa and India. The lungs are infected first but then dissemination can occur to various organs. Very rarely, the infection may involve the larynx or oral cavity. A 2014 review of the literature found only 28 cases of laryngeal blastomycosis and 16 cases involving the tongue or oral cavity [42]. Lesions, which may be painful and tender, are typically polypoid or verrucous and mimic cancer [42]. Treatment of blastomycosis is with amphotericin or itraconazole, depending on the severity and location of the infection.

Coccidioides immitis (or *C. posadasii*) is endemic to the southwestern U.S. (especially Arizona and southern California), Washington state, Mexico, and parts of South America. Coccidioidomycosis is a pulmonary infection that may disseminate in 0.5% of cases, including (rarely) to the larynx [43]. Extrapulmonary disease occurs within 2 years of primary infection [44]. The treatment is a prolonged course of antifungal antibiotics (e.g., months of fluconazole). A case of a retropharyngeal abscess due to *C. immitis* has been described in an 18-year-old student [45] (Fig. 21.6). The patient was from Georgia and his initial symptoms, which included a sore throat, developed several months after starting college in Arizona.

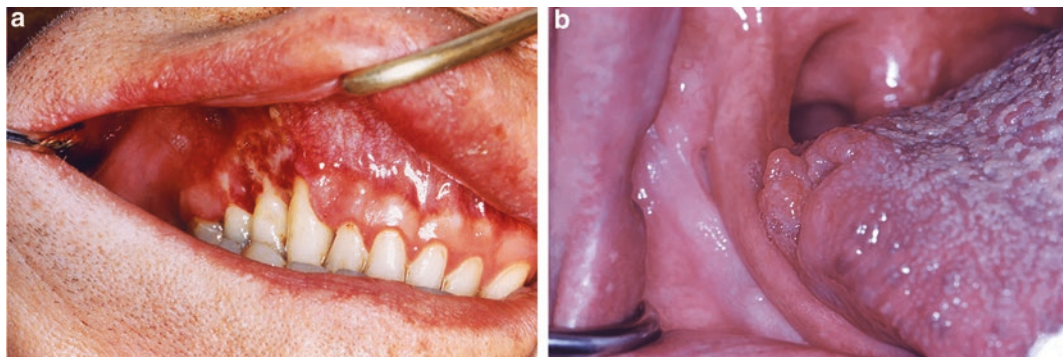

Fig. 21.5 *Histoplasma capsulatum* infection involving (**a**) the gingiva, and (**b**) the tongue. Courtesy of Centers for Disease Control and Prevention (CDC), Public Health Image Library

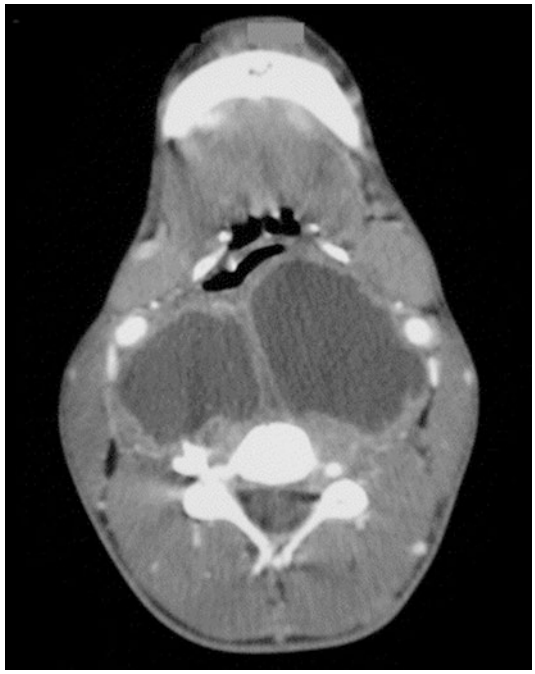

Fig. 21.6 *Coccidioides immitis* causing retropharyngeal abscess (computed tomography image). Reproduced from Sipp et al. [45] with permission from SAGE Publications

Paracoccidioides brasiliensis causes an important endemic fungal infection in South America that often has oral manifestations. The infection is most common in Brazil (80% of cases), followed by Colombia, Venezuela, Argentina, Ecuador, and Paraguay [46]. Most people living in a highly endemic area acquire the infection at an early age but are asymptomatic. Approximately 2% of infected individuals eventually develop symptoms of "chronic progressive" infection, but only after a very long latency (15 years). At the time symptoms begin, the patient may no longer live in an endemic area so diagnosis may be delayed. The chronic progressive infection is seen primarily in men (85–95% of cases), ages 30–60 years old, who have a history of farm work or prolonged exposure to a rural environment in South America [47]. Patients with chronic progressive infection may only have pulmonary involvement (20–30% of cases) [46]. Oral manifestations occur in up to 80% of chronic cases and are often manifested as painful, "mulberry-like," ulcerated masses [48]. Lesions most often affect the gingiva but can also affect the lips, tongue, palate, other parts of the oral cavity or pharynx, and larynx (Fig. 21.7). Indurated violaceous infiltration of the lips is common [46]. Nodular or papular skin lesions near the mouth or nostrils often occur and eventually ulcerate. Diagnosis is by histopathology, culture, and serology. The infection is usually treated with 6 months of itraconazole [46].

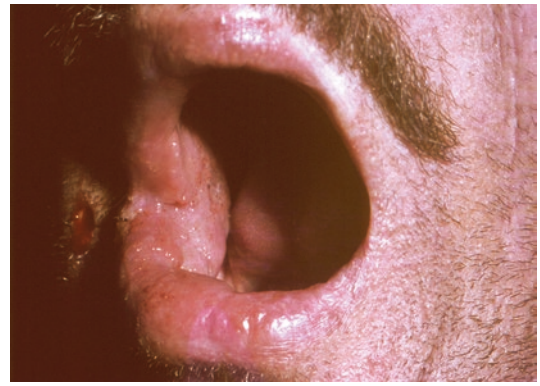

Fig. 21.7 Paracoccidioidomycosis in a patient from Brazil. Note the mass-like lesions on the right side of the lower lip and adjacent mucosa, as well as the ulcerated lesion in the nearby skin. Courtesy of Centers for Disease Control and Prevention (CDC), Public Health Image Library

Conclusion

Most cases of chronic sore throat have a non-infectious etiology, such as gastrointestinal reflux or chronic irritant exposure. Autoimmune diseases and malignancy are other considerations. Physical examination will distinguish between these entities. Biopsy is required to diagnose autoimmune conditions and malignancy. Infectious causes of chronic sore throat or hoarseness include *Mycobacterium tuberculosis* and various types of fungi, such as *Candida*, *Cryptococcus*, *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Paracoccidioides*. The appearance of some infectious lesions can mimic malignancy, and biopsy and culture are required for diagnosis.

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Osteomyelitis of the Mandible

22

Tyler H. Haeffs, Tiffany H. Campbell, and Meredith August

Introduction

The term "mandibular osteomyelitis" nearly always refers to an infectious process of the bone but also may be used to refer to a non-infectious, inflammatory condition. Infectious cases may be acute or chronic and are sometimes called "suppurative" regardless of whether pus is present. Several classification schemes for mandibular osteomyelitis have been published, but most divide the entity into three major categories, as in the Zurich classification system: (1) acute infectious, (2) secondary chronic infectious, and (3) primary chronic (non-infectious) osteomyelitis [1]. The third category includes rare inflammatory processes of unknown etiology, some of which also involve other parts of the skeleton and/or skin.

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Acute and Chronic Infectious Mandibular Osteomyelitis

Acute and chronic infectious mandibular osteomyelitis are distinguished by time; infections lasting more than one month are considered chronic [2, 3]. Both acute and chronic forms occur in patients of all ages and both sexes. In a retrospective analysis of 251 cases, Baltensperger et al. noted a 2:1 male predominance and mean age of approximately 43 [4]. Calhoun et al. noted that most (83%) cases occur in the body of the mandible [5]. Additional mandibular sites were anterior (20%), angle (18%), ramus (7%), and condyle (2%). Other studies have reported similar demographic findings and site-specific involvement [6, 7].

Epidemiology

Since the introduction of penicillin in the 1940s and better access to routine dental care, the incidence of mandibular osteomyelitis has decreased. Rare cases still occur, however [8]. The majority have a dental etiology or occur after trauma, particularly mandibular fracture [2, 6]. Radiation therapy, malignancy, sickle cell disease, osteopenia/osteoporosis, Paget's disease, and fibrous dysplasia may increase the incidence of infec-

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_22

tion. Osteonecrosis resulting from bisphosphonates or other medications may result in mucosal breakdown and secondary bony infection. Chronic dental disease and poor oral hygiene are likely to be additional risk factors.

Pathophysiology

The pathophysiology of osteomyelitis involving various bones of the body has been studied in animal models. Intact bone in immunocompetent hosts is highly resistant to infection, and usually either a large inoculum of bacteria, associated trauma, or the introduction of a foreign body is required to initiate the process. Once microorganisms invade bone, resistance to antimicrobial therapy increases dramatically and short term antibiotic therapy is often inadequate to halt the process. Expression by inflammatory cells of various cytokines (interleukins and tumor necrosis factor) allows for osteolytic changes that promote extension of the infection through compromised bone [9]. With spread of infection into the vascular channels of bone, blood flow is further impaired resulting in avascular fragments (sequestrum, involucrum) that are commonly found at the time of debridement. These necrotic portions of bone contain lacunae devoid of osteocytes.

In osteomyelitis of the mandible, it has been postulated that infection within the bone increases intramedullary pressure, which leads to vascular compromise, ischemia, elevation of the periosteum, and possible compression of the neurovascular bundle [10]. Without adequate blood supply, bone fragments become necrotic and sequestrate. Equilibrium between the host's immune response and the continued pathogenic challenge leads to persistence in symptoms and chronicity.

Clinical Presentation

Patients with mandibular osteomyelitis usually present with jaw pain and may have swelling and tenderness over the involved mandible. In acute osteomyelitis, there may be submandibular lymphadenopathy and fever, while these features are often absent in chronic osteomyelitis. The patient's breath may have a fetid odor. Local edema, if severe, can involve the muscles of mastication leading to trismus. Further extension into the mandibular canal and compression of the inferior alveolar nerve can result in paresthesia or anesthesia. Additionally, teeth in the affected area may become increasingly mobile. In chronic infectious osteomyelitis, symptoms are less intense than in acute osteomyelitis and jaw pain tends to be dull. Examination often shows mucosal breakdown. There may be intra- and extraoral fistulae (Fig. 22.1). Cortical destruction is also seen, especially in aggressive infections or those that have gone untreated for a substantial time period. Alteration in occlusion and pathologic fracture may follow. The white blood cell count is usually elevated in acute but normal in chronic osteomyelitis. Other laboratory tests such as the erythrocyte sedimentation rate (ESR) and C-reactive protein do not aid in diagnosis nor help in assessing clinical course.

Diagnosis

Early diagnosis of mandibular osteomyelitis can be difficult. Many reported cases that involved removal of lower third molars, for example, were initially diagnosed and treated as localized osteitis (dry socket) [11]. Radiographic imaging is useful in identifying osteomyelitis and ruling out primary bone disease and bone tumors. Conventional radiology is the first step in diagnosis and the orthopantomogram is still a helpful screening tool (Fig. 22.2). If demineralization of bone exceeds 30–40%, changes will be seen on this image. These changes may include areas of bone destruction, sequestration, changes in cortical outline (easily seen at the inferior border of the mandible), pathologic fracture, or a mixed pattern of progressive sclerosis with scattered areas of osteolysis [12]. In cases where infection was preceded by third molar removal, assessment of the extraction site, including retained tooth fragments and bone spicules, is very helpful.

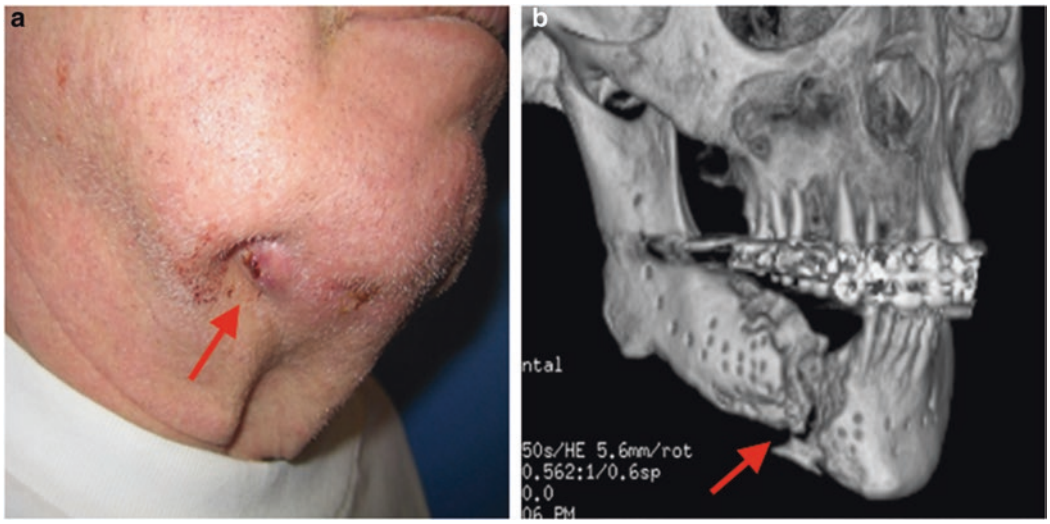

Fig. 22.1 Chronic infectious osteomyelitis. (**a**) Orocutaneous fistula (arrow) developing in the setting of chronic infectious osteomyelitis with (**b**) associated pathologic fracture (arrow) of the mandible

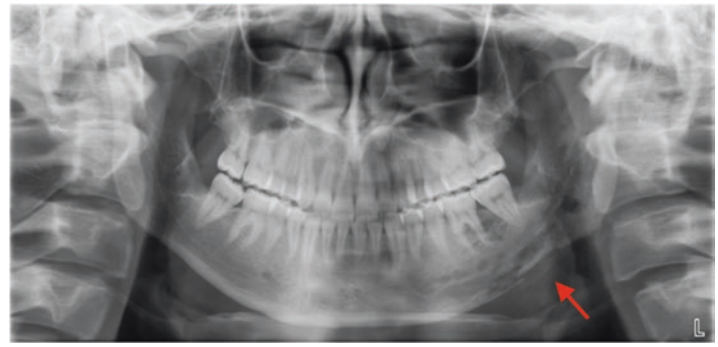

Fig. 22.2 Acute osteomyelitis. Orthopantomogram demonstrating diffuse left mandibular bony changes 6 weeks after the extraction of tooth # 17. Note extensive lytic changes and involvement of the lower cortex of bone (arrow)

Acute osteomyelitis can be difficult to identify radiographically within the first month of onset. In a study evaluating and staging patients with mandibular osteomyelitis, Schuknecht et al. were only able to successfully identify 38% of patients within 4 weeks of onset of symptoms [13]. Early signs in this group included: ill-defined radiolucencies, decreased bony trabeculation, and widening of the mandibular canal and mental foramen. As infection progressed, plain films revealed increased radiopacity due to sequestration and linear irregular radiolucencies related to fistula formation. Computed tomography (CT) scanning provides a better assessment of cortical bone involvement, sclerotic changes, and periosteal reaction (Fig. 22.3). A high resolution CT scan provides detailed information regarding cor-

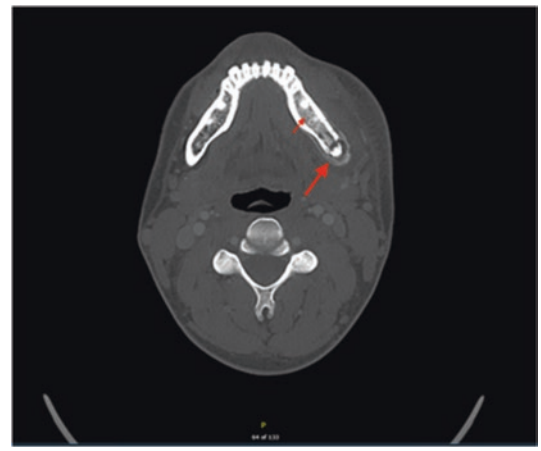

Fig. 22.3 Acute osteomyelitis. Axial CT scan demonstrating sclerotic medullary changes (small arrow) and exuberant periosteal reaction (large arrow) involving the left mandible

tical destruction, extent of disease, and sequestration. Multiple CT patterns have been described in patients with chronic infectious osteomyelitis. Mixed lucency and sclerosis are often found. A "frosted glass" pattern correlates with intramedullary formation of tiny trabeculae and a compact bone pattern correlates with thickening of the osseous trabeculae [14].

Perhaps the best imaging to detect very early disease is a bone scan (Technetium 99 radionucleotide scintigraphy). The 3-phase imaging demonstrates radionucleotide accumulation in bony foci that are inflamed or remodeling fairly rapidly. Findings may be abnormal just days after the onset of symptoms. Phase 1 (early blood flow phase) shows areas of hyperemia in the affected site. Phase 2 (blood pool phase) and phase 3 (bone phase images) reflect increased uptake in both acute and chronic osteomyelitis [15]. Although helpful in early diagnosis, bone scanning is associated with a high rate of false positivity especially in cases of bone healing (post extraction) or secondary to other osseous diseases such as Paget's disease or fibrous dysplasia. In addition, bone scans are not helpful to follow the progress of disease as areas of bone healing will be associated with increased uptake as well. Alternative radionucleotides are also used including indium (In111) which tags white blood cells and can increase specificity [16].

Magnetic resonance imaging (MRI) studies are relatively insensitive for the diagnosis of bony or odontogenic disease. However, alteration of the normal bone marrow signal is well seen on MRI and may be helpful in demonstrating early medullary changes, such as exudate or edema. Contrast-enhanced T1-weighted images demonstrate hypervascularity that can be seen with inflammation. In addition, contiguous soft tissue changes are well seen on MRI. One caveat with the use of MRI for disease surveillance is that abnormal marrow signals persist for many months after presumed successful treatment [17].

Microbiology

Many oral microbes can play a role in the development of infectious osteomyelitis. Most infections are polymicrobial and due to a combination of aerobes and anaerobes, an average of 4 or more different species has been reported [2, 5]. Marx and Tursun reported that 87% of cultures grew obligate or facultative anaerobic species [18]. The most common bacteria cultured are mouth flora bacteria such as viridans streptococci and anaerobes (e.g., *Peptostreptococcus*, *Prevotella*, and *Porphyromonas*) [5]. Occasionally bacteria that are not part of the normal oral flora, such as *Staphylococcus aureus* or MRSA (methicillin-resistant *S. aureus*), enterococci, or Gram-negative bacilli, may colonize the oral cavity, particularly in patients who have received antibiotics. These bacteria may also contribute to mandibular osteomyelitis.

The microbiology of acute and chronic mandibular osteomyelitis is similar except that in chronic cases, there is an increased prevalence of *Actinomyces* [19, 20]. *Actinomyces*, a Gram-positive anaerobe that is a part of the normal oral flora, may cause a chronic mandibular osteomyelitis due to an odontogenic infection (e.g., "lumpy jaw") [10]. Cervicofacial actinomycosis is a slowly progressive infection often characterized by a violaceous, woody induration of the skin and sinus tracts that discharge distinct yellow "sulfur granules." On pathology, these sulfur granules demonstrate a cluster of filamentous bacteria characteristic of *Actinomyces* (Fig. 22.4).

It should be noted that cultures obtained via the mouth will be contaminated by oral flora, so distinguishing pathogens from oral flora contaminants is often impossible in this situation. Cultures of the mandible obtained via the skin side will not be contaminated by oral flora, and obtaining such cultures may be helpful in some cases.

Therapy

Successful treatment often requires surgical intervention followed by prolonged antibiotic therapy. Case reports of successful medical management of acute mandibular osteomyelitis highlight the importance of early recognition to minimize bony destruction [21]. Once the chronic phase is reached, the aim of therapy is to remove involved devitalized bone. Debridement, seques-

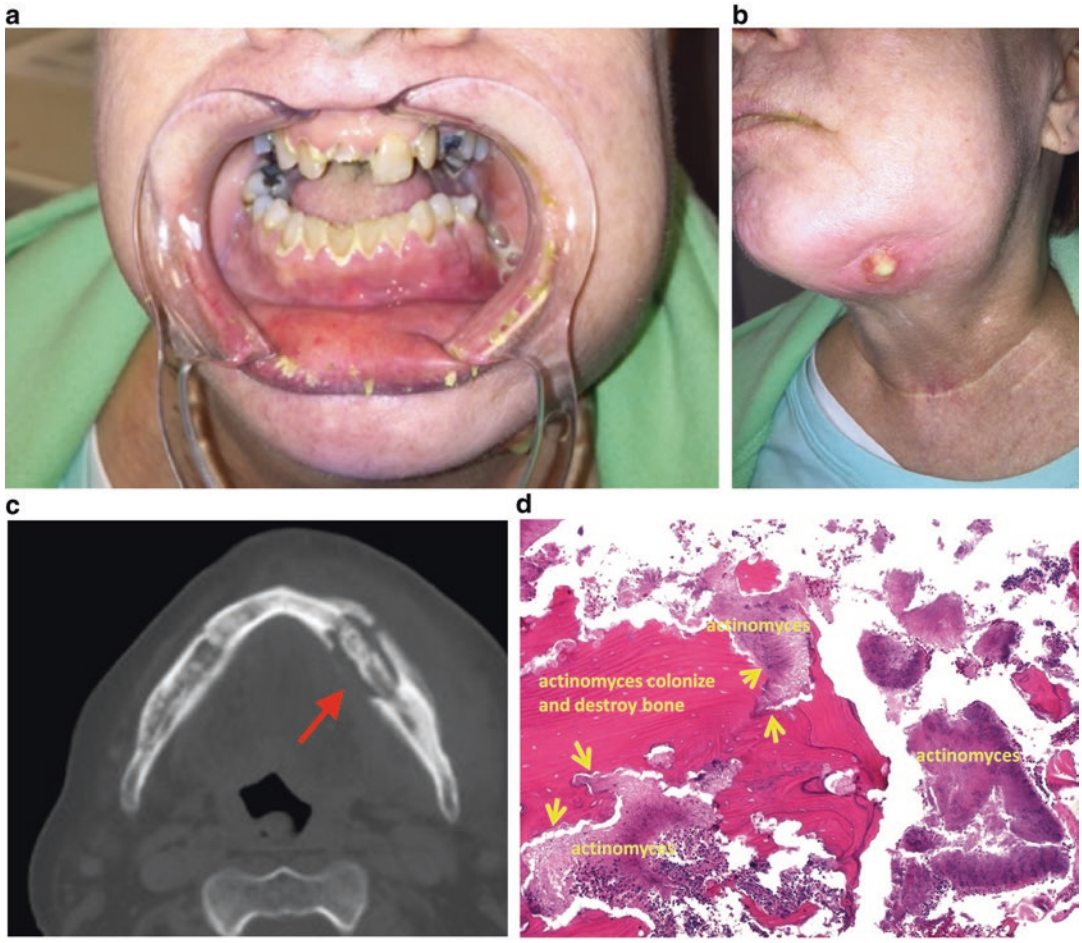

Fig. 22.4 (**a**–**d**) Chronic infectious osteomyelitis. Patient with (**a**) rampant dental disease presenting with chronic osteomyelitis, (**b**) an actively draining orocutaneous fistula (arrow), (**c**) CT findings of a large sequestrum within the left mandible (arrow), and (**d**) histologic evidence of *Actinomyces* colonization of the bone

trectomy, saucerization, and resection have all been described [22]. Following adequate surgical treatment, a prolonged course of systemic antibiotics is often required. Severe compromise to bony integrity may necessitate maxillomandibular fixation or stabilization with bone plates and screws. The use of hyperbaric oxygen as adjunctive therapy remains controversial [23], but may be considered in refractory cases.

Depending on the severity of the infection, various surgical procedures may be employed. Initial therapy often begins with incision and drainage if an abscess is present. Teeth, implants, and foreign bodies may be removed along with avascular sequestrated bone. Following these conservative procedures, more extensive debridement may be required. Saucerization allows direct access to the medullary cavity by "unroofing" the bone so that granulation tissue, pus, and other avascular fragments can be removed. Decortication then removes infected cortical bone and brings well-perfused tissue into contact with the affected site to promote healing. Irrigation drains may also be placed in cases of deep, well-established infections. Extensive, recurrent, or aggressive infections may require en bloc resection if other modalities have been unsuccessful or if pathologic fracture occurs.

Broad-spectrum antibiotic therapy is often initiated at the time of diagnosis, although treatment should be withheld until culture specimens can be obtained. A biopsy of involved mandibular

bone obtained from the skin side may be helpful in determining the pathogens of osteomyelitis, as cultures obtained from an intraoral approach will be contaminated by oral flora as noted above. Generally, four to eight weeks of antibiotic therapy is recommended for both acute and chronic variants, despite lack of strong clinical evidence to support this recommendation [24]. Kim and Jang reported a 94% success rate in treating chronic suppurative osteomyelitis with 2 weeks of intravenous antibiotics followed by a 6-week oral regimen [25]. However, duration of antibiotic treatment is not standardized and should be tailored to the patient. Remission of signs of infection and wound healing are clinical goals for therapy and this is often supported by cessation of osteolysis on imaging. In the event of persistent symptoms, other possible infective foci should be sought.

Chronic Non-infectious Osteomyelitis

There are several inflammatory diseases of the jaw that have a non-infectious, idiopathic etiology, including primary chronic osteomyelitis, chronic diffuse sclerosing osteomyelitis, SAPHO syndrome, and chronic recurrent multifocal osteomyelitis (CRMO). The term Garré's osteomyelitis, originally ascribed to non-infectious osteomyelitis cases in children, is still frequently encountered in medical and dental literature but should be considered a descriptive term and not a distinct disease entity [1].

Primary Chronic Osteomyelitis

Primary chronic osteomyelitis (PCO) is an inflammation of the bone that characteristically lacks suppuration and formation of sequestra. It affects both children and adults. The disease lacks a distinct acute phase and is diagnosed based on symptomology, recurrence, and most importantly, lack of pus formation. Prevailing theories for the development of PCO include an altered or heightened immune response to an organism of low virulence, vascular insufficiency, or autoimmunity. All theories are subject to intense debate and active investigation [26]. An infectious etiology has not been identified.

Patients with PCO may present clinically with recurrent pain, swelling, and trismus. Radiographic evidence of patchy trabeculation and "onion-skin" subperiosteal bone formation may be present (Fig. 22.5). Histologically, samples from affected patients will demonstrate thickened bony trabeculae surrounded by medullary fibrosis. When there is an acute exacerbation of disease, bone samples may demonstrate invasion of the medullary space with chronic and acute inflammatory cells, including scattered giant cells. Sclerotic bone with multiple irregular lines of resorption and remineralization may also be observed on biopsy.

Treatment of PCO can range from antibiotics alone to surgical debridement or resection of affected bone [26]. Primary chronic osteomyelitis often recurs when managed by antibiotics alone, so adjuvant non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, or hyperbaric oxygen may be considered. Case studies of children treated secondarily with pamidronate have demonstrated excellent response with marked reduction of symptoms, although recurrence was not prevented [27, 28]. Owing to the high recurrence rate, patients need to be followed vigilantly.

Chronic Diffuse Sclerosing Osteomyelitis (CDSO)

Chronic diffuse sclerosing osteomyelitis (CDSO) is a variant of PCO sharing the clinical characteristics of recurrent pain, swelling, and trismus in the absence of pus, fistula, or sequestration formation. Radiographically, it is characterized by a pattern of intermingled sclerotic and osteolytic changes with either periosteal reaction or external bone resorption. As in PCO, the etiology is unknown. In 1994, Marx et al. suggested that CDSO was linked to coinfection with *Actinomyces* and *Eikenella corrodens* [29], but other researchers have not corroborated this [30].

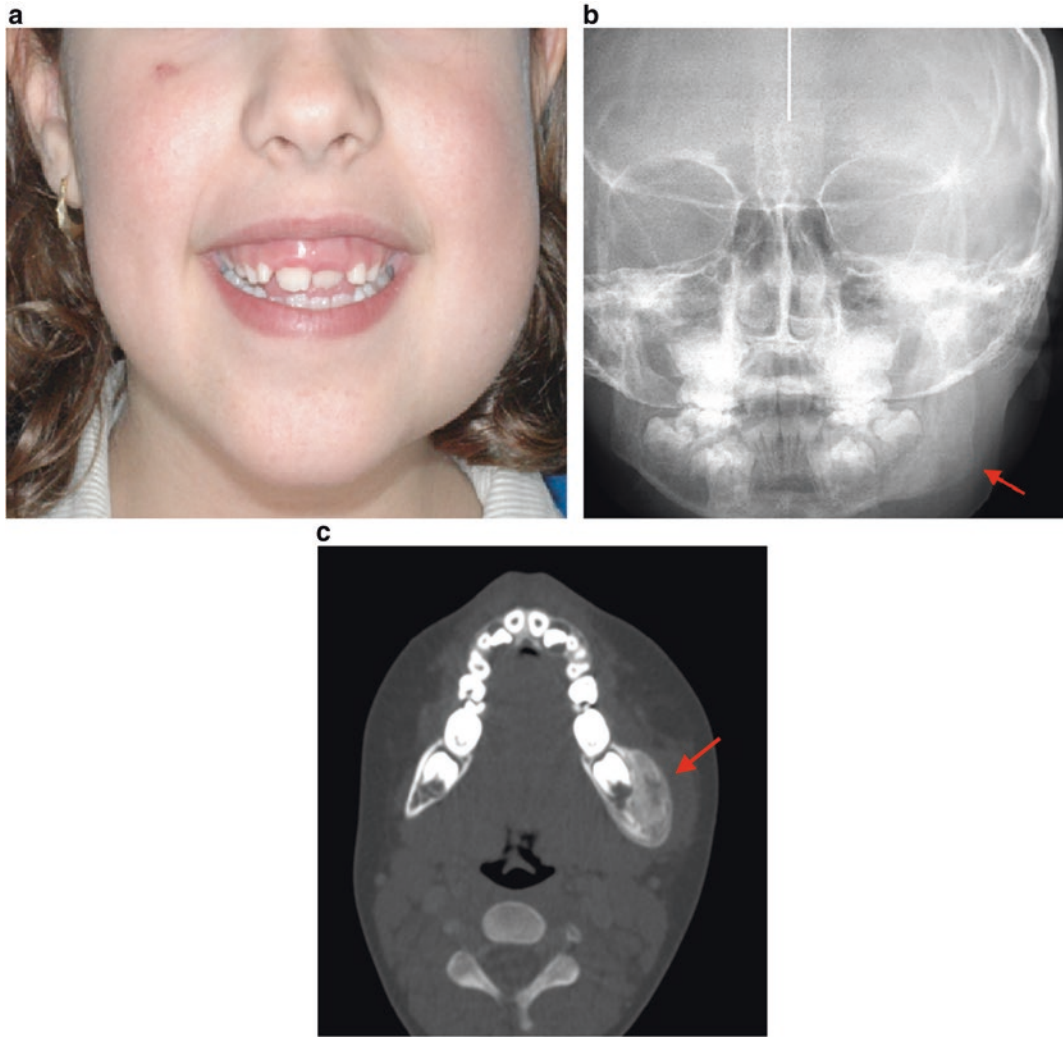

Fig. 22.5 (**a**–**c**) Primary chronic osteomyelitis (PCO). The child presented with pain, swelling, and tenderness of the left mandible (**a**). Radiographic changes included (**b**) bony expansion and sclerosis (arrow) on plain film and (**c**) extensive subperiosteal bone formation on CT (arrow)

Chronic diffuse sclerosing osteomyelitis can occur in the mandible, maxilla, and long bones. It can affect patients of any age, but typically is found in young adults. Mean age of onset has been reported to be 27 years with a 4:1 female:male ratio [31]. When diagnosed in the mandible, involvement is usually unilateral. Patients will often have an elevated ESR but otherwise normal laboratory values. Histologically, biopsies may appear normal early in the process and subsequently demonstrate coarse trabeculae surrounded by medullary fibrosis, sclerotic bone, and granulomatous areas with abundant inflammatory cells [31]. Immunologic staining demonstrates areas of bone undergoing active osteolysis. Early stage CDSO can easily be misinterpreted on intraoral films as either periapical pathology and/or focal condensing osteitis. As the disease progresses, radiographic features more closely resemble florid osseous dysplasia.

The treatment of CDSO includes removal of compromised teeth, antibiotics, NSAIDs, and surgical debridement or resection. Antibiotic courses appear most effective at relieving symp-

toms in earlier stage disease. Recurrence is common. Case reports have demonstrated the efficacy of pamidronate in managing recurrent disease that is unresponsive to antibiotic therapy [32]. Kuijpers et al. reported that seven patients with CDSO treated with pamidronate had reduction of pain, with two patients remaining pain free 30 months after initial treatment [33]. The effectiveness of anti-inflammatory medications in managing CDSO suggests an autoimmune etiology, although as in other forms of PCO, this is not well understood.

While CDSO is still considered a distinct disease entity, some authors suggest that CDSO may be part of the disease spectrum of SAPHO syndrome but with a localized expression of immune-mediated osteitis and without other clinical features of SAPHO syndrome. Research on the effectiveness of anti-tumor necrosis factor alpha (anti-TNFα) medications in managing the osteomyelitis in SAPHO syndrome may also benefit patients suffering from CDSO [34].

SAPHO Syndrome

SAPHO syndrome derives its name from the constellation of symptoms which characterize this form of osteomyelitis: *s*ynovitis; *a*cne; *p*almoplantar pustulosis; *h*yperostosis; and *o*steitis. It is a rare condition and occurs mostly in children, adolescents, and young adults [35]. Diagnosis is based on clinical presentation and radiographic imaging (Fig. 22.6). The clinician should be aware that all components of SAPHO may not be present at the outset. Some patients have synovitis and osteitis without any skin manifestations, for example [36]. Various symptoms may manifest years apart and, without clinician awareness, diagnosis may be delayed. Osteitis and synovitis most commonly affect bones of the anterior chest wall but also may occur in vertebral, peripheral, and flat bones. Palmoplantar pustulosis is the most common dermatologic manifestation, occurring in about 60% of patients with skin manifestations. Severe acne that is unresponsive to antibiotics can occur in up to 25% of patients. Rarely, pyoderma gangrenosum, a severe ulcerative skin condition, and Sweet's syndrome (acute febrile neutrophilic dermatosis) may be found in patients with SAPHO syndrome [37].

The etiology and pathogenesis of SAPHO syndrome is unknown. One theory is that exposure to certain bacterial species triggers an autoimmune reaction in genetically predisposed individuals. *Propionibacterium acnes* is a common isolate from the bones of SAPHO patients, but a causal link has not been established [38]. Symptoms can also resemble those of rheumatoid arthritis and ankylosing spondylitis. Przepiera-Będzak compared the expression of several inflammatory markers in SAPHO syndrome, ankylosing spondylitis, and rheumatoid arthritis and noted increased levels of interleukin-18 in SAPHO patients compared to the other groups [39]. Interleukin-18 is a proinflammatory molecule that induces cell-mediated immunity following infection but is frequently elevated in other autoimmune diseases, such as Hashimoto's thyroiditis.

Treatment of SAPHO syndrome includes use of NSAIDs, intra-articular steroids, and bisphosphonates. Antibiotics are used for secondary infection. In refractory or unresponsive cases, interleukin-1 and TNFα inhibitors may be helpful [37].

Chronic Recurrent Multifocal Osteomyelitis (CRMO)

Chronic recurrent multifocal osteomyelitis (CRMO) is characterized by chronic, non-infectious osteitis with multiple foci of disease. It is usually a diagnosis of exclusion. It occurs most often in children ages 9–14 but has been reported in infants and adults as well. Bone pain and swelling are common presenting symptoms and patients are variably febrile. Multiple foci of inflammation in a single bone or lesions in multiple bones, including the clavicles, vertebrae, and the mandible, have been reported [40]. Despite radiographic changes, patients may remain asymptomatic. Routine laboratory tests are nonspecific and cultures are negative. Radiographically, osteolytic lesions are seen near

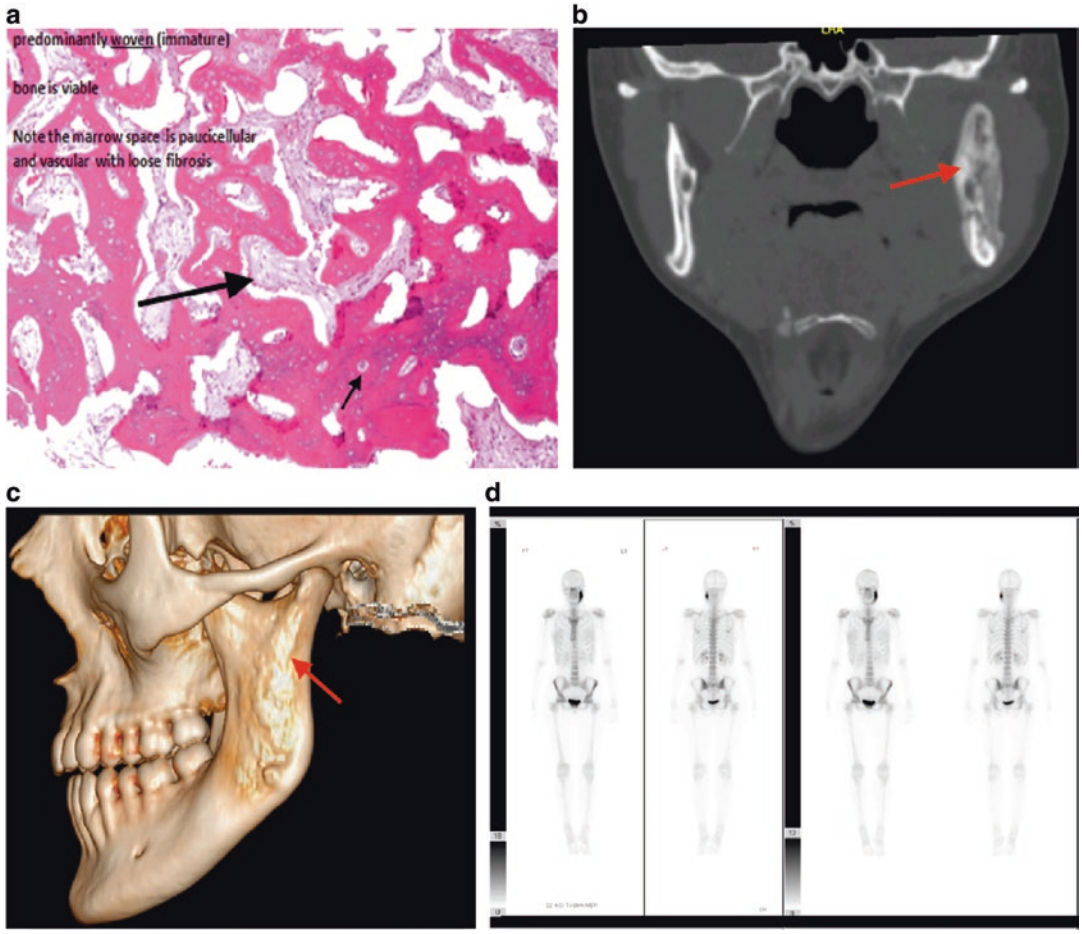

Fig. 22.6 (**a**–**d**). SAPHO Syndrome. (**a**) Pathology demonstrates the largely woven nature of the bone with osteocytes present within the lacunae (small arrow) and paucicellular, fibrous medullary spaces (large arrow). Computed tomography (**b**) coronal section and (**c**) 3-dimensional reconstruction demonstrate extensive mandibular involvement approaching the condyle (arrows). (**d**) Technetium-99 bone scan shows the mandible to be the only bone involved in this patient

growth plates in the long bones. Presentation in the mandible tends to be more sclerotic [41]. Histologically, bone samples will demonstrate nonspecific features of inflammation, with fibrosis, sclerosis, and varying acute and chronic inflammatory infiltrates based on the disease phase at the time of biopsy.

Magnetic resonance imaging is one of the most useful imaging modalities for evaluating CRMO as it can demonstrate both bone and soft tissue involvement. Bone scintigraphy is commonly used to demonstrate multiple foci of skeletal involvement. Manson et al. reviewed seven cases of CRMO in children and found that bone scintigraphy could detect asymptomatic disease sites that later progressed [42]. Although CRMO classically demonstrates multiple lesions near metaphyseal growth plates, this is not pathognomonic and bone biopsy is often necessary to rule out benign and malignant bone tumors.

The pathogenesis of CRMO is strongly linked to other autoimmune disorders. There is a female predilection (female:male ratio of 2:1). Patients with CRMO are more likely to have a family history of an inflammatory disease and up to 25%

will have psoriasis, inflammatory bowel disease, or another inflammatory condition [41]. CRMO is also associated with the genetic disorder Majeed syndrome (defined by a mutation in *LPIN2*) causing a triad of CRMO, congenital dyserythropoietic anemia, and inflammatory dermatosis [40]. Chronic recurrent multifocal osteomyelitis is also a phenotypic expression of deficiency of interleukin-1 syndrome, which is caused by a mutation in *IL1RN* [43]. There is also some belief that due to the links between CRMO and dermatologic inflammatory diseases, CRMO is related to SAPHO syndrome, either as a pediatric equivalent of SAPHO or as a milder variant [30]. However, this theory is not well supported by genetics research and the two are still considered separate entities.

Treatment of CRMO can be delayed due to misdiagnosis, with patients undergoing prolonged courses of antibiotics without improvement. Initial treatment is usually with NSAIDs, but if there is a poor response, anti-TNFα and bisphosphonates can be considered.

Conclusion

Mandibular osteomyelitis is usually due to infection. Most cases have an odontogenic etiology or arise following a traumatic mandibular fracture. Early diagnosis can be difficult, and orthopantomogram demonstrates characteristic abnormalities once bony demineralization exceeds 30–40%. Cultures of infected bone usually grow a mixture of oral flora organisms, although cultures obtained via the mouth may be hard to interpret as these are contaminated by oral flora. *Actinomyces* plays an important role in many cases of chronic infectious mandibular osteomyelitis. Treatment involves a combination of surgery and prolonged antibiotics. Non-infectious mandibular osteomyelitis may be part of a systemic immune-mediated condition such as SAPHO syndrome or chronic recurrent multifocal osteomyelitis. It is important for clinicians to be familiar with these syndromes to avoid delays in diagnosis.

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Mumps and Other Types of Viral Parotitis

23

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Mumps

Mumps is the most common viral etiology of acute parotitis. Mumps virus is a paramyxovirus that belongs to the *Rubulavirus* genus. Clinical mumps was first described by Hippocrates in the fifth century BC during a mumps outbreak on the island of Thasos [1]. A causative agent for mumps was not demonstrated until 1934, when Johnson and Goodpasture showed that mumps was caused by a virus present in the saliva of infected patients [2, 3]. The name mumps may be derived from the old English verb that means to grimace, grin, or mumble [4]. Classic mumps is characterized by parotitis and is usually a mild disease, although in the pre-vaccine era up to 15% of mumps patients developed meningitis [5]. Other complications included encephalitis, orchitis, oophoritis, mastitis, pancreatitis, and deafness.

Introduction of the measles, mumps and rubella (MMR) vaccine greatly reduced the incidence and morbidity of mumps. In the U.S., for example, the first mumps vaccine was licensed in 1967 and by 2005, widespread use of the two-dose vaccine had reduced mumps incidence by 99% [6]. There were 186,000 cases of mumps annually before 1967 and only 200–1000 cases annually between 2000 and 2016 except for 4 outbreak years. The worst outbreak (2006) affected 6500 patients, or 3% of the pre-vaccine era annual number [6]. Various mumps outbreaks have occurred among MMR vaccinated populations worldwide, usually affecting primarily adolescents and young adults, indicating that vaccination is not 100% effective and that protection wanes with time.

Epidemiology

In the pre-vaccine era, mumps was an endemic childhood disease with epidemic peaks every 2–5 years and the majority of cases occurring in children 5–9 years old [7, 8]. Most children were infected by early adolescence. A study from the Netherlands found that 50% of children in the

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_23

pre-vaccine era had antibodies to mumps by age 4 and over 90% by age 14 [9]. A similar study from England found that 63% of children had antibodies to mumps before age 5 and 87% by age 10 [10]. In Poland, mumps vaccine was not included in the national vaccination program before 2003, and a seroprevalence study of the population 1990–2003 found mumps immunity in only 24% of children ages 1–4, 45% in ages 5–9, and 73% in ages 10–14 [11]. These findings have justified mumps vaccination beginning in early childhood.

In temperate climates the incidence peaks in winter and spring, whereas the disease may occur at any time of the year in tropical areas [12]. Mumps outbreaks in the post-vaccine era predominantly affect young adults, including those who were vaccinated against mumps during childhood. Outbreaks among vaccinated persons have been reported worldwide in countries that have mumps vaccination as part of their national immunization programs, such as the United States, Canada, Australia, Spain, Israel, the Netherlands, Germany, and Belgium [13–20].

Mumps virus genotyping is based on the 316 nucleotides of the small hydrophobic (SH) gene. Twelve mumps virus genotypes have been defined so far, named A-N. Because the earlier proposed genotypes E and M are not validated by the phylogenetic analysis of the most updated dataset, these genotypes no longer exist [21]. In contrast with the pre-vaccine era when genotypes of wild type mumps virus strains were more diverse, mumps outbreaks among vaccinated persons are predominantly caused by genotype G mumps viruses. Therefore, a possible mismatch in epitope regions between the Jeryl Lynn vaccine strain that belongs to genotype A and the recently circulating mumps viruses that belong to genotype G has been hypothesized as the cause of the recent mumps outbreaks among MMR vaccinated persons. This hypothesis is strengthened by the finding that vaccine-induced neutralization titers seem to be lower against genotype G mumps virus strains [22–24].

Recent mumps outbreaks have occurred most frequently in young adults and particularly in students, which suggests that the social behavior of this group could play a role in the occurrence of these outbreaks [25–27]. Many students live in a closed environment (e.g., dormitories), and prolonged exposure to someone with mumps is associated with an increased risk for mumps [28, 29]. Furthermore, most students have only vaccine-acquired immunity, as the incidence of mumps rapidly decreased after the introduction of MMR vaccination in the national immunization programs.

Clinical Manifestations

Mumps virus is transmitted via direct contact or by airborne droplets and the usual incubation period is 16–18 days (range 12–25 days) [12, 30]. The virus has been isolated from saliva from 7 days before until 9 days after onset of symptoms [31, 32]. A prodrome of approximately 48 h of symptoms such as fever, headache, myalgia, fatigue, and loss of appetite often precedes the onset of parotitis. Patients may be contagious during this prodromal phase and for at least 5 days after the onset of parotitis. Isolation of patients with mumps includes standard and droplet precautions during the contagious period. In 2008, the Centers for Disease Control and Prevention (CDC) shortened the isolation period for mumps patients from 9 to 5 days after onset of parotitis [33].

The clinical hallmark of mumps is parotitis. Parotitis can be unilateral or bilateral and occurs in up to 98% of clinically identified mumps cases, although this high frequency reflects the fact that physicians are unlikely to diagnose a presumptive case of mumps without parotitis [34–37]. Parotid swelling usually peaks in 1–3 days and subsides within a week, but may last up to 10 days. The swollen tissue lifts the ear lobe outward and obscures the angle of the mandibule [37]. The submandibular and sublingual glands are less commonly affected. Figures 23.1 and 23.2 illustrate the salivary glands and a case of mumps in a young child. Besides parotitis, symptoms may include fever, malaise, headache, abdominal pain, nausea, and vomiting. In an outbreak in Israel 2009–2011, symptoms included swelling of one or more salivary glands (94%), fever (55%), malaise (29%), headache (15%), abdominal pain (7%), nausea (7%), vomiting

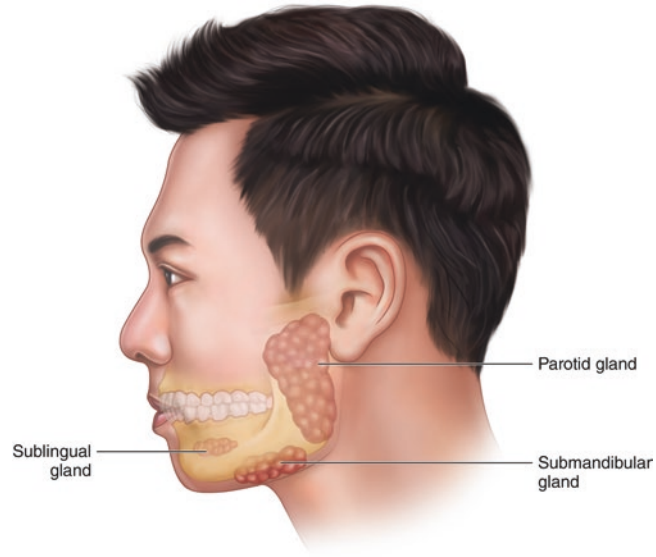

Fig. 23.1 Diagram of the salivary glands

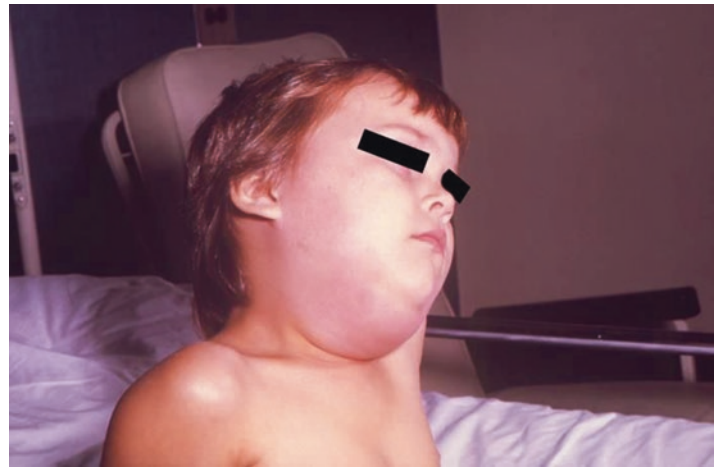

Fig. 23.2 Image of a young child with mumps. From the Public Health Image Library, Centers for Disease Control and Prevention

(5%) [36]. These symptoms may occur before the onset of parotitis. Furthermore, many mumps virus infections run an asymptomatic course or present only with nonspecific symptoms; about one-third of mumps virus infections are asymptomatic in unvaccinated persons and this proportion is probably higher in vaccinated persons, which underlines the protective effect of mumps vaccination [21, 22, 29, 38].

Complication rates reported for mumps strongly fluctuate and are dependent on vaccination status, as mumps in vaccinated persons usually runs a milder course. The most common complication in adult males is orchitis. The clinical manifestations of orchitis are usually milder in vaccinated patients than in unvaccinated patients and sterility after orchitis is rare [39, 40]. Replicating mumps virus has been isolated from the testis and semen, which indicates that orchitis is the result of direct invasion of the testicular cells [41, 42]. On the other hand, the rapid development of orchitis after MMR vaccination in 2 persons who were exposed to mumps in the past suggests that these cases of post-vaccine orchitis may be a result of pre-existing immune responses in the testis, which react immediately upon exposure to

Table 23.1 Complications reported in mumps patients

Complications	Unvaccinated patients, %	Vaccinated patients (two doses MMR), %
Meningitis	0.4–10	0.1–1
Encephalitis	0–0.7	0
Pancreatitis	0–4	0–0.6
Orchitis[a]	8–38	2–7
Oophoritis[b]	0–4	0.8
Mastitis[b]	0–31	0
Deafness	0–4	0.1

From refs. [7, 34, 36, 44, 45, 47–49]
MMR mumps, measles, rubella vaccine
[a]In males age 12 years and older
[b]In females age 12 years and older

mumps virus antigen [43]. Vaccine effectiveness against orchitis is estimated as 72%–81% for two MMR doses [36, 44–46]. In adult females, oophoritis is reported at low frequencies [47]. Other complications associated with mumps include meningitis, encephalitis, pancreatitis, mastitis, and deafness (Table 23.1). Myocarditis and nephritis have been rarely reported as complications associated with mumps [50]. Long term complications and deaths associated with mumps are rare. Mumps virus reinfections have been reported, but are usually milder than primary mumps virus infections [51].

Diagnosis

The diagnosis of mumps relies on clinical features and laboratory findings. Laboratory confirmation is based on mumps virus isolation, detection of viral nucleic acid, or measurement of mumps-specific antibody concentrations. Mumps virus can be isolated from saliva, throat swabs, urine, cerebrospinal fluid (CSF), or seminal fluid within the first week after onset of symptoms [37]. After growth in cell culture, mumps virus can be detected by immunohistochemical staining or by reverse transcription polymerase chain reaction (RT-PCR). Alternatively, viral nucleic acid can be directly detected in clinical specimens via RT-PCR.

The adequacy and timeliness of sample collection affects diagnostic accuracy: the yield of virus from saliva samples declines as time elapses following symptom onset. The saliva sample should be obtained by swabbing around Stensen's duct (buccal swab) following a 30 s gentle parotid massage [30]. Synthetic swabs are preferred over cotton because cotton swabs may contain substances inhibitory to enzymes used in RT-PCR. Swabs should be placed in tube with 2 ml of standard viral transport medium. In countries such as the United Kingdom and the Netherlands, the use of a sponge device has been introduced as a successful alternative to the swab in the collection of saliva.

In the case of IgM serologic testing, a blood sample should be obtained at the time of presentation. Because the IgM response is usually not detectable during the first few days after symptom onset, the CDC recommends sending an additional serum sample for IgM testing 5–10 days after onset of parotitis in patients whose initial acute serum and RT-PCR assays were collected within 3 days of symptom onset and were negative [52]. It should be noted that a significant proportion of mumps patients never develop IgM antibodies, notably those patients who were fully vaccinated against mumps [35].

The most recent case definition of mumps by the CDC is from 2012 (Table 23.2) [52]. Cases are classified as suspected, probable, or confirmed. Probable cases are those with compatible clinical findings (e.g., parotitis for at least 2 days) along with a positive IgM or epidemiologic link to a probable or confirmed mumps case. A confirmed case is one with compatible clinical findings plus laboratory identification of mumps virus by RT-PCR or viral culture.

Results of IgG testing are not part of the CDC mumps case definition. Testing of paired sera for IgG is not recommended in vaccinated patients, due to the rapid rise in IgG shortly after mumps infection. As a result, paired analysis of sera rarely demonstrates a four-fold rise in titer in vaccinated patients [53]. In unvaccinated patients, a four-fold rise between acute and convalescent titers is usually evident.

Laboratory diagnosis of mumps is challenging in previously vaccinated patients. Mumps cases should not be ruled out by negative laboratory findings since the IgM may be negative in cases

Table 23.2 Mumps case definition, from the Centers for Disease Control and Prevention (CDC) [52]

Suspected
• Parotitis, acute salivary gland swelling, orchitis, or oophoritis unexplained by another more likely diagnosis *OR*
• A positive lab result with no mumps clinical symptoms (with or without epidemiological linkage to a confirmed or probable case)
Probable
• Acute parotitis or other salivary gland swelling lasting at least 2 days, or orchitis or oophoritis unexplained by another more likely diagnosis, in:
– A person with a positive test for serum anti-mumps immunoglobulin M (IgM) antibody, *OR*
– A person with epidemiologic linkage to another probable or confirmed case or linkage to a group/community defined by public health during an outbreak of mumps
Confirmed
• A positive mumps laboratory confirmation for mumps virus with reverse transcription polymerase chain reaction (RT-PCR) or culture in a patient with an acute illness characterized by any of the following:
– Acute parotitis or other salivary gland swelling, lasting at least 2 days
– Aseptic meningitis
– Encephalitis
– Hearing loss
– Orchitis
– Oophoritis
– Mastitis
– Pancreatitis

of prior vaccination or natural infection, and RT-PCR or viral culture may be falsely negative if the buccal culture is obtained too long after parotitis onset [52]. In an analysis of samples from confirmed cases in a 2009 mumps outbreak in New York City, only half of the previously vaccinated patients had positive IgM results [35]. In this same study, RT-PCR was positive in 78% of buccal samples obtained within 2 days of symptom onset but in only 41% of samples collected 3 or more days after symptom onset [35].

A practical approach to a patient who presents with acute parotitis or other acute symptoms consistent with mumps is to immediately obtain serum for mumps IgM and IgG, and a buccal swab for viral RT-PCR, as described above. A history of vaccination should be obtained; unvaccinated patients are at highest risk for mumps although even individuals who have received two doses of MMR are susceptible, as discussed above. A history of contact with a person with known or suspected mumps should be elicited. Patients suspected of having mumps should be placed on droplet precautions for 5 days while in healthcare settings; outpatients with mumps should stay home from school or work for 5 days, unless mumps has been definitively ruled out earlier than this. The local public health authorities should be notified of a mumps suspect case and will help determine the appropriate public health response. For confirmed cases, close contacts of the case-patient during the two days prior through five days after onset of parotitis are usually identified, assessed for immunity, offered vaccine as appropriate, and educated about signs and symptoms of mumps.

Treatment

Mumps is a self-limiting disease, and treatment is symptomatic and supportive. Patients may benefit from antipyretics such as acetaminophen, and anti-inflammatory medications. Aspirin should be avoided in children and adolescents with viral infections due to the increased risk of Reye's syndrome.

Various measures have been tried for treating serious complications of mumps, in addition to supportive care, but none have proven efficacy. High concentrations of anti-mumps antibodies are present in most commercial intravenous immunoglobulin (IVIG) preparations [54], but an unvaccinated child who developed mumps encephalitis worsened despite a brief course of IVIG [55]. Interferon alpha 2b has been proposed as a treatment for mumps orchitis to prevent infertility, but the results have been conflicting. Erpenbach first described this treatment in 1991 and reported successful outcomes in 4 patients with mumps orchitis treated with 7 days of interferon alpha 2b [56]. Ku et al. reported successful outcomes in 13 patients with mumps orchitis treated with interferon alpha 2b, while some untreated patients developed low sperm counts [57]. Yenigol et al., however, found that 39% of

18 mumps orchitis patients treated with interferon alpha 2b developed testicular atrophy [58]. Randomized controlled trials would be necessary to determine if there is any benefit to interferon treatment of acute orchitis.

Prevention

Vaccination is the best way to prevent mumps and all available mumps vaccines consist of live attenuated mumps virus. Different mumps virus strains have been introduced as vaccine components worldwide. The predominant mumps vaccine strains include Jeryl Lynn, RIT 4385, Urabe Am9, Leningrad-3, L-Zagreb, Rubini, and S79 [59]. In addition, a few other vaccine strains are used on a limited scale [12]. The Rubini strain is the only strain that is not recommended for use in national immunization programs, because of its low effectiveness as compared with the other mumps vaccine strains [12]. The Urabe strain has been associated with a substantial increase in the occurrence of aseptic meningitis and febrile convulsions following vaccination, and was therefore withdrawn from several countries [7]. The vaccine strain used in most countries worldwide is the Jeryl Lynn vaccine strain, which was isolated in 1963 by Hilleman [60]. The Jeryl Lynn vaccine, which is part of the MMR vaccine, is administered in a two-dose schedule during childhood. In the U.S., the first mumps vaccine is given at age 12–15 months and the second at age 4–6 years. The Jeryl Lynn vaccine contains a mixture of 2 independently replicating mumps virus genotype A strains, designated JL2 and JL5 [61–63]. Vaccine effectiveness for two doses of Jeryl Lynn vaccine ranges from 66% to 95%, depending on the study population and exposure setting [20, 25, 64–70]. Although the recent mumps outbreaks show that the Jeryl Lynn vaccine does not fully protect against mumps virus infection, the vaccine reduces the incidence and severity of complications.

Mumps vaccine induces both humoral and cell-mediated immune responses [71, 72]. Mumps-specific IgG concentrations in the blood are long-lasting, although antibody concentrations induced by MMR vaccine are lower than those following mumps virus infection [73–75]. A 20-year follow-up study showed that the decrease in both antibody concentration and avidity after MMR vaccination was greater for mumps than for measles or rubella, the other components of the MMR vaccine [76]. Furthermore, mumps vaccination induces strong memory T cell immunity, as was measured in a study of adults who received MMR vaccine during childhood [71, 73]. Since the cell-mediated responses seem to last longer than the humoral responses, the waning in humoral responses seen in adults who received MMR during childhood does not necessarily mean that these adults are susceptible to mumps virus infection [73].

Other Viral Causes of Acute Parotitis

The differential diagnosis in patients with acute parotitis mimicking mumps includes acute bacterial parotitis and acute viral parotitis due to other viruses. Acute bacterial parotitis is usually readily distinguished from mumps because the former is almost always unilateral and is typically characterized by purulent drainage from Stenson's duct. Acute bacterial parotitis may complicate acute parotid swelling secondary to ductal obstruction from a stone. Bacterial parotitis is discussed further in Chap. 24.

Acute viral parotitis may be due to several non-mumps viruses and patients may present with a mumps-like illness. A study from Finland found that only 2% of 601 vaccinated children and adolescents with mumps-like illness had mumps, while another viral etiology was identified in 14% by use of paired serologies [77]. The other viruses included Epstein-Barr virus (EBV), parainfluenza virus, adenovirus, enterovirus, and human herpesvirus 6 (HHV-6) [77]. A study from Spain found a viral etiology in 52% of 101 patients with mumps-like illnesses not due to mumps [78]. The viruses were identified by PCR testing of oral samples and included EBV (25%), parainfluenza viruses (13%), adenoviruses (4%), enterovirus (1%), influenza virus A (1%), or a mixture of two or more viruses [78]. Investigators at the CDC used PCR to evaluate oral samples of 101 patients with acute parotitis and found that

none tested positive for mumps but 38% tested positive for another virus including EBV (23%), HHV-6 (10%), parainfluenza virus (4%), and human bocavirus (1%) [79]. While detection of EBV may represent reactivation of latent virus in the setting of acute parotitis due to another etiology, EBV does appear to cause some cases of acute parotitis. A study from Nova Scotia of buccal samples and serologies obtained during a 2007 mumps outbreak found PCR evidence of EBV in 12% of oral samples from 85 mumps-negative patients, and serologies confirmed that 30% of these EBV cases were due to acute EBV [80]. Adenovirus, parainfluenza 3, and influenza A were also detected in a few cases of acute parotitis in this study. Adenovirus has also been recovered in viral culture from a child with acute parotitis [81]. Parainfluenza viruses 1–4 are common causes of respiratory infections, particularly in children, although the incidence of parotitis is unknown and very likely rare. Two recent large series did not list parotitis as one of the clinical features of parainfluenza virus infection [82, 83]. Influenza virus, primarily influenza A (H3N2), was the etiology of several hundred cases of parotitis reported to the CDC during the 2014–2015 influenza season [84]. Over 80% of these patients had one or more respiratory symptoms (cough, sore throat, coryza) in addition to parotitis, and most had mild illness.

It is possible that other viruses in addition to those discussed above may rarely cause acute parotitis. A case report of ipsilateral parotitis during an episode of herpes zoster ophthalmicus has been described [85]. A case of parotitis, orchitis, and meningoencephalitis was reported in 1961 and ascribed to lymphocytic choriomeningitis virus, although subsequent cases of parotitis associated with that virus have not been reported [86].

Chronic Parotid Disorders Related to Viral Infections

Chronic salivary gland disorders have been associated with some viruses, including human immunodeficiency virus (HIV), cytomegalovirus (CMV), hepatitis C virus (HCV), and EBV. Malignancy should be considered when evaluating patients with chronic masses or enlargement of the parotid or other salivary glands.

Human immunodeficiency virus-associated salivary gland disease (HIV-SGD) involves chronic swelling of the major salivary glands, with the parotid being most commonly affected [87, 88]. Parotid enlargement in HIV-SGD patients is usually bilateral and painless [89]. HIV-SGD affects only a small subset of HIV-infected persons [88], but children are affected more often than adults [90]. The time of onset of parotid swelling may vary from early to late in the course of untreated HIV infection, and HIV-SGD may be associated with reduced stimulated parotid flow rates [88]. Most cases of HIV-associated parotid enlargement are due to benign lymphoepithelial cysts (BLEC), but some cases are associated with diffuse lymphocytic infiltrative syndrome (DILS) [91, 92]. The pathogenesis of BLEC is controversial, and histologically the cysts are located within parotid lymph nodes [91, 93]. The response of many cases of BLEC to highly active antiretroviral therapy (HAART) emphasizes the role of HIV in BLEC pathogenesis, however [94, 95]. In HIV-SGD related to DILS, there is some evidence that BK virus also plays a role in pathogenesis [90]. Patients with HIV may develop acute parotitis from other viral infections; a report from the pre-HAART era documented acute unilateral parotitis due to adenovirus in an HIV-infected patient with CD4 count of 7 [96].

Cytomegalovirus has been purported to be a cause of xerostomia secondary to chronic salivary gland infection, but this has not been substantiated. Cytomegalovirus infects over 70 percent of the general population and establishes latency at several sites, including the salivary glands [97]. Reactivation may occur during an unrelated illness or during immunosuppression, so detection of CMV in the saliva does not establish that CMV is the etiology of a particular condition. A study from 1997 of 20 HIV-infected patients, for example, found that CMV was recovered more often in those with xerostomia than those without this condition, but the difference was not significant [98].

Hepatitis C virus has been associated with histological signs of sialadenitis, often in the absence

of symptoms [99]. Patients with HCV frequently have evidence of lymphocytic inflammation of the salivary glands, but HCV may not be directly responsible [100]. In a study of 65 patients with chronic HCV, 35% had xerostomia and 20% had hyposalivation, but there was no correlation between these findings and the presence of HCV RNA in saliva or minor salivary gland tissue [101].

Epstein-Barr virus infects over 90% of the human population and can remain latent in salivary glands, so a link between EBV and Sjögren's syndrome (SS) has been hypothesized for many years [102]. Different studies have reported conflicting results for the relatively frequency of EBV expression in SS salivary glands versus controls, so the link between EBV and SS remains controversial. Ectopic lymphoid structures within salivary glands are features unique to SS, although present in only 30–40% of SS patients. Stratification by the presence or absence of these ectopic lymphoid structures may resolve the controversy, since an EBV-SS link appears to be present in SS patients with ectopic lymphoid structures [103].

Conclusion

Mumps is an acute viral infection that typically presents with unilateral or bilateral parotitis, often following a 48-hour prodrome of "viral" type symptoms such as fever, headache, fatigue, loss of appetite, and myalgias. Other viruses may also cause acute parotitis, such as influenza A, EBV, parainfluenza, adenovirus, and enteroviruses. Mumps is diagnosed by a combination of clinical and laboratory findings. Vaccination with two doses of MMR in early childhood has successfully reduced the incidence of mumps by 99% from the pre-vaccine era. However, outbreaks in vaccinated populations continue to occur, primarily in adolescents and young adults living in close quarters (e.g., a college dormitory). Complications in vaccinated patients who develop mumps occur less often and are less severe than in unvaccinated patients.

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Bacterial Sialadenitis

24

Neerav Goyal and Daniel G. Deschler

Introduction

Inflammation and infection of the salivary glands can occur throughout one's lifetime from as early as a neonate and well into the elder years. Infectious causes of sialadenitis include viral and bacterial pathogens. This chapter will discuss the etiology and risk factors of bacterial salivary gland infections as well as the diagnosis and management of these disease processes.

Salivary Gland Physiology

The major salivary glands include the paired parotid, submandibular, and sublingual glands, while the minor salivary glands are scattered throughout the oral cavity and oropharynx including the lip, buccal mucosa, hard and soft palate. In the adult, there are an estimated 600–1000 minor salivary glands [1].

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The salivary glands have similar architecture with a group of exocrine cells formed into an acinus with a striated/secretory duct routing the saliva to a larger outflow tract or collecting duct (Stensen's duct for the parotid, Wharton's duct for the submandibular gland, and ducts of Rivinus for the sublingual gland). Figure 24.1 depicts the typical salivary gland architecture.

Salivary glands are exocrine organs that secrete a mixture of a serous or mucinous material. An estimated 1–1.5 L of saliva is produced daily [2]. The parotid produces approximately 20–25% of the daily saliva output which is largely serous in nature. The submandibular gland produces the majority of unstimulated saliva (70–75%) with a mixed serous and mucoid mixture. The sublingual and minor salivary glands secrete largely mucoid saliva [3]. The biologic properties of saliva provide a natural barrier to infection. Salivary composition varies depending on a variety of factors including stimuli, circadian rhythm, as well as the rates of secretion and reabsorption of organic and inorganic compounds [1]. Salivary proteins include amylase, cystatins, mucins, peroxidases, lysozymes that all serve as antimicrobials. There are also secretions of immunoglobulins including IgA, and to a lesser degree IgG and IgM. These components are found in the mucoid secretions [3, 4]. Not only are there antibacterial properties to saliva, its flow also helps remove debris and bacteria from salivary ducts and prevents an ascending infection.

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_24

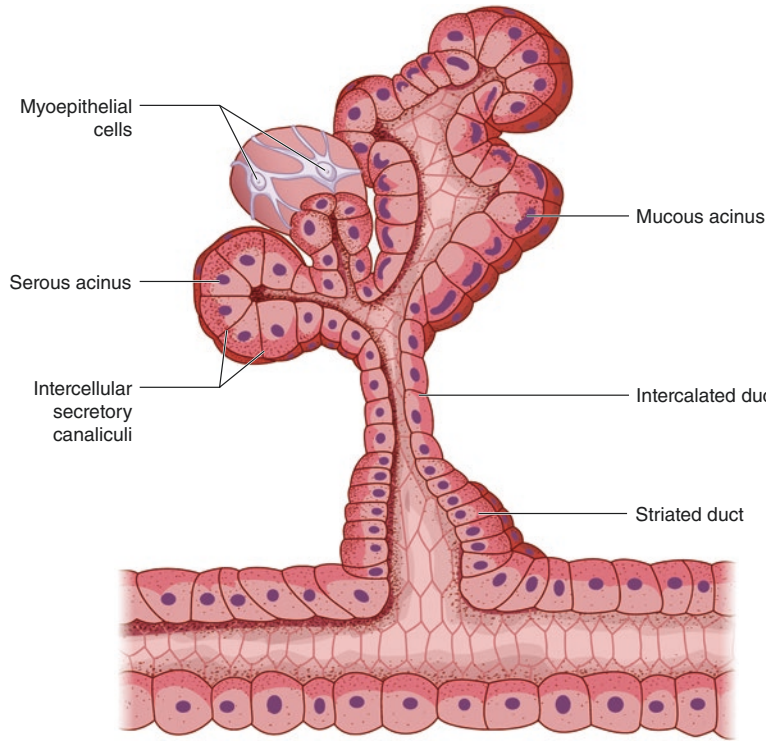

Fig. 24.1 The structure of the typical salivary unit including the acinus, intercalated duct and striated duct

Risk Factors for Infection

Risk factors for salivary gland infection include conditions that decrease the flow of saliva as well as those associated with immunosuppression (Table 24.1). A dental infection also increases the risk of an adjacent salivary gland infection. The transmission of bacteria from the oral cavity into the salivary ducts and salivary glands promotes an infection [5]. Notably, problems with salivary output can include decreased production or decreased outflow [6]. Decreased production can occur secondary to oral dehydration. This can be secondary to iatrogenic causes such as placing a patient on bowel rest or restricting water intake. Other medical conditions such as dementia or renal failure may predispose patients to dehydration. Additionally, a variety of medications

Table 24.1 Risk factors for infectious sialadenitis [5, 6, 14]

Decreased production of saliva
Autoimmune disorders
Primary biliary cirrhosis
Sarcoidosis
Sjögren's syndrome
Dehydration
Iatrogenic causes (abdominal surgery, bowel rest), elderly, neonates
Medications (see the list in Table 24.2)
Radiation
Radioactive iodine
Renal failure
Decreased flow of saliva
Cystic fibrosis
Ductal strictures
Sialolithiasis
Tumors causing ductal obstruction
Iatrogenic injury
Immunosuppression
Dental infection

Table 24.2 Medications affecting salivary production and flow [6, 7]

Amphetamines
Anti-arrhythmics, class IB (e.g., mexiletine)
Anticholinergics (e.g., atropine, propantheline, tiotropium)
Antidepressants
Bupoprion
Lithium
Selective serotonin uptake inhibitors
Tricyclics
Antihistamines
Antihypertensives
Alpha blockers (e.g., doxazosin, terazosin)
Beta blockers
Calcium channel blockers
Centrally acting (e.g., clonidine)
Anti-neoplastic (e.g., monoclonal antibodies)
Antipsychotics
Antiretrovirals
Antispasmodics (e.g., baclofen, tizanidine)
Appetite suppressants (e.g., sibutramine)
Bisphosphonates
Botulinum toxin
Diuretics
Monoamine-oxidase-B inhibitors (e.g., selegiline, rasagiline)
Opioids
Proton pump inhibitors
Urinary frequency/incontinence drugs

(Table 24.2) can contribute to oral dryness and decreased salivary flow [6, 7]. Radiation therapy for head and neck cancer often includes the salivary glands within the radiation field. Total radiation doses as low as 10–35 Gy to the glands can cause destruction of the salivary acini with some selection toward destroying serous producing glands [8, 9]. As a result, the saliva is significantly thicker and there is increased oral dryness. This is additionally seen in patients undergoing radioactive iodine treatment for thyroid cancer [10]. Some autoimmune conditions such as Sjögren's syndrome, sarcoidosis, and primary biliary cirrhosis are associated with decreased salivary production.

Decreased outflow is usually secondary to obstruction. This can be due to ductal strictures or sialolithiasis and also tumors. This can also be due to iatrogenic injury to the outflow tracts of the glands. Cystic fibrosis can cause decrease in salivary flow as well, secondary to the production of a thicker saliva.

Immunosuppression appears to increase the risk for bacterial sialadenitis. Additionally, patients actively being treated for a malignancy with chemotherapy will not only be immunosuppressed, but can also present with mucositis and odynophagia leading to dehydration and poor oral hygiene.

Diabetes is often listed as a risk factor but the frequency of diabetes in series of acute bacterial sialadenitis appears to be similar to that of the general population. In a study by Brook of 47 patients (85% adults) who developed acute bacterial sialadenitis in the greater Washington, DC area 1975–1999, a risk factor was identified in 28 (60%) patients, although at a higher rate in patients with submandibular (seven of nine infections) or sublingual (five of six) sialadenitis than in parotitis cases (16 of 32) [11]. Risk factors in these 28 patients included dehydration (39%), immunosuppression (17%), dental infection (11%), and medications (4%); one patient (2%) had hypothyroidism and one (2%) had diabetes. Raad et al. reviewed 29 patients with acute bacterial sialadenitis hospitalized in Florida 1970–1987, including parotitis (17 cases) and submandibular siadadenitis [12]. Seven cases were nosocomial. Risk factors for xerostomia were present in 48% of patients (e.g., hypovolemia, diuretic therapy, recent surgery/anesthesia, Sjögren's syndrome, local radiation), while prior sialadenitis (10%), sialolithiasis (10%), and trauma to the gland (7%) were other risk factors. Immunosuppression and dental infections were not noted. As in the Brook study, only one patient (3%) had diabetes.

Acute Bacterial Sialadenitis

Acute sialadenitis can be secondary to a retrograde ascending contamination from oral flora bacteria through the collecting ducts of the salivary glands. While all glands can be affected, the parotid gland is disproportionately affected due it its largely serous secretions. These do not contain the antimicrobials and immunoglobulins found in

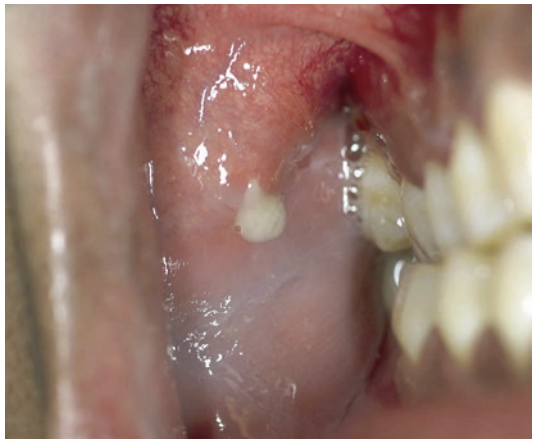

Fig. 24.2 Intraoral view of Stenson's duct (parotid duct) with evidence of purulence on parotid massage. (Reprinted from Levine G, et al. [32], with permission from Elsevier)

mucoid secretions that are in higher concentration in other salivary glands. Specifically affected populations include the elderly and those who are inadequately hydrated. Patients undergoing hip or abdominal surgery are specifically at risk, though the overall risk in the surgical population is low between 1 in 1000 and 2000 procedures [5].

Patients usually present acutely with swelling and significant tenderness over the affected gland; 30% have erythema over the gland [12]. Patients may have systemic symptoms including fevers, chills, and malaise in a setting of a leukocytosis; one study reported that 31% had fever and 34% had leukocytosis [12]. Physical examination will also often demonstrate warmth and induration overlying the affected gland. Intraoral examination usually demonstrates dry mucous membranes. Bimanual palpation of the parotid gland will often result in the expression of purulent material (Fig. 24.2).

Imaging may be performed, though acute bacterial sialadenitis is largely a clinical diagnosis. Sialography may exacerbate the inflammation, however, CT or ultrasound imaging can be considered if the patient does not improve with medical management to evaluate for an abscess. If purulence is identified on examination, this should be cultured for both anaerobic and aerobic bacteria to assist with directing medical management.

The majority of acute bacterial infections are due to *Staphylococcus aureus*. Raad et al. reported that the major pathogens in 29 patients with acute sialadenitis were *S. aureus* (41%) and viridans streptococci (24%); specific anaerobic cultures were not sent in most cases [12]. Brook reviewed cultures obtained by salivary gland aspirate through the skin or by a surgical incision and drainage; careful anaerobic and aerobic cultures were sent [11]. *Staphylococcus aureus* was the most common organism (35% of cases), while *Haemophilus influenzae* (13%), viridans streptococci (13%), *Streptococcus pneumoniae* (9%), *S. pyogenes* (6%), and *Escherichia coli* (4%) were other pathogens [11]. Methicillin-resistant *S. aureus* (MRSA) may be a pathogen in hospital-associated infections but also has been reported in community-acquired cases [13]. As discussed later, MRSA is an important pathogen in some neonatal cases. Anaerobic bacteria, including *Peptostreptococcus, Prevotella,* and *Fusobacterium*, are present in many patients with sialadenitis [11, 12, 14], including two-thirds of the cases in the study by Brook [11]. There are case reports of *Salmonella* species as causative organisms [15]. In East Asia, *Klebsiella pneumoniae* has become an important pathogen for several infections (e.g., liver abscess and endogenous endophthalmitis), and this organism has also been described as causing parotid abscess in a series from Taiwan [16].

Management with directed antibiotics as well as treatment of the underlying condition causing the parotitis are crucial to resolution. Initial therapy should be with broad-spectrum antibiotics that have both anaerobic and aerobic coverage, such as amoxicillin-clavulanate for outpatients or intravenous ampicillin-sulbactam or piperacillin-tazobactam for inpatients or for patients requiring admission. Concentrations of antibiotics in saliva vary depending on antibiotic class, but a review of published studies 1985–2013 did not include any studies with intravenously administered penicillins or antibiotics such as ampicillin-sulbactam that include a beta-lactamase inhibitor [17]. In patients with risk factors for MRSA colonization, such as recent or current hospitalization or residence in a long-term care

facility, the inclusion of intravenous vancomycin (or similar MRSA-active agent) in the antibiotic regimen should be considered. A regimen that treats *S. aureus*, including MRSA, plus streptococci and Gram-negative pathogens should be considered as initial empiric therapy for sialadenitis in neonates; treatment should be tailored by culture results.

In many of these patients there is both reduced salivary flow and reduced production. As such, measures such as aggressive oral hygiene, hydration, and salivary stimulation using sialagogues (e.g., sour candies, lemon wedges, citrus juices) are important. Medications that promote dry mucous membranes (Table 24.2) should be avoided. Salivary flow can also be improved using warm compresses as well as parotid massages. Patients or nursing staff should be instructed to perform the massages with firm external pressure starting at the angle of the mandible and going toward the oral commissure (for the parotid gland) or to the submentum (for the submandibular gland). A positive response should be seen within 2–3 days.

With appropriate therapy (including hydration), most patients will improve and complications are rare. Complications can include the formation of a parotid abscess as well as the spread of infection causing septicemia, thrombophlebitis, or osteomyelitis. Facial paralysis is rare and could be suggestive of an underlying parotid tumor or malignancy causing an obstruction leading to the sialadenitis.

There is a high associated mortality with a diagnosis of acute bacterial sialadenitis, especially in the elderly. In this population, bacterial sialadenitis often occurs in the setting of multiple comorbidities that promote reduced cellular immunity (e.g., cancer), immobility (e.g., ambulatory dysfunction or fall risk), poor oral hygiene (e.g., dementia), dehydration and malnutrition. In several reports, mortality can approach 50% [12, 18], with one case series demonstrating a mortality of 80% among patients diagnosed with acute bacterial parotitis, though notably secondary to the other medical conditions [19].

In addition to presenting in the elderly, there is a rare presentation of bacterial sialadenitis in the newborn, termed either acute neonatal parotitis or neonatal suppurative parotitis when the parotid is involved. Neonatal submandibular gland infection may also occur. The incidence neonatal suppurative parotitis is rare and has been estimated to be 13.8 per 10,000 admitted neonates [20]. Case reports and case series are reported in the literature [21–23]. There is some predilection among premature patients and boys. As with adults, infants usually present with unilateral induration, erythema, and warmth over the parotid gland with expressed purulence from Stensen's duct. Blood cultures should be obtained as some cases are associated with bacteremia. Infants usually present between 7 and 14 days after birth but may present any time during the first month or two of life. Suppurative parotitis is associated with dehydration and prematurity.

Staphylococcus aureus is the most common pathogen, accounting for over 50% of cases [14]; MRSA has caused some severe cases in neonates, and may be associated with bacteremia. Donovan et al. reported two cases of MRSA neonatal parotitis and reviewed 45 cases of neonatal suppurative parotitis published 1951–2013 [22]. *Staphylococcus aureus* accounted for 61% of cases, including some (number not specified) due to MRSA; Donovan reported that 20% of cases had MRSA bacteremia. Unlike acute sialadenitis in adults and older children where Gram-negative bacilli are rarely cultured, Gram-negative bacilli (*E. coli*, *Klebsiella*, *Pseudomonas*, and *Moraxella*) were isolated in 16% of 32 neonatal cases reviewed by Spiegel et al. [23] and 22% of the 45 cases reviewed by Donovan et al. [22] More than one organism was cultured in 18% of the cases in the latter series. Suppurative submandibular gland infection is even more rare than suppurative parotitis in neonates, but this is also usually caused by *S. aureus*. McAdams et al. reported a case of a premature infant (born at 26 weeks) who developed acute submandibular gland infection on hospital day 32 due to a virulent strain of MRSA which contained the Panton-Valentine leukocidin gene, a virulence factor [24]. Blood cultures also grew MRSA and fortunately the infection responded to antibiotics. McAdams et al. included 16 other

cases of neonatal submandibular sialadenitis reported in the literature and found that 82% occurred in premature infants (versus 38% of suppurative parotitis in premature infants) and 16 of 17 cases grew *S. aureus*, including three with MRSA, while one grew *Pseudomonas* [24]. Medical management with culture directed antibiotics is sufficient in the majority of cases and those that fail to improve within 48 h should be further evaluated with ultrasound to rule out the presence of an abscess [21].

Chronic Recurrent Bacterial Sialadenitis

Chronic sialadenitis primarily affects the parotid gland, and various entities have been included in the "chronic parotitis" category. An important category to distinguish from recurrent bacterial sialadenitis is juvenile recurrent parotitis (JRP). Juvenile recurrent parotitis is a condition of unknown etiology that usually affects young children and is characterized by repeated episodes of swelling and redness over one or occasionally both parotid glands. Patients may have fever but infection is not usually found. In a series of 53 children seen at a hospital in Australia 1983–2004, Leerdam et al. reported that the age of onset was biphasic with one peak ages 2–5 and another at age 10 [25]. The most common symptoms in that series were swelling (100%), pain (93%), and fever (42%); children had a mean of 8 episodes per year. Purulence from Stenson's duct is not seen, and antibiotics appear to have no role except in cases of superinfection [25]. Episodes may last several days and typically recur every 3–4 months [26]. Only a small percentage of patients is found to have a rheumatologic or immunosuppressing condition. Although the recurrences usually resolve by puberty, repeated episodes prior to then may lead to the loss of parotid function. Until recently, no treatments appeared to be effective in preventing recurrences. Recently, sialendoscopy has been used to prevent relapses and this appears to be a promising approach, based on reviews of the literature and meta-analysis studies [26, 27]. A retrospective series of 12 patients, mean age 6.7 years, treated at a single center reported mean duration of symptoms to be 22 months prior to the sialendoscopy procedure, with recurrences a mean of 2 months apart [28]. Post-procedure, seven patients reported no recurrences (although follow-up was relatively short) and five had a longer interval between recurrences (4 months); four required a second sialendoscopy procedure.

Confounding the decision regarding treatment is the fact that spontaneous remission is common in children with JRP. Wang et al. followed 28 patients with JRP for mean of >10 years and found that 57% had resolution of episodes before age 15; none developed Sjögren's syndrome [29]. These authors also reported that long-term follow-up of another group of 22 patients who presented ages 15–45 with recurrent parotitis demonstrated that 12 who had onset only in adulthood subsequently developed Sjögren's syndrome, while the ten with a history of JRP did not; seven of these ten had spontaneous resolution of episodes [29].

In patients with adult onset recurrent parotitis, without an identifiable obstruction (e.g., stone, tumor, ductal stricture), efforts should be made to identify a bacterial etiology with each episode and provide appropriate antibiotic treatment. Consultations with a rheumatologist and an infectious disease physician should be considered. In the rare patient in whom neither obstruction, a systemic rheumatologic condition, nor a persistent infection is identified, sialendoscopy may be helpful both diagnostically and therapeutically. If this fails, then surgical intervention can be considered a last resort, utilizing a near total parotidectomy approach [29]. Such surgery is made challenging by the frequent infections, inflammation, and scarring, which occurs in the setting of such long-term illness. In these cases, patients must be informed of an increased risk of facial nerve paresis, which may be transient, or a potential long-term facial nerve paresis and paralysis. Similarly, surgical intervention does not guarantee that all symptoms will be addressed and patients may still be prone to discomfort in the region [30]. If surgery is considered for recurring and chronic bacterial sialadenitis, it should

be performed when the patient does not have an active infection. This may require pretreatment with antibiotics and then consideration of further prolonged treatment postoperatively. Such treatment courses will be determined by cultures obtained intraoperatively. Fortunately, it is rare that such surgical intervention is required. As noted, parotidectomy surgery for recurring bacterial sialadenitis is not to be considered lightly.

Salivary Gland Abscess

In patients where antibiotics fail to show improvement within 72 h, there should be concern for progression to an abscess. Ultrasound (Fig. 24.3) or CT imaging (Fig. 24.4) can be used to identify the presence of a salivary gland abscess. This coalescence presents as a hypoechoic or hypodense circumscribed lesion on imaging. In evaluating the imaging, it is also important to eliminate other possible pathologies that can have a similar initial presentation such as a parotid malignancy, lymphoma, or masticator space abscess related to dental caries.

Once a salivary gland abscess has developed, medical management alone will not be sufficient for resolution. Case reports have suggested a role for percutaneous image guided needle aspiration, though the risk of incomplete drainage and recurrence of the abscess are higher for deep and larger abscesses [31]. This may be used for select smaller and non-loculated abscesses, but close follow-up is essential and repeat aspirations may be required. The recommended definitive management would include surgical drainage [5].

Surgical management involves an incision and drainage of the abscess, usually with the placement of a temporary passive drain (such as a Penrose drain) to ensure continued drainage. In select cases, such as lower volume, superficial, non-loculated, and easily accessed abscesses, a direct approach can be undertaken. In this approach, a small stab incision through the facial or neck skin in a cosmetically acceptable location is created. Then blunt dissection, along the direction of the facial nerve branches, is done to enter the abscess cavity in the least traumatic fashion to afford drainage and irrigation of the abscess cavity. A passive drain is placed and repeat irrigation and probing of the abscess cavity can be performed to prevent re-accumulation and loculation of the abscess.

The traditional surgical approach to the parotid abscess is very similar to that used for a parotidectomy for the removal of benign or malignant tumors of the gland [16]. A modified Blair incision can be used, hiding the incision

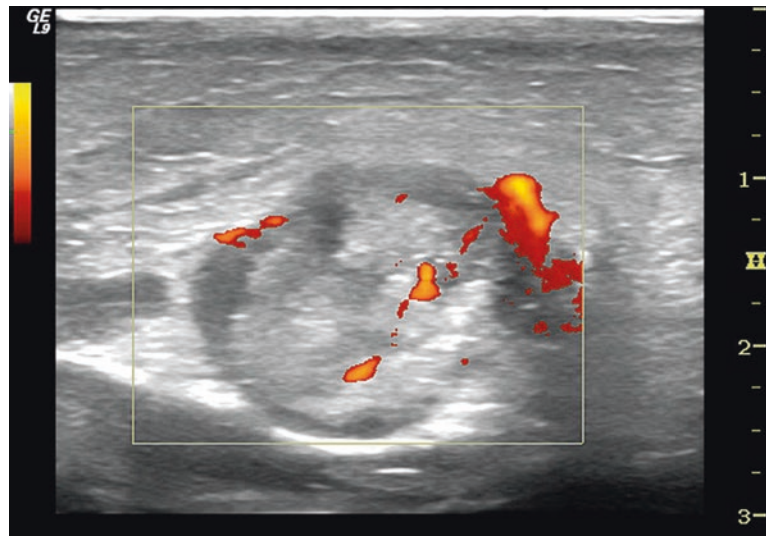

Fig. 24.3 Ultrasound imaging demonstrating a parotid abscess. (Reprinted from Katz P, et al. [33], with permission from Elsevier)

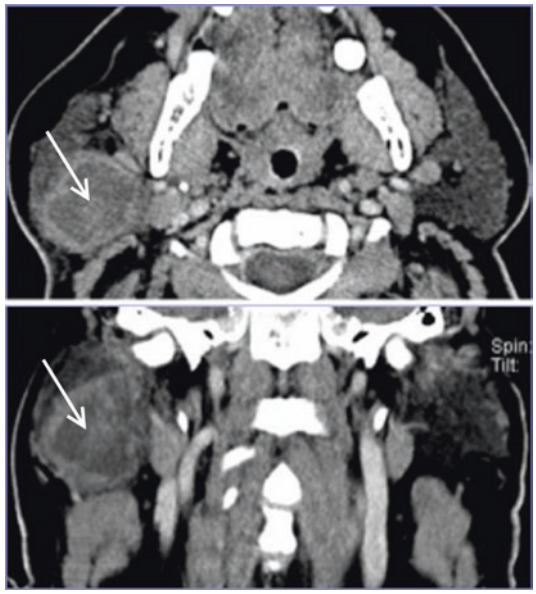

Fig. 24.4 Axial (top) and Coronal (bottom) CT with contrast noting a hypodense well-circumscribed area (white arrow) within the parotid gland

within the pretragal crease as well as a wrinkle in the neck. Care should be taken to have the cervical incision at least two fingerbreadths below the inferior border of the mandible to avoid the marginal mandibular branch of the facial nerve.

A subplatysmal, sub-SMAS (superficial muscular aponeurotic system) plane should be elevated, ideally just over the parotid fascia. These planes may be distorted or adherent secondary to the inflammation. After the skin flap has been elevated with good exposure of the parotid gland, the abscess can be drained. Blunt dissection in a direction parallel to the direction of the facial nerves will help prevent iatrogenic facial paresis or paralysis. Dissection should be carried into the pocket of the abscess and allow for sufficient drainage.

After irrigating the wound thoroughly and ensuring complete drainage, the wound should be closed over a passive drain exiting a dependent portion of the incision. Postoperatively, the patient should continue on culture directed antibiotics as well as good oral hygiene and hydration. The drain can often be removed in 2–3 days once the drainage has ceased.

Conclusion

Bacterial sialadenitis represents a significant complication of decreased salivary flow or production allowing for retrograde bacterial contamination. Risk factors include ductal obstruction, conditions, or medications leading to xerostomia or dehydration, immunosuppression, dental infections, and the extremes of age (neonates and the very elderly), but some patients have no identifiable risk factor. *Staphylococcus aureus* is the major pathogen. Treatment is primarily medical with goal-directed antibiotics and conservative therapies (e.g., compresses, massages, hydration) to improve salivary production and flow. Rarely patients will progress to developing an abscess that requires surgical drainage.

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Scrofula and Other Tuberculous Infections of the Head and Neck

25

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Introduction

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis*. It is a disease that has been known since antiquity but remains prevalent today, despite the availability of effective anti-TB antibiotics. In recent decades, the increasing prevalence of drug-resistant TB has complicated treatment. Untreated TB is deadly and carries a high mortality rate (70% for untreated smear-positive cases) [1]. The World Health Organization (WHO) reports that TB remains one of the top ten causes of death worldwide and caused 1.7 million deaths in 2015 alone [1]. Early diagnosis of TB is essential, both for treating the infected patient and for preventing spread of TB to the community.

Discussions about TB should note the distinction between latent TB infection (LTBI) and active TB, the latter also called "TB disease" or a "TB case." Patients with LTBI have no clinical manifestations of their infection and are not contagious. Reactivation of LTBI to active TB may occur at any point during the patient's lifetime but the risk is highest during the first 3 years after the primary infection (approximately 2% risk of reactivation per year for 3 years). The lifetime risk is approximately 10%, but the risk of reactivation is higher in patients who have HIV or who are otherwise immunocompromised. Most cases of active TB are due to reactivation of LTBI, rather than primary infection. According to the Centers for Disease Control and Prevention (CDC), 90% of TB cases in foreign-born individuals in the U.S. are due to reactivation of LTBI rather than primary infection [2]. The number of people with latent TB worldwide is huge—2–3 billion people—and untreated, 5–15% of these individuals will develop active TB at some point during their lifetime [1]. Treatment of LTBI is important to prevent this later conversion to active TB.

The most common manifestation of TB disease is pulmonary infection. However, extrapulmonary

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_25

TB, defined as TB disease involving an organ outside the lungs, occurs in approximately 20% of all TB cases [1, 3]. An additional 5–10% of cases of extrapulmonary TB also have pulmonary TB [3]. The most common manifestation of extrapulmonary TB in the head and neck is cervical lymphadenitis, or scrofula. Scrofula, derived from Latin word for a brood sow (a female pig used for breeding), is sometimes used to refer to cervical lymphadenitis caused by any type of mycobacteria but most often refers to infection by *M. tuberculosis*. The latter meaning will be used here. Cervical lymphadenitis in children due to atypical mycobacteria is discussed in Chap. 26.

In addition to causing cervical lymphadenitis, TB can affect many other parts of the head and neck, including the larynx, oral cavity, nose, ear, and cervical spine. This chapter reviews the manifestations of extrapulmonary TB in the head and neck.

Epidemiology

Humans are the only known reservoirs for *M. tuberculosis* (a related organism, *M. bovis*, causes bovine TB and may be transmitted to humans via unpasteurized milk). An indication that the tubercle bacillus has enjoyed a long period of evolution with the human host is the ability of *M. tuberculosis* to survive in a latent state and reactivate many years after the original infection. This ability has enabled the bacillus to survive in small population groups for long periods and is an impediment to the eradication of the disease from a community.

With improvement in economic and social conditions and the use of effective anti-tubercular therapy, developed nations and most developing nations have enjoyed a decline in TB for several decades. Patients infected with HIV are at increased risk of active TB, and the HIV epidemic in the 1980s and 1990s led to a flare up of TB across continents. The subsequent widespread use of antiretroviral therapy, especially in developed countries, sharply reduced the incidence of TB in HIV-infected patients and overall. The current incidence of TB worldwide is declining at a rate of 1.5% per year, according to the WHO [1]. However, 11% of new TB cases worldwide still occur in HIV-infected individuals. More patients with and without HIV should be screened and treated for LTBI to prevent reactivation to TB disease [1].

Tuberculosis remains endemic in many developing nations. In developed countries where TB is uncommon, immigrants from TB-endemic countries have a higher rate of TB than do native-born residents [3–5]. A study from Spain of nearly 1300 TB cases admitted to a tertiary care hospital 1995 through 2013 illustrates recent trends in developed countries [3]. This study found a steady decline in both the overall number of cases (113 to 35 cases per year) and in the proportion of TB patients with HIV (41% to 15%) over the 19 years reviewed, but an increase in the proportion of TB cases occurring in immigrants (7% to 40%). In the U.S., two-thirds of the 9300 new TB cases reported in 2015 occurred in foreign-born individuals [2].

Extrapulmonary presentations form a significant proportion of new TB cases, especially since the advent of the AIDS epidemic. The WHO reported that 15% of new TB cases in 2015 were extrapulmonary [1], excluding cases that had both extrapulmonary and pulmonary diseases. Some centers have reported rates of extrapulmonary TB as high as 30–47% [3, 6]. Head and neck TB, including cervical lymphadenitis, accounts for 10–40% of extrapulmonary TB cases [7, 8]. It is important for otolaryngologists and other clinicians to recognize the various manifestations of TB in the head and neck, as a high index of suspicion can help direct investigations, allowing early diagnosis and quick commencement of appropriate treatment.

Although most cases of TB worldwide are caused by *M. tuberculosis*, an estimated 150,000 cases annually are caused by *M. bovis* (also caused zoonotic TB) [1]. Zoonotic TB is primarily acquired by consuming unpasteurized dairy products from an infected cow. It is indistinguishable from TB due to *M. tuberculosis* except through culture and specialized testing of the bacterium. *Mycobacterium bovis* is inherently resistant to pyrazinamide, one of the first-line

anti-TB drugs. Compared with *M. tuberculosis*, *M. bovis* is more likely to cause extrapulmonary TB but is rare. A study from the United Kingdom found that *M. bovis* caused only 0.6% of all TB cases (2002–2014) [9]. A higher proportion of patients with *M. bovis* than *M. tuberculosis* infection had extrapulmonary TB (41% vs 36%), were born in the U.K. (72% vs 25%), and lived in a rural area (25% vs 3%) [9]. Two-thirds of patients with *M. bovis* reported consumption of unpasteurized milk or other dairy products.

Pathophysiology

Tuberculosis is spread by way of airborne droplet nuclei that contain bacilli. Droplet nuclei are generated by coughing, sneezing, singing, and talking. Droplet nuclei are defined as 1–5 μm in diameter, small enough to reach the alveoli if inhaled [10]. A cough generates approximately 3000 droplet nuclei, the same number as talking for 5 min [10]. Droplets greater than 5 μm are larger than droplet nuclei and settle within 1 m of the infected individual, whereas droplet nuclei can easily drift more than 1 meter and can remain suspended in the air for over 30 min. Primary infection usually occurs in the lungs but may be occult. Spread to other organs, which typically occurs at the time of primary infection, can occur via the bloodstream and lymphatics. Reactivation at sites distant from the lungs can lead to extrapulmonary TB, including TB in the head and neck. Extrapulmonary TB can also arise from autoinoculation of the mucosa by infected pulmonary secretions, or by contiguous spread [11].

Risk Factors

Risk factors for developing active TB include HIV, immunosuppression from medications (e.g., corticosteroids, anti-tumor necrosis factor (TNF) alpha agents), alcohol abuse, malignancy, malnutrition, low body mass index, diabetes, renal failure, smoking, and the extremes of age (including children under age 5). Living in crowded conditions in a TB-endemic area also increases the risk of acquiring TB [12], as does poverty and homelessness. Prior contact with a TB-infected patient increases the risk of acquiring TB but only 7–35% of TB patients relay a history of prior contact [13, 14]. HIV is a major risk factor for TB, and increases the risk of developing active TB approximately 30-fold [15]. In 2016, over 40% of HIV deaths worldwide were due to TB [1].

Several studies have looked at risk factors for extrapulmonary versus pulmonary TB. Treatment with TNF-alpha inhibitors increases the risk of TB up to 25-fold and nearly 60% of such patients have extrapulmonary TB [16, 17]. Several studies have reported that HIV is a risk factor for extrapulmonary TB, with a study from Texas reporting a three-fold higher prevalence of HIV in extrapulmonary than pulmonary TB [18]. A study from Thailand found no significant difference in overall HIV rates between similar cohorts, however, although some types of extrapulmonary TB such as TB lymphadenitis did have a higher incidence of HIV [6]. Infection with *M. bovis* is also a risk factor for extrapulmonary TB, as noted above.

Clinical Presentation

The most common manifestations of TB in the head and neck region are noted in Table 25.1 [13, 19–24]. Cervical TB is the most common manifestation, followed by laryngeal TB in most studies. Concurrent pulmonary disease is present in less than 40% of cases overall (Table 25.1).

TB Lymphadenitis (Scrofula)

Tuberculous cervical lymphadentitis (scrofula) is the most common manifestation of TB in the head and neck region, accounting for 70–90% of cases [13, 19, 24]. Tuberculous lymphadenitis usually presents with subacute, painless unilateral swelling involving a single group of lymph nodes. Patients typically present with a history of 1–2 months of lymph node swelling but the duration varies from 3 weeks to 8 months [25].

Table 25.1 Relative frequency of sites affected by tuberculosis (TB) in the head and neck

Study (country)	*N* (HIV %)	Lymph nodes (%)	Larynx (%)	Oral, oropharynx, nasopharynx (%)	Salivary gland (%)	Ear (%)	Spine (%)	Pulmonary TB (%)
Bruzgielewicz [19] (Poland)	73	36	27	14	12	4	0	36
Khuzwayo [20] (S. Africa)	358 (65%)	84	3	3	0	4	0	38
Menon [21] (U.K.)	128	87	2	2	4	2	0	17
Sriram [22] (India)	104 (26%)	87	5	1	4	0	2	16
Nalini [23] (India)	117	95	2	1	0	1	1	38
Das [13] (India)	63 (0%)	91	8	0	0	2	0	10
Prasad [24] (India)	165 (30%)	73	15	5	2	2	2	24

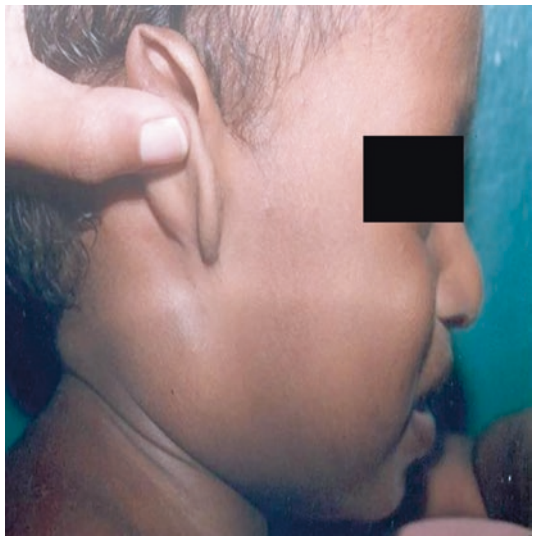

Fig. 25.1 Cervical tuberculous lymphadenitis in a child

Lymph nodes have an average size of 3 cm on clinical presentation but may be much larger. A draining sinus is present in some cases (1.4% in one series) [26].

In many studies, the lymph nodes that are most commonly involved are the upper deep cervical lymph nodes (Fig. 25.1). Nodes often present with matting, ulceration, and abscess (Fig. 25.2). However, the posterior triangle cervical lymph nodes are also often involved and in developing countries it is not unusual to see multiple groups of lymph nodes involved, even in immunocompetent individuals. One study involving 893 cases found that unilateral, matted adenopathy in the posterior triangle of the neck was the most common manifestation [27]. Another study involving 219 patients also found that posterior triangle nodes were most often involved (48% of cases), followed by supraclavicular nodes (18%) [26].

Systemic symptoms and evidence of coexisting pulmonary disease are often absent in patients with tuberculous lymphadenitis. A large study reported that fever was present in only 7% of patients and cough in 4% [27]. Another study reported systemic symptoms in 56% of scrofula patients but a productive cough in only 10% [26]. Concurrent pulmonary TB is often absent [25, 27]. Systemic symptoms and coexisting pulmonary TB are more common in HIV-positive patients. A study from Taiwan of tuberculous lymphadenitis (72% cervical) reported that systemic symptoms were present in 76% of HIV-positive patients but only 12% of HIV-negative patients [28].

Deep neck space abscess may be present in patients with tuberculous cervical lymphadenopathy, and accompanied 4% of scrofulous lesions in one large series [27]. Deep neck space abscess due to pyogenic bacteria such as streptococci and staphylococci can be rapidly life-threatening [29], but neck abscess due to TB (often called a "cold abscess") usually follows a more indolent course. Tuberculous retropharyngeal abscess may occur in association with involvement of retropharyngeal lymph nodes [23] but is often secondary to TB of the cervical spine, discussed later.

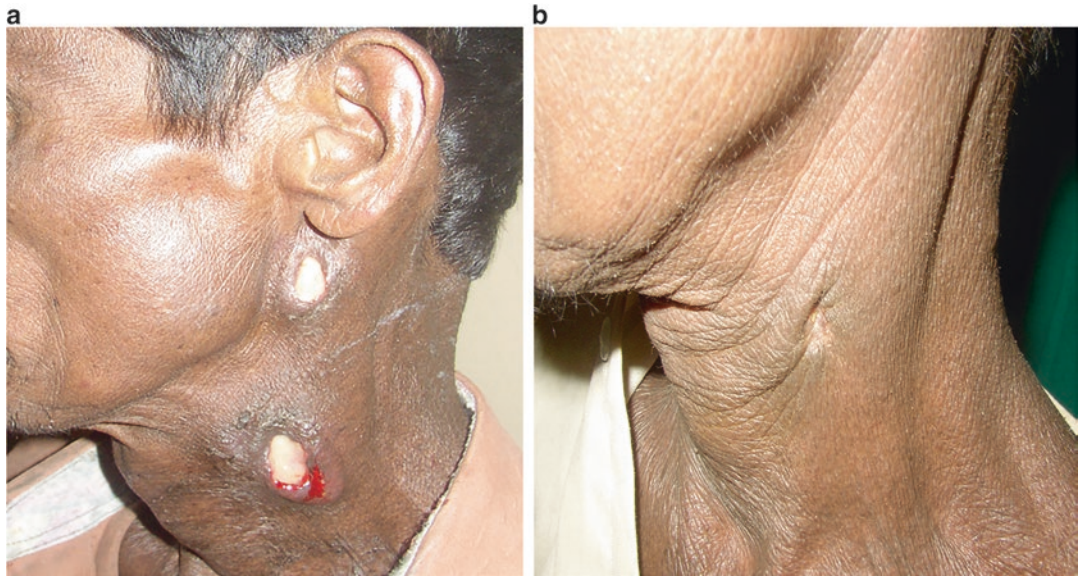

Fig. 25.2 Multiple, ulcerated tuberculous cervical lymph nodes in a patient who also had laryngeal tuberculosis (TB). (**a**) Before treatment with anti-TB therapy. (**b**) After treatment

Since smoking is a risk factor for TB and for head and neck malignancies, malignancy must be ruled out. Concurrent cancer was found in 3% of patients in one series [24].

Laryngeal TB

Laryngeal involvement by TB is usually the second most common manifestation of TB in the head and neck (Table 25.1). Unlike tuberculous cervical lymphadenitis, concomitant pulmonary TB is common in laryngeal TB, occurring in approximately 70% of laryngeal TB cases [30]. Patients present with hoarseness ranging from vocal fatigue to complete aphonia, and odynophagia. The clinical findings vary from ulcers on the true vocal folds, to hypertrophic nodules and inflammation (hyperemia and edema) of the arytenoids and aryepiglottic folds. Exophytic, broad-based lesions without significant erythema and edema may also be seen. The true vocal folds are the most common site of involvement, followed by the false vocal folds [31]. The lesions of laryngeal TB may be mistaken for laryngeal cancer until biopsy proves otherwise. Tuberculous lymphadenitis may accompany some cases of laryngeal TB [24].

TB of the Cervical Spine

Pott's disease (spinal TB) is one of the most crippling manifestations of extrapulmonary TB. The thoracic spine is affected most often. The cervical spine is affected in less than 10% of Pott's disease cases [32, 33]. Spinal disease is more common in prepubertal children than in adults. In cervical spine TB, neck pain is the most common symptom, followed by fever, dysphagia, dyspnea, and stridor due to pressure effects. Abscess formation is initially contained behind the prevertebral fascia and will present as a retropharyngeal abscess or, more rarely, as a sternocleidomastoid abscess or even as a parotid mass [24].

TB of the Nose and Paranasal Sinuses

Nasal involvement by TB is rare, with only 35–40 cases reported in the literature [34]. There is no particular preponderance for any age group,

ranging from 19 to 85 years, and one-third of cases have occurred in patients younger than 20 years [34]. The lesions may be ulcerated, infiltrative or polypoidal, and the most common sites of occurrence are the cartilaginous septum and the inferior turbinate. Nasal TB is discussed further in Chap. 16. Tuberculous lesions of the paranasal sinuses present as pale, polypoidal mucosa of the maxillary antrum or multiple polyps of the ethmoid. Rarely, bone involvement with fistula formation can be seen. Nasal TB infection may spread to the maxillary palatal region causing palatal perforation.

Oral Cavity TB

The oral cavity is involved in less than 1 per cent of cases [35, 36]. Implantation of TB bacilli may occur because of a breach in the protective barrier of the mucosa, such as ulcerations, abrasions, poor oral hygiene, tooth eruptions, or dental infections. The incidence of oral TB in pulmonary TB is reported to be in the range of 0.1–0.5% [36]. In the mouth, the lesions usually occur in the following order: (1) tongue tip, (2) tongue border and floor of the mouth, (3) soft palate (Fig. 25.3), (4) anterior tonsillar pillar and uvula, and (5) dorsum and base of the tongue. The oral lesions appear as painful ulcers, nodules, fissures, and tuberculous granulomas [24]. The lesions are often mistaken for malignant, mycotic, syphilitic, or aphthous lesions.

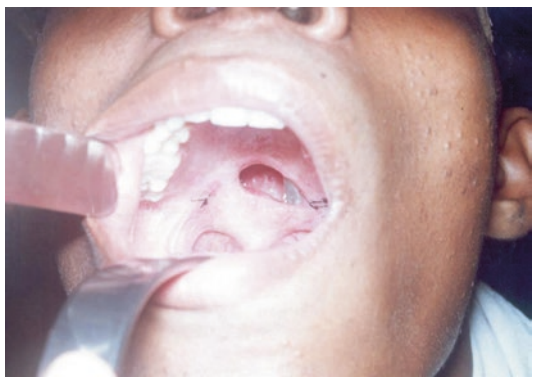

Fig. 25.3 Tuberculosis of the soft palate

TB of the Mandible

Only a handful of cases have been reported of TB of the mandible. The TB lesions occurred more frequently on the mandibular ramus followed by the body, the condylar process, and the temporomandibular joint (Fig. 25.4). TB of the mandible has been reported usually in young patients. TB of the temporomandibular joint can be a primary infection or a fistulous communication from a tuberculous otitis media. Patients complain of a painful, fluctuant swelling in front of the ear, associated with trismus (Fig. 25.5) [1, 37, 38].

TB Otitis

Also called tuberculous otomastoiditis, tuberculous otitis media, or chronic tuberculous otomastoiditis, TB otitis usually affects children and young adults. In the early twentieth century, 1.3–18.6% of all chronic otitis media cases were reportedly caused by TB, but TB otitis media is now very rare in developed countries. TB otitis is also rare in TB-endemic countries but may be on the rise. One recent study from India found TB in 5% of 500 patients who underwent tympanomastoidectomy over a 2-year period [39]. Though some characteristic features have been attributed to TB otitis, such as profuse ear discharge, profound hearing loss, facial paralysis, multiple perforations, and acute onset hearing loss that is disproportionate to the extent of the disease, many authors have observed that these features are not always present. Multiple perforations are now hardly ever seen, as they are at most a temporary phase. Severe or permanent hearing loss is a frequent occurrence. Pale mucosa, pale granulations, or a pale-looking tympanic membrane are the most significant features mentioned by most authors [24]. Bone necrosis and sequestration in the mastoid are not uncommon findings (Fig. 25.6). Superimposed infection changes the clinical picture. There may be otalgia, foul-smelling infection, and even acute mastoid infection and fistulization. The clinical picture may closely resemble an unsafe ear with complications.

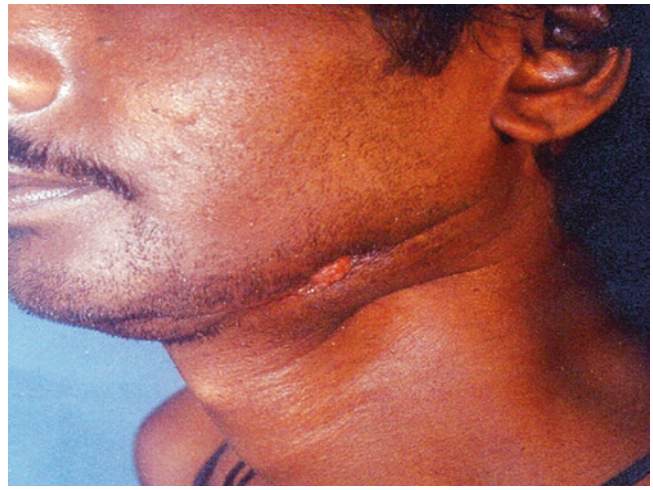

Fig. 25.4 Tuberculosis of the body of the mandible resulting in a cutaneous fistula

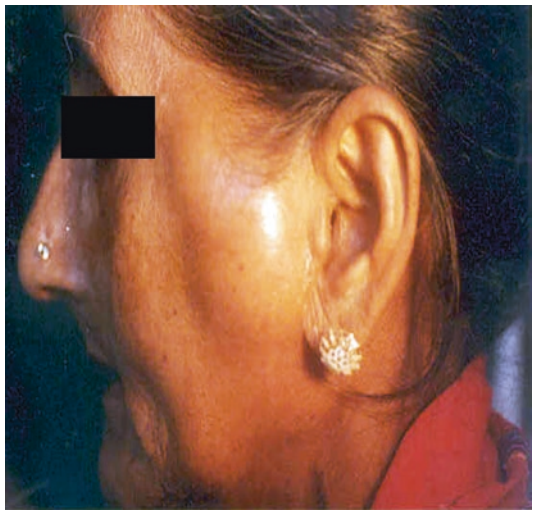

Fig. 25.5 Tuberculous otitis resulting in a parotid abscess and temporomandibular joint infection. The patient presented with swelling in front of the ear

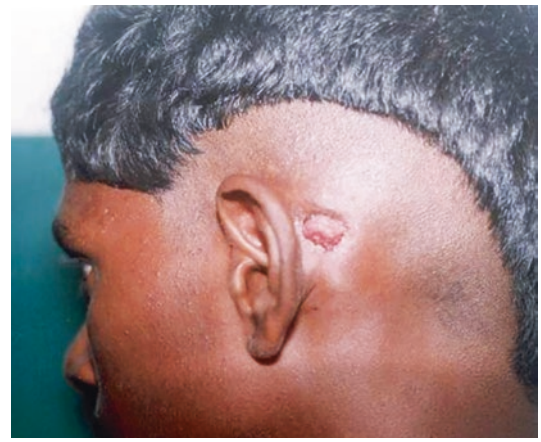

Fig. 25.6 Tuberculous otitis that presented with discharge and cutaneous fistula and granulations. Reproduced from Prasad KC, Sreedharan S, Chakravarthy Y, Prasad SC. Tuberculosis in the head and neck: experience in India. J Laryngol Otol 2007; 121:979–98 [24] with permission from Cambridge University Press

TB of the Salivary Glands

Salivary gland TB is rare even in TB-endemic countries, and most often involves the parotid. A study in Romania reported that the parotid was involved in 6 of 11 salivary gland TB cases at that center and nearly 80% of the 48 cases of salivary gland TB reported in the literature [36]. The salivary gland involvement is unilateral in nearly all cases [36]. A concomitant malignancy has been reported in 6% of cases [36]. Tuberculous infection of the salivary gland can be focal, with the involvement of the intra-glandular lymph nodes, or diffuse, with the involvement of the parenchyma. Usually, parotid involvement presents as a firm, non-tender mass (Fig. 25.7). Abscess formation and fistulization may also occur. Rarely, facial nerve palsy is seen.

Diagnosis

Initial Testing

Initial testing of patients suspected of having extrapulmonary TB should include a chest x-ray, HIV testing, and tuberculin skin test or interferon gamma release assay (IGRA). A chest x-ray should be performed as soon as possible for infection control as well as for diagnostic reasons. The definitive diagnosis of head and neck TB, however, often requires sampling of the involved tissues by fine needle aspiration (FNA) or biopsy, as discussed later. The incidence of positive results for PPD, chest x-ray, and FNA in cervical tuberculous lymphadenitis is noted in Table 25.2.

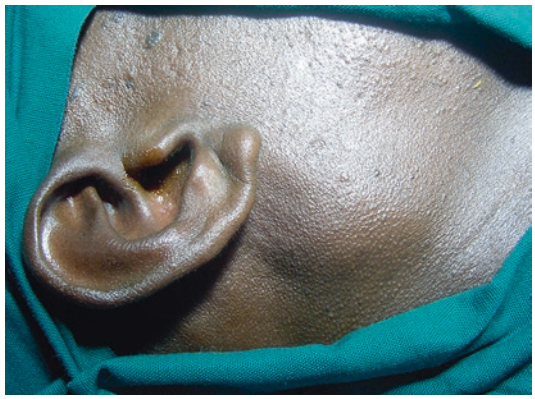

Fig. 25.7 Tuberculosis of the parotid. The lesion presented as a swelling below the ear lobule

Tuberculin Skin Tests

The tuberculin skin test, known as the Mantoux test or PPD (purified protein derivative), is the traditional screening test for exposure to TB. However, the PPD test can give high number of false negative results for various reasons, including cutaneous anergy due to immunocompromise (including HIV infection), extremes of age, malnutrition, and significant illness due to TB disease [40]. Failure to administer or interpret the test correctly can also lead to a false-negative result [40]. The rate of PPD positivity in tuberculous cervical lymphadenitis has ranged from 13% to 84% in several studies [13, 24, 27, 41–43] (Table 25.2). A positive PPD in a TB-endemic country has a low specificity for TB disease because of the high baseline rate of positive PPDs in the general population due to LTBI or prior vaccination with BCG (bacille Calmette-Guerin).

Interferon Gamma Release Assays (IGRA)

These tests are assays of whole blood that can be used instead of a PPD, but like the PPD cannot distinguish between latent and active TB. The IGRA tests are much more expensive than PPD tests but save the patient an extra visit to the clinic for the reading of the PPD. The IGRA tests are specific for *M. tuberculosis*. These tests have similar sensitivity as PPD tests, so a negative test does not exclude TB, but higher specificity for *M. tuberculosis* versus non-tuberculous mycobacteria or BCG.

Table 25.2 Diagnostic considerations in tuberculous cervical lymphadenitis (scrofula)

	Country	*N*	Positive PPD (Mantoux)[a]	Pulmonary TB (concurrent)	FNA cytology positive (% ZN positive)
Prasad [24]	India	121	13%	16%	92% (NR)
Ammari [41]	Jordan	58	39%	12%	75% (39%)
Das [13]	India	57	NR	10%[b]	74% (40%)[b]
Maharjan [42]	Nepal	83	NR	14%	92% (30%)
Khan [27]	India	893	84%	18%	90% (26%)
Memish [43]	Saudi Arabia	79	83%	27%[b]	31% (33%)[b]

N total number of patients with tuberculous cervical lymphadenitis, *PPD* purified protein derivative (skin test), TB = tuberculosis; FNA = fine needle aspiration; ZN = Ziehl-Neelsen stain; NR = not reported.

[a]Of those tested.

[b]Percentage of all 63 head and neck TB cases (90% cervical lymphadenitis) in Das et al. Percentage of all 99 cases with TB lymphadenopathy (80% cervical) in Memish et al.

Chest X-Ray

A chest x-ray should be performed in all patients with suspected extrapulmonary TB. A clear chest x-ray does not exclude extrapulmonary TB, and several series have reported the absence of pulmonary TB in 80–90% of cases of tuberculous cervical lymphadenitis (Table 25.2). Concurrent pulmonary TB is more common in laryngeal TB.

Classic chest x-ray findings in pulmonary TB due to reactivation of a latent infection include upper lung (apical) infiltrates and cavitation. Primary infection with TB usually causes middle or lower lobe infiltrates without cavitation, and mediastinal or hilar lymphadenopathy. Atypical chest x-ray findings may be present in patients with HIV, and it is important for clinicians to recognize this because a significant proportion of patients with head and neck TB have HIV (30% in one study) [24]. Chest x-rays may be normal in patients with HIV even when sputum cultures are positive, signifying the presence of pulmonary TB. A U.S. study from 1994 (before the era of HAART, highly active anti-retroviral therapy) examined 133 HIV-positive patients who had active pulmonary TB (positive sputum or bronchoalveolar lavage cultures) and found that one-third had normal (14% of patients) or atypical (18%) chest x-ray findings [44]. Nearly all patients with clear chest x-rays and active pulmonary TB had very low CD4 counts (<200 T cells/μl).

Histopathology, Cultures, and Molecular Diagnostic Tests

Histopathology

Fine needle aspiration (FNA) is an appropriate initial diagnostic method for cervical lymphadenitis. In TB-endemic countries, positive cytology (e.g., granulomas) may be seen in 70–90% of lymphadenitis cases (Table 25.2). A series of nearly 1200 patients evaluated for TB lymphadenitis in Hong Kong found that the sensitivity of FNA for TB was 77% and specificity 93% [45]. If FNA is non-diagnostic, surgical biopsy or excision of the lymph node is often necessary for diagnosis.

Histopathological features of TB in the head and neck include granulomas, necrosis, and in some cases fibrosis. It should be noted that while granulomatous lesions with "caseous" necrosis are classic for TB, granulomas without necrosis can be seen in tuberculous lymphadenitis [46]. Tissue stains for mycobacteria (e.g., Ziehl-Neelsen stain) often show few or no acid fast bacilli (AFB) in tuberculous cervical lymphadenopathy. In a histopathology study of 100 tuberculous lymph nodes, over two-thirds had strong histologic evidence for TB with the combination of giant cells plus granulomatous lesions with necrosis, but stains were positive for TB in less than 10% [46]. Other studies have found higher rates of positive stains for TB, but still less than 50% (Table 25.2).

Cultures

Cultures for TB have been the gold standard for diagnosis for over a century. Cultures are also the gold standard for drug susceptibility testing. However, mycobacterial cultures on standard solid media (e.g., Löwenstein-Jensen) can take 6–8 weeks and require laboratory facilities that may not be available in many developing nations. Culture methods using liquid media (e.g., Mycobacterium Growth Indicator Tube) with automated detection systems significantly shorten the time to culture positivity. A study from Ethiopia comparing these two methods in 908 TB samples found that the liquid media method was superior in growing TB (87% vs 67%) and had a shorter turnaround time (16 vs 31 days) compared with solid media culture [47]. However, liquid media tests methods are generally more costly.

Tissue samples from FNA or biopsy should be sent for AFB stains and cultures and for molecular diagnostic tests. Purulent drainage may also be sent for culture and other microbiologic studies, although the sensitivity is variable. Culture of abscess material or drainage was positive in cases of cervical spinal TB and mandibular TB but not otic TB at one center in India [24, 48].

Some centers in developing nations lack the availability of laboratory facilities capable of performing culture for mycobacteria and have relied

on histopathology and other features for diagnosis [49]. The WHO reported that in 2015, only 57% of pulmonary TB cases, for example, were bacteriologically confirmed [1]. However, recent WHO guidelines recommend that all patients diagnosed with presumed TB have bacteriologic confirmation of TB and drug susceptibility testing [1]. In studies of extrapulmonary TB, the sensitivity of TB culture from TB lymph node aspirates is only 60–70% and molecular diagnostic tests are more sensitive [50]. Monitoring of response to therapy, however, requires AFB stains and cultures rather than rapid molecular testing. The WHO notes that "a well-equipped and staffed, quality-assured laboratory network with an efficient specimen referral systems in an essential requirement for any national TB program in the post-2015 era" [1]. In 2016, the WHO launched "a framework of indicators and targets for laboratory strengthening under the End TB Strategy," and emphasized the importance of diagnostic testing to confirm TB and drug susceptibility in this era of increasingly resistant TB strains.

Patients with possible concurrent pulmonary TB should have sputum samples sent for bacteriologic TB testing (smears, culture, molecular diagnostic tests), in addition to testing of samples from the extrapulmonary site.

Molecular Diagnostic Tests

Rapid molecular diagnostic tests for TB are now the method of choice in diagnosing TB in many countries. Nucleic acid amplification tests (NAAT) are more sensitive than AFB smears for TB lymphadenopathy, for example. Currently, one rapid diagnostic test, a NAAT, is recommended by the WHO and that is Xpert MTB/RIF (Cepheid, Sunnyvale, U.S.) [1]. This test can provide results within 2 h. This test was originally recommended in 2010 by the WHO for the diagnosis of pulmonary TB in adults but since 2013, it has also been recommended for children and for certain types of extrapulmonary TB, including diagnosis of TB lymphadenitis (and TB meningitis) [1]. This recommendation was based on a study commissioned by the WHO that found that the Xpert MTB/RIF assay had a pooled sensitivity of 83% and specificity of 94% for diagnosing TB lymphadenitis [50]. The WHO noted that as of 2015, 15 TB-endemic countries that account for 10% of all TB cases had adopted a national policy stipulating Xpert MTB/RIF as the initial diagnostic test [1]. In the U.S. (as of 2017), no NAAT has been approved by the Food and Drug Administration for the diagnosis of extrapulmonary TB. However, the CDC recently advised that a positive NAAT test can be used for diagnosis because false-positive results are unlikely [51]. The CDC cautioned that a negative NAAT does not exclude extrapulmonary TB, however, given the frequency of false-negative test results. The CDC recommends that specimens from extrapulmonary sites be submitted for AFB smears, cultures, and NAAT in addition to histopathology [51].

Other molecular diagnostic tests for TB include polymerase chain reaction and whole gene sequencing. Molecular typing tools, including spoligotying (spacer oligonucleotide typing), are widely used worldwide for determining the molecular epidemiology of the various *M. tuberculosis* strains [52].

The WHO recommends testing for drug susceptibility in all cases of TB to provide appropriate therapy [1]. The gold standard is based on culture, but rapid diagnostic test methods of primary specimens provide results within hours although these may have false-negative results. There are several types of rapid diagnostic tests (e.g., NAAT and line probe assays) that can detect the most common genes responsible for rifampin resistance (rifampin-resistant TB, e.g., Xpert MTB/RIF), as well as isoniazid and rifampin resistance or additional resistance to quinolones and second-line injectable agents (e.g., GenoType MTBDRPlus and GenoType MTBDRs/, Hain Lifescience, Nehren, Germany).

Radiologic Evaluation

Radiological evaluation of TB of the head and neck may be helpful in the evaluation of the extent of involvement. Evaluation is done using

ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), depending on the location of the infection.

Cervical Lymphadenitis and Abscesses

Ultrasonography is used in the evaluation of lymph nodes, abscesses of neck region, and for guided FNA. On ultrasonography, the common pattern is of multiple enlarged nodes of reduced echogenicity, loss of fatty hilum, internal necrosis, and conglomeration. Initially (early phase) enlarged lymph nodes show homogeneous enhancement on post-contrast CT and MRI suggesting the granulomatous stage of mycobacterial infection. This is followed by progressive phase of caseation necrosis, formation of abscess with peripheral enhancement of the inflammatory response. Post-treatment (late phase) lymph nodes undergo fibrosis, calcification, and show reduced size with absent post-contrast enhancement. Neck abscesses are better evaluated by CT and MRI in which they appear as low attenuation collections with peripheral rim enhancement [53].

Oral, Salivary Gland, and Nasal TB

Oro-nasopharyngeal TB is better evaluated with contrast enhanced CT and MRI. Typical features include polypoidal mass, diffuse mucosal thickening, and adenoid lesions [54]. In the oral cavity, enhancing nodules, enlarged enhancing tonsils with necrosis, and tonsillar fossa abscess formation may be seen. Salivary gland involvement is well evaluated by ultrasonography. The patterns of involvement are intraglandular hypoechoic granulomatous lesions and microabscesses, and intraglandular lymph nodes. Nose and paranasal sinus involvement may be in the form of septal destruction, mucosal polyps, enhancing necrotic nodules which may extend to involve periosteum and cause progressive bone destruction. Late stages show calcifications. In the absence of calcification, lesions may mimic neoplasms.

Otomastoiditis

Radiologic evaluation for TB otomastoiditis is by using high resolution CT. MRI may be used as an adjunct to assess involvement of the membranous labyrinth and facial nerve. The characteristic findings include extensive soft tissue density involving middle ear and mastoid, often extending to involve the external auditory canal beyond the tympanic eminence, without mastoid sclerosis and with preserved architecture of the mastoid air cells. Erosions of ossicles, bony labyrinth, facial nerve canal, tegmen tympani, and sigmoid sinus plate may be seen. Cases with advanced disease may have cochlear fistulae [55, 56].

Laryngeal TB

Radiologic evaluation of laryngeal tuberculosis can demonstrate, in acute stages, diffuse thickening of the bilateral vocal cords and the epiglottis. In chronic stages of disease, CT may demonstrate focal or asymmetrical involvement with nodules or masses. Laryngeal TB can mimic laryngeal carcinoma on radiologic imaging, the main differential features being lack of cartilage involvement or destruction, and the presence of diffuse bilateral involvement [57].

Spinal TB

Cervical spinal tuberculosis can present in four patterns: para-disc, anterior, central, and posterior lesions. MRI with contrast is the imaging modality of choice. Para-disc infection demonstrates destruction of the adjacent vertebral end plates with sharp margins, absent reactive sclerosis, and disc destruction causing narrowing of the disc space. Surrounding anterolateral soft tissue spread and abscess formation are common. In anterior pattern involvement, infection starts at the anterior corner of the vertebral body and causes a subligamentous abscess that spreads to several vertebral levels. The disc space is preserved. Central pattern involvement affects a single vertebra, hence the disc is unaffected.

Posterior lesions are rare, involve the posterior elements, and hence can mimic metastatic spinal lesions [58].

Positron emission tomography (PET)/CT and ^{18}F-FDG PET are advanced imaging modalities that may be used in follow-up of extrapulmonary tuberculosis. These tests are very expensive. The ^{18}F-FDG (also written FDG) notation refers to a glucose analogue molecule, fluorodeoxyglucose, in which one of the normal hydroxyl groups is replaced with the positron-emitting radionuclide fluorine 18. High uptake of ^{18}F-FDG correlates with high glucose metabolism in tissues, which in turn correlates with high metabolic activity. High uptake can occur in metastases and in bacterial infections. Increased ^{18}F-FDG uptake is seen in active TB granulomas [59].

Treatment

Conservative therapy with anti-TB drugs is the mainstay of treatment. Ideally, treatment of head and neck TB should be managed with the help of an infectious disease specialist. Infection due to drug-susceptible TB isolates responds very well to standard anti-tuberculous therapy. This consists of an initial 2 months of 4-drug therapy with first-line TB drugs (isoniazid, rifampin, pyrazinamide, and ethambutol), followed by several months of treatment with isoniazid and rifampin. The optimal duration of treatment depends on the type of TB infection (e.g., treatment duration of cervical lymphadenitis is shorter than that of cervical spine TB), as well as the patient's HIV status or degree of immunosuppression.

Drug-resistant TB is becoming an increasing problem worldwide. Isoniazid and rifampin are the most powerful anti-tuberculous agents, and resistance to rifampin or to both rifampin and isoniazid ("multidrug" resistant—MDR) is now reported in 5.6% of TB cases worldwide [1]. The WHO recommends treating rifampin-resistant and MDR-TB the same way, and this requires the use of second-line agents (e.g., fluoroquinolones, kanamycin, amikacin, and capreomycin) and a much more prolonged course. Extensively drug-resistant TB, termed "XDR-TB," is defined as resistance to rifampin, isoniazid, fluoroquinolones, and at least one injectable agent (kanamycin, amikacin, capreomycin). Cases of XDR-TB have been reported from over 100 countries worldwide, with the largest numbers of cases in Eastern Europe and in countries of the former Soviet Union as of the WHO 2016 report [1]. Treatment is complex and mortality rates are high. Recent guidelines for treating extrapulmonary TB, including in cases due to drug-susceptible TB or MDR-TB, have been published by the WHO [1] and the CDC [51].

Adjuvant surgical excision of an isolated lesion, or incision and drainage of a TB-associated abscess, may be necessary in advanced cases of head and neck TB. However surgical excision must be limited to the lesion. In case of abscesses, drainage may be all that is necessary. Cervical spine TB with retropharyngeal abscess requires drainage via an external approach. Additional surgery for cervical spine TB follows the principle for Pott's disease in other parts of the spine, where surgery to stabilize the spine may be necessary if the spine is unstable or the spinal instability is causing neurologic deficits [60]. Some cases of mandibular TB may require sequestrectomy and saucerization, but this should be determined on a case-by-case basis. Tuberculosis of the larynx, oral cavity, ear, and salivary gland usually respond very well to anti-tuberculous medications and do not require surgical management, except where excisional biopsy is needed to establish a diagnosis.

Adjuvant surgery may also be indicated in some cases of XDR-TB that fail attempts at treatment; treatment options for XDR-TB are limited.

Cancer and TB

Tuberculosis can coexist with cancer in different organs or in the same organ. In the head and neck region, TB can coexist with carcinoma of the tonsil, pharynx, nasopharynx, or larynx. Patients diagnosed with head and neck cancer in TB-endemic regions appear to have a higher risk of pulmonary TB. One study from Taiwan found

that this risk was nearly three-fold higher than in patients without cancer [61]. Smoking is a risk factor for TB as well as for head and neck cancer, so this may contribute to the association.

Conclusion

The most common presentation of TB in the head and neck is cervical lymphadenitis, which accounts for 70–90% of cases, but TB can also affect the larynx, oral cavity, ear, salivary glands, and cervical spine. Deep neck abscesses may be caused by TB, and retropharyngeal abscesses may result from infection of adjacent nodes or cervical spine infection. The clinician must have a high index of suspicion for head and neck TB because symptoms typical for pulmonary TB, such as cough and fever, are often absent. Treatment with multidrug anti-TB regimens, based on results of drug susceptibility testing, is highly effective for most head and neck TB cases.

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Cervical Lymphadenitis in Children

26

C. Mary Healy

Introduction

Swelling of the lymph nodes of the neck (cervical lymphadenopathy) is a common complaint of childhood and, unlike similar findings in adults, does not usually indicate malignancy or serious disease. Cervical lymphadenitis or inflammation of the lymph node(s) often indicates a local or systemic infectious etiology. Cervical lymphadenitis may present acutely or follow an indolent course leading to subacute/chronic lymphadenitis. Determining the acuity of presentation is important when considering the likely etiologies and in deciding appropriate initial diagnostic evaluation and/or empiric therapy. In addition, knowledge of the anatomy of lymphatic drainage of the neck is helpful in determining the source of infection along with likely etiological agents [1, 2].

The regional lymph nodes commonly affected in cervical lymphadenitis are divided into those of the superficial and deep chains. The superficial nodes are situated on the top of the sternocleidomastoid muscle and follow the course of the external jugular vein. The superficial tissues of the neck, mastoid, superficial parotid, and submaxillary glands all drain here. The mastoid lymph nodes drain the parietal scalp and pinna; occipital nodes drain the occipital scalp and superficial areas of the posterior neck. The superficial chain, mastoid and occipital lymph nodes all drain ultimately to the deep cervical lymph nodes [1, 2].

The deep cervical chain lies deep to the sternocleidomastoid muscle along the internal jugular vein. This chain is divided into upper and lower groups. One of the most common nodes of the upper group that becomes inflamed is the jugulodigastric node which drains the tonsils. This node lies at the angle of the jaw below the digastric muscle and is frequently detected during episodes of tonsillitis. The submental nodes located beneath the chin drain the anterior tongue, lower lip, and chin before they drain into the submandibular and upper deep cervical nodes. The submandibular lymph nodes also receive drainage from the lateral lip, nose, cheeks, medial eyelids, and forehead, and from the posterior mouth, gums, teeth and tongue as well as the superficial nodes. Lower deep cervical nodes receive drainage from the larynx, trachea, thyroid gland, and esophagus [1, 2].

Epidemiology

The epidemiology of cervical lymphadenitis is directly related to the etiology and varies according to host characteristics and mode of presentation. Bacterial pathogens generally represent organisms

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_26

that colonize the upper respiratory tract and skin such as Group A *Streptococcus* (GAS), *Staphylococcus aureus*, anaerobic organisms and less commonly mycobacteria or actinomyces. Spread of these pathogens from person to person via the air is unusual apart from GAS (droplet spread) and *Mycobacterium tuberculosis* (airborne spread). Infants under 3 months of age (3 months corrected gestational age if born prematurely) are also at risk of adenitis from Group B *Streptococcus* (GBS) and for this pathogen a male predominance has been reported [3].

Acute bacterial lymphadenitis may occur in all groups although the relative frequency of pathogens varies by age group. When a pathogen is isolated, the most common are GAS and *S. aureus* which account for 65–89% of cases in most case series [1, 4]. A history of pharyngitis is not a prerequisite to GAS infection [1]. *Staphylococcus aureus* is particularly likely to lead to suppurative infections, and this organism predominates in recent studies of cervical lymphadenitis in infants [5–7]. Methicillin-resistant *S. aureus* (MRSA) infections, both community and hospital-acquired, have increased in the United States and worldwide over the past two decades [8]. MRSA has a similar spectrum of illness as methicillin–susceptible *S. aureus* (MSSA). MRSA was the etiology of 33% and 44% of cases of neck abscesses in two recent prospective series [7, 9]. Anaerobic organisms arising from the oral cavity are suggested by the presence of periodontal diseases.

More unusual bacterial pathogens are found when appropriate risk factors such as travel to an endemic area or animal contact are present. *Yersinia pestis* (plague) associated with contact with rodents and their fleas, and with rural areas, is found throughout Asia, Africa, and the Americas. Plague is very rare but endemic in western states of the U.S. (approximately 85% of reported cases are from New Mexico, Colorado, Arizona, and California) and a resurgence in the southwestern U.S. was reported as recently as 2015 [10, 11]. Tularemia (caused by *Francisella tularensis*) is a possibility when there is direct contact with the animal host (rabbits, hares, rodents such as voles, mice, or lemmings, or infected domestic cats) or the arthropod vector (deer flies, ticks), ingestion of contaminated water or meat, or inhalation of aerosols through occupational or recreational exposure. In the U.S., 90–154 cases of tularemia are reported annually with most cases reported in May through September; cases have been reported from all states apart from Hawaii [12]. Although fortunately uncommon, diphtheria has been reported in various countries around the world, particularly those with inadequately vaccinated populations. From 5000 to 8000 cases of diphtheria are reported to the World Health Organization annually, with a high number of cases reported from Madagascar, India, and the Lao Democratic Republic. A large outbreak of diphtheria occurred in the 1990s in the New Independent States (e.g., Baltic States) of the former Soviet Union and cases are still seen in those countries. Diphtheria rarely has been reported in countries with highly vaccinated populations such as Spain, with those cases probably resulting from increased migration [13].

Acute cervical lymphadenitis may also result from viral infections, more likely as part of a generalized lymphadenopathy. Cervical node involvement is more prominent with Epstein Barr virus (EBV) and Cytomegalovirus (CMV) infections. However, other viral syndromes should also be considered. Other common viral syndromes such as adenovirus, enterovirus, parvovirus and human herpesvirus 6 (HHV-6) may have other features to suggest the diagnosis such as fever, conjunctivitis (adenovirus), respiratory or gastrointestinal symptoms and rash (roseola). Most cases of HHV-6 occur in children aged 4 or younger, and enterovirus is more common during June through October in temperate climates.

While the epidemiology and etiology of acute cervical lymphadenitis may occasionally overlap with subacute and chronic, some pathogens have a characteristically indolent presentation. Tuberculous (TB) and non-tuberculous (NTM) mycobacterial infection can be predicted by some epidemiological features [1]. Tuberculous cervical lymphadenitis occurs in all age groups, may have a history of association with individuals with pulmonary tuberculosis or a "coughing illness," or an abnormal chest X-ray, and is not uncommonly bilateral. It is more common among

individuals born in or with a history of travel to an endemic area [14]. Tuberculous lymphadenitis is discussed further in Chap. 25. In contrast, NTM disease occurs predominantly in young children (mainly aged 6 years and younger), who tend to live in a suburban settings and is usually unilateral. Non-tuberculous mycobacteria are found in soil, water, animals, and food [15]. In the U.S., *M. avium-intracellulare* (MAC) is the most common NTM agent isolated from cervical nodes followed by *M. haemophilum* and *M. lentiflavum*, with *M. kansasii, M. fortuitum*, and *M. malmoensae* (common in northern Europe) less commonly isolated [1, 15, 16]. However, the advent of improved diagnostic methods mean that more fastidious and/or slow growing species are increasingly recognized [1, 15].

A history of contact with cats is an important epidemiological clue to lymphadenitis caused by *Toxoplasma gondii*, especially contact with cat litter, or by *Bartonella henselae* (cat scratch disease) [17, 18]. An antecedent scratch or bite from a kitten or young cat is an important clue for cat-scratch disease; however, the presence of *Bartonella* DNA in fleas from cats suggests that arthropods may also have a role in transmission [1, 18–20].

Clinical Presentation

The clinical presentation of cervical adenitis may be differentiated by the various etiologies. Although considerable overlap occurs, duration of symptoms is useful in categorizing the presentation and forming a differential diagnosis. Cervical adenitis may be acute, subacute, or chronic and location may also provide some helpful clues.

Acute Unilateral Lymphadenitis

Staphylococcus aureus and Group A *Streptococcus* (GAS)

Most cases of acute unilateral cervical adenitis (up to 80%) are due to *S. aureus* or GAS [2]. Infection can occur at any age but most typically arises in a child aged one to four years who often has a history of upper respiratory symptoms (sore throat, coryza, otitis media) or impetigo. Lymph node enlargement occurs within a few days and most commonly involves the submandibular nodes (50–60%) followed in decreasing order of frequency by the upper cervical (25–30%), submental (5–8%), occipital (<5%), and lower cervical nodes (<5). Affected nodes typically measure 2.5–6 cm in diameter and are warm, erythematous, and tender. Approximately 30% of nodes that come to medical attention suppurate, most within 2 weeks of the onset of illness. Suppuration can occur even if the patient is treated with appropriate antibiotics. More severe systemic symptoms, bacteremia, and distant foci of infection can develop, especially in nodes that suppurate. Fever, vomiting, and signs of septic shock may occur in the most severe cases, prompting hospitalization and parenteral therapy.

It is difficult to differentiate adenitis caused by GAS from that caused by *S. aureus* since an antecedent pharyngitis is not a prerequisite for GAS and prodromal respiratory symptoms and signs are common to both etiologies. There tends to be a longer duration of illness prior to diagnosis when adenitis is due to *S. aureus* and these nodes are more likely to suppurate than those due to GAS [4, 21–23]. Some studies report clinical resolution of *S. aureus* disease after treatment with antibiotics not usually effective against *S. aureus*. Recent reports show a predominance of *S. aureus*, often MRSA, among nodes where the etiology is microbiologically proven (i.e., from nodes that suppurate) [21–23].

Group B *Streptococcus* (GBS)

Group B *Streptococcus* causes a characteristic form of cervical lymphadenitis in the neonate, the so-called cellulitis-adenitis syndrome. While this is a manifestation of late-onset GBS and thus infants are susceptible until corrected age of 3 months, the typical case occurs in a male infant aged 2–6 weeks with abrupt onset of fever, irritability, and poor feeding or emesis, who is found to have an erythematous, tender swelling over the face or submandibular area. The majority of infants have a concomitant bacteremia and meningitis may occur [24, 25]. Ipsilateral otitis media may also be found.

Anaerobic Bacteria

Cervical adenitis in the presence of dental caries and poor oral hygiene prompts consideration of anaerobic bacteria, usually in older children. When severe, anaerobic infection can lead to the development of complications such as abscess and Lemierre's syndrome (septic thrombophlebitis of the jugular vein, septic pulmonary emboli, and other septic sequelae, see Chap. 18). Presentation is with fever and systemic toxicity.

Francisella tularensis

Tularemia is characterized by the abrupt onset of fever, chills, myalgia, and headache and should be considered in patients with a history of recreational or occupational exposure to the appropriate vectors (animals, ticks, deer flies). A number of tularemic syndromes present with cervical adenitis. The most common is the ulceroglandular syndrome characterized by painful, inflamed regional nodes that drain spontaneously. A maculopapular lesion is present at the inoculation site. The glandular syndrome consists of painful lymphadenitis without the ulcer. The oropharyngeal syndrome is characterized by severe exudative stomatitis, pharyngitis, or tonsillitis with accompanying cervical adenitis. Severe and painful conjunctivitis associated with pre-auricular lymphadenitis is found in oculoglandular tularemia [12].

Yersinia pestis

Acute onset of fever with painful swollen nodes (buboes) and a history of exposure to rodents and their fleas is characteristic of infection with *Y. pestis*. The cervical area may be affected although buboes are most commonly found in the inguinal regions. Occasionally, the lymphadenitis is mild which may obscure and delay the diagnosis. Consideration of this diagnosis is important to avoid progression to overwhelming sepsis [10].

Diphtheria

Diphtheria is a very rare diagnosis, as noted above, in countries where vaccine uptake rates are high, but cases occur with increased migration and also occur in countries with lower vaccination rates. Diphtheria starts with low-grade fever, and membranous nasopharyngitis with a bloody nasal discharge over 24–48 h. Extensive neck swelling with cervical lymphadenitis, so called "bull neck", is a sign of severe disease. Life-threatening complications such as upper airway obstruction, myocarditis, cranial and peripheral neuropathies may occur [26]. Palatal palsy (common with nasopharyngeal disease) is suggested by nasal speech. Diphtheria is discussed in detail in Chap. 19.

Kawasaki Disease

Kawasaki disease is an acute vasculitis of childhood that can lead to coronary artery aneurysms in one-quarter of untreated children [27]. The disease primarily affects children under age 5, and the diagnosis may be delayed in infants or older children and adolescents, or in children with atypical presentations. The etiology is unknown, although an immune response to an infectious agent has been postulated especially since there is often an infectious prodrome. Classical Kawasaki disease is characterized by fever for five days or more and at least four of the following five criteria; (1) non-exudative bilateral bulbar conjunctivitis (this usually spares the area around the limbus), (2) erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, (3) generalized polymorphous erythematous rash, (4) changes in the peripheral extremities consisting of swelling, induration and palmar and plantar erythema, and (5) acute cervical lymphadenopathy. Without treatment, the fever typically lasts 1–3 weeks. Lymphadenopathy is usually unilateral, non-suppurative and at least one node measures 1.5 cm or more clinically. It is the least commonly found of the five diagnostic criteria. However incomplete manifestations occur so Kawasaki disease should be considered in the differential of cervical adenitis with prolonged fever, some of the above findings (which may be subtle), and lack of response to usually effective antimicrobial therapy, because the risk of cardiac complications is reduced in children who are treated before day 10 of illness [27, 28]. The American Heart Association recently published an algorithm to aid the clinician in deciding

which patients with fever and fewer than four of the classic criteria should be treated [27]. Initial treatment is with intravenous immunoglobulin and aspirin,

Acute Bilateral Lymphadenitis

Epstein Barr Virus (EBV)

Acute EBV (mononucleosis) manifests as fever, pharyngitis with petechiae, fatigue, lymphadenopathy, and hepatosplenomegaly. Although lymphadenopathy may be generalized, over 90% of cases in children have cervical adenopathy that is typically bilateral. Illness ranges from asymptomatic or mild infection (more likely in infants and young children) to severe illness requiring hospitalization due to critical enlargement of cervical nodes impinging on the airway. A generalized rash may occur and is more common in children treated with ampicillin and other penicillins [29].

Cytomegalovirus (CMV)

Acute CMV produces a mononucleosis illness similar to that caused by EBV, although the frequency of cervical node involvement is lower in CMV. Sore throat is less common than with EBV. CMV is more common in children aged less than 4 [30].

Adenovirus

Adenovirus infections of the upper respiratory tract are characterized by the abrupt onset of fever, pharyngitis, and conjunctivitis (unilateral or bilateral), a syndrome called pharyngoconjunctival fever. Cervical adenopathy is present in approximately 30% of cases, commonly in conjunction with a generalized lymphadenopathy and hepatosplenomegaly [31].

Human Herpesvirus 6 and 7 (HHV 6 and 7)

HHV-6 infection causes an undifferentiated febrile illness in 80% of cases with the remainder presenting as roseola (exanthum subitum). Fever is usually high (> 103F) and lasts 3–7 days. Cervical and post-occipital adenopathy in addition to respiratory and gastrointestinal symptoms occur. When roseola occurs, the erythematous, maculopapular rash appears once fever resolves and can last from hours to days. HHV-7 infections have a less clear presentation and may either resemble HHV-6 or may be milder or asymptomatic [32].

Enterovirus

Enteroviruses commonly present as nonspecific febrile illnesses with fever, malaise, sore throat, upper respiratory symptoms, nausea, and gastrointestinal disturbance. In some illnesses, conjunctivitis, pharyngitis, and bilateral cervical adenitis is present [33].

Subacute/Chronic Lymphadenitis

Bartonella henselae (Cat-Scratch Disease)

Infection with *Bartonella henselae* may be asymptomatic, but in an immunocompetent host classically results in regional lymphadenitis 1–2 weeks following a cat scratch or contact with a cat, especially cats aged 2 years or less. A nodule develops at the inoculation site, followed some time later (range 7–60 days) by lymphadenopathy of regional nodes. Fever and mild systemic symptoms may occur in up to one-third of patients. The skin overlying the nodes may become warm, erythematous, indurated, and tender. Even without therapy, most nodes resolve spontaneously within 4–6 weeks although treatment accelerates resolution [18]. Up to 33% of affected nodes will suppurate [34, 35]. Inoculation of the periocular area results in Parinaud's oculoglandular syndrome with conjunctivitis and ipsilateral preauricular lymphadenopathy [36].

Toxoplasma gondii (Toxoplasmosis)

Many acquired infections will be asymptomatic in the immunocompetent host. When symptomatic, toxoplasmosis can result in mild fever, fatigue, headache, sore throat and myalgia. Cervical lymphadenopathy is the most common sign. Nodes are generally not very inflamed or tender. Suppuration does not occur. Illness is generally benign and self-limited [17].

Nontuberculous Mycobacteria (NTM)

The classic patient with NTM lymphadenitis is aged between 1 and 4 years. The organism is ubiquitous in soil and is most likely ingested leading to unilateral swelling of lymph nodes in the submandibular region. A single large swelling usually represents a deeper cluster and it is rare for affected nodes to be bilateral. Clinically, the presentation can be indistinguishable from cat-scratch disease. The involved nodes feel firm and are generally non-tender. Without intervention, the skin overlying the infected nodes becomes pink or violaceous as the disease progresses and becomes thinner and more paper-like, before suppuration and spontaneous draining sinus tracts occur [15].

Mycobacterium tuberculosis

Cervical adenitis due to TB is frequently bilateral and may be associated with exposure to a TB-infected individual. Patients are less likely to be aged under 4 years. Nodes are enlarged, painless, and rubbery [14]. Evidence of pulmonary disease is often absent (see Chap. 25).

Nocardia

Lymphocutaneous disease due to *Nocardia*, an organism found in soil, can occur in immunocompetent children. Enlarged, tender, usually submaxillary lymphadenitis, sometimes with fever, follows the development of a facial papular lesion [37].

Actinomycosis

Actinomycosis causes a chronic granulomatous inflammation of the face and jaw that crosses tissue planes and causes cervical abscess with chronic draining sinuses. A history of dental caries or mouth trauma is often present.

Periodic Fever, Aphthous Ulcer, Pharyngitis, Adenitis (PFAPA) Syndrome

Chronic recurrent cervical adenitis is part of the Periodic fever, Aphthous ulcer, Pharyngitis, Adenitis syndrome (PFAPA), and was first described in 1987 [38]. Affected children have recurrent episodes of high fever lasting 3–6 days every 3–8 weeks. In the classical syndrome the attacks start before age 5, are self-limited and cease spontaneously, but considerable overlap with other periodic fever syndromes occurs. The etiology is unknown.

Diagnosis

The initial step in establishing the diagnosis is through taking a complete history. Particular attention should be paid to the duration and laterality of the swelling, the presence of any associated symptoms and immunization history. Other important factors include exposure history such as ill contacts (viral infections, TB), dietary habits such as ingestion of undercooked meats (toxoplasmosis) or pica (NTM), animal or tick exposures (cat-scratch disease, tularemia, toxoplasmosis, plague), urban versus rural location, and travel. A complete physical examination documenting the location, size, warmth, tenderness, erythema of the skin over the node(s), and the presence or absence of fluctuance is indicated. Evaluation of conjunctivitis, pharyngitis and oral cavity abnormalities, involvement of other lymph nodes, presence or absence of hepatosplenomegaly, and evaluation of skin for rash or single lesions can provide valuable clues to the diagnosis.

For children with bilateral lymphadenitis, mild disease may not require further evaluation since viral upper respiratory tract infection is the most common cause of acute disease. Group A streptococcal infection should be excluded by a throat swab sent for rapid antigen testing and culture in those with exudative pharyngitis. In adolescents and young adults, the laboratory should also be asked to specifically exclude *Arcanobacterium haemolyticim* which requires special conditions for isolation [39]. In children who are ill-appearing or in whom the lymphadenitis is persistent or worsening, complete blood count (CBC), inflammatory markers (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), liver panel (looking for systemic

inflammation), blood culture, or serology for EBV and CMV may be indicated. The etiologies of acute and subacute/chronic disease overlap, therefore with the appropriate exposure history, further testing for infection such as toxoplasmosis, brucellosis, *Bartonella* (more commonly unilateral), TB (tuberculin skin test, interferon gamma release assay [IGRA]) may be considered.

Acute unilateral lymphadenitis is usually caused by GAS, *S. aureus*, or oral anaerobes. If the child is febrile and/or the node is warm and tender, it is important to exclude bacteremia and a blood culture, CBC and inflammatory markers are usually indicated. A throat culture is indicated if the child has pharyngitis; however, the isolation of GAS does not necessarily indicate that this is the etiology. If the swelling is large or the node is fluctuant, imaging such as ultrasound or in severe cases computerized tomography (CT) may be indicated to define the extent of lymph node involvement and identify areas of necrosis or purulence that may require incision and drainage for both diagnosis and therapy. Any fluid drained should be sent for Gram stain and aerobic and anaerobic cultures. When Kawasaki disease is a consideration, supportive laboratory tests such as liver panel, serum albumin, and urinalysis and microscopic examination should be performed, along with an echocardiogram.

Unilateral subacute/chronic lymphadenitis requires a more extended approach to diagnosis, and serology for many of the aforementioned conditions is indicated. Evaluation for TB by a chest X-ray and tuberculin skin testing or IGRA may be indicated, although a normal chest X-ray and negative skin test or IGRA do not rule out TB. Ultimately biopsy may be needed to establish the diagnosis. If biopsy is performed, the samples should be sent for histology and cultures (including acid-fast stains and mycobacterial cultures). Increasingly, it is possible to detect pathogens by performing molecular diagnostic tests such as polymerase chain reaction on tissue samples, and this will likely become more important in the future.

Treatment

The optimal treatment of lymphadenitis depends on an accurate assessment of the likely etiology, as suggested by the history and physical examination. Ideally, the appropriate diagnostic tests are performed prior to initiating therapy, should the child's severity of illness allow for this possibility. Empiric therapy while awaiting results or due to severe illness may be appropriate.

The treatment of acute bilateral lymphadenitis where a viral etiology is most likely is supportive in immunocompetent children. Occasionally, in EBV infection where lymph nodes are sufficiently enlarged so as to cause concern for respiratory complication, hospital admission and consultation with a specialist in otolaryngology may be needed. If airway obstruction is imminent, therapy with a short course of corticosteroids may be beneficial but this should be used with caution given the potential for adverse effects [29].

Acute unilateral lymphadenitis that is likely bacterial in origin should be treated by antibiotics active against both GAS and *S. aureus*, the two most common causes (Table 26.1). The antibiotic chosen should take into account local and community rates of MRSA infection and rates of clindamycin-resistant MRSA and MSSA isolates in the community. Clindamycin is a popular first choice therapy but may fail due to resistance. Where MSSA and GAS are most likely, appropriate choices are dicloxacillin or cephalexin. In children with periodontal disease in whom anaerobic organisms are also strong considerations, antibiotic choice should also include coverage against this possibility. Amoxicillin-clavulonate has good activity against MSSA and GAS, as well as oral anaerobic bacteria. In regions where MRSA accounts for a significant proportion of *S. aureus* isolates and clindamycin-resistance is low, clindamycin may be an appropriate choice. If clindamycin-resistance is an issue, alternatives to cover *S. aureus* include trimethoprim-sulfamethoxazole and linezolid; however, trimethoprim-sulfamethoxazole has variable activity against GAS so a second antibiotic may

Table 26.1 Presentation, etiology and possible treatment regimens[a] for cervical lymphadenitis

Presentation	Likely etiology	Empiric treatment
Acute unilateral	*S. aureus* (MSSA)	*Oral*: Cephalexin; dicloxacillin *IV*: Nafcillin or oxacillin; cefazolin
	S. aureus (MRSA)	*Oral*: Clindamycin[b]; trimethoprim-sulfamethoxazole; linezolid *IV*: Clindamycin[b]; vancomycin
	Group A Streptococcus	*Oral*: Penicillin or amoxicillin (proven GAS); cephalosporin; clindamycin *IV*: Penicillin (proven GAS), cephalosporin; clindamycin
	Anaerobic bacteria	*Oral*: Amoxicillin-calvulanate; clindamycin[c] *IV*: Clindamycin[c]; penicillin plus metronidazole; ampicillin-sulbactam or piperacillin-tazobactam; or carbapenem
	Group B Streptococcus (<3 months corrected age)	*IV*: Penicillin (Perform blood culture and lumbar puncture)
	Francisella tularensis	*Oral*: Ciprofloxacin (≥18 years); doxycycline (≥8 years)[d] *IV*: Gentamicin[e,f] or streptomycin
	Yersinia pestis	*IV/IM*: Streptomycin/gentamicin *Alternative*: Tetracycline (≥8 years), doxycycline (≥8 years), levofloxacin, ciprofloxacin (≥18 years), trimethoprim-sulfamethoxazole[g]
Acute bilateral	Epstein Barr virus Cytomegalovirus Adenovirus Human herpesvirus 6 and 7 Enterovirus	Supportive care (Consider otolaryngology and infectious diseases specialist opinion if swelling is extreme or airway threatening)
Subacute/ chronic	*Bartonella henselae*	*Treatment may not be necessary but may shorten duration of illness* *Oral*: Azithromycin[h]
	Toxoplasma gondii	Supportive care (immunocompetent)
	Mycobacterium tuberculosis	Drug-susceptible isolates: Isoniazid plus rifampin plus pyrazinamide plus ethambutol for 2 months followed by isoniazid plus rifampin for 4 months (see text for details)
	Nontuberculous mycobacteria	Surgical excision, or curettage plus azithromycin or clarithromycin plus rifampin or rifabutin or ethambutol
	Nocardia	Trimethoprim-sulfamethoxazole
	Actinomycosis	*IV*: Penicillin G/ampicillin followed by oral Alternative: Amoxicillin, erythromycin, clindamycin, doxycycline (≥8 years)

[a]This is not intended to be an all-inclusive list. Consult local antibiogram and disease-specific guidelines
[b]If clindamycin-resistance rates are low
[c]If Lemierre's syndrome is suspected, clindamycin alone may be inadequate (see Chap. 18)
[d]Although not usually given in those <8 years, doxycycline is an option for this indication and should be given for 14 days
[e]Treatment of choice
[f]Monitor therapeutic levels and renal function
[g]Not considered first-line therapy for this indication
[h]Alternative antimicrobial agents with activity against *B. henselae* are trimethoprim-sulfamethoxazole, rifampin, doxycycline (≥8 years), ciprofloxacin (≥18 years), clarithromycin, and gentamicin

be needed if this organism has not been ruled out. Wherever possible, antibiotics should be adjusted according to the results of cultures when these are obtained [1, 2].

The choice and route of antibiotic depends on disease severity. For mild disease oral therapy alone may be adequate, especially if started early in the course. However, for more severe illness and for toxic-appearing children, admission to the hospital and parenteral antibiotics (at least initially) are often required until clinical improvement is demonstrated and the child is tolerating appropriate oral therapy (see Table 26.1 for options for more severe illness). Should the nodes suppurate, surgical incision and drainage provides both a diagnostic and therapeutic role.

Suppuration may not be an indication of antibiotic failure but simply reflect the natural history of the disease, especially where *S. aureus* is the etiology.

Regardless of severity of illness, clinical improvement is expected within 48–72 h of initiating therapy. If improvement is sustained, antibiotics should be continued for 10 days or for 5 days after the acute inflammation has subsided, whichever is longer. Longer courses may be required for patients with severe illness and for those in whom suppuration occurs. If after 48 hours of antibiotic therapy there is not an appreciable clinical response, the patient should be re-evaluated for complications (abscess formation), or for the accuracy of the diagnosis. Further diagnostic tests and a different treatment regimen may be indicated.

Cervical adenitis due to TB is very rarely associated with disseminated disease, although pulmonary or hilar lymphadenopathy may coexist [40]. For isolated tuberculous cervical adenitis due to drug-susceptible strains, a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol is recommended for the first 2 months of therapy, followed by a regimen of isoniazid and rifampin for another 4 months. In areas where multidrug-resistant TB is a concern, an aminoglycoside (streptomycin, amikacin, kanamycin, or capreomycin) is added for initial therapy until susceptibilities are obtained. A fifth drug should only be added after obtaining expert opinion. Regression is usual within 3 months but lymph nodes may remain palpable due to scarring and fibrosis [14].

Cervical adenitis due to NTM is optimally treated by complete surgical excision that is curative [15]. Where this is not possible, for example when surgery carries a high risk of damage to the facial nerve, thorough curettage has been effective although this may result in delayed healing and higher relapse rate [41–43]. Antimicrobial therapy alone is less effective and is associated with a 30% lower cure rate than surgery (66% versus 96%) [41], but when used in combination with curettage may reduce the risk of relapse and the need for further surgery. The recommended regimen is clarithromycin or azithromycin, used in combination with rifampin or rifabutin or ethambutol [15]. A recent meta-analysis of 60 pediatric publications showed cure rates of 98%, 73.1%, and 70.4% for complete surgical excision, medical therapy, and no intervention. Complete excision was complicated by facial palsy in 10% of cases, and in 2% this was permanent [43]. Evidence from existing studies therefore suggests that while complete excision is the mainstay of therapy, medical therapy (with or without curettage) is an option for cases where complete excision would endanger the facial nerve, a reduction in the size of the swelling would facilitate complete excision at a later date, for recurrent disease, or if surgery is refused. The optimal duration of therapy is not known but most regimens are continued for a minimum of 4–6 months [1, 2, 15]. The child should also be monitored for antibiotic side effects.

Cervical adenitis due to cat-scratch disease is a benign self-limited condition that resolves in 2–4 months. Nodes may be painful and suppuration may occur. Antibiotic therapy may hasten recovery. Azithromycin for 5 days is usually recommended. Alternative choices in patients intolerant of azithromycin include trimethoprim-sulfamethoxazole, rifampin, and ciprofloxacin (the latter in patients older than 17 years) [18].

Other therapies are targeted against the specific pathogens (Table 26.1).

Prognosis

With prompt effective antibiotic therapy, complete resolution of lymphadenitis secondary to GAS, *S. aureus*, anaerobic bacteria, and *M. tuberculosis* can be expected. Delay in diagnosis and therapy can lead to a more complicated course. Even when suppuration occurs, appropriate drainage and antibiotic therapy leads to excellent clinical recovery in the majority of cases. When complete surgical resection is performed, disease due to NTM is cured; when this cannot occur, curettage plus antimicrobial therapy can shorten the course and improve the aesthetic result. Cat-scratch disease is a benign self-limited disease but antibiotic therapy can shorten the illness and avoid suppuration.

Conclusion

Cervical lymphadenitis in children is very common. A thorough history and careful clinical examination provides valuable clues to the likely etiology, enabling appropriate diagnostic evaluation and appropriate therapy. While complications such as suppuration and/or more invasive infection may occur, prompt assessment and early surgical intervention if needed may reduce morbidity. Successful treatment and complete recovery is generally achieved.

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Deep Neck Space Infections

27

Heather A. Osborn and Daniel G. Deschler

Introduction

Deep neck space infections have been described since the time of Hippocrates and Galen, using terms such as angina maligna and cynache (strangulation) [1, 2]. They continued to be of great importance throughout the pre-antibiotic era, reportedly causing the death of Michel de Montaigne and Pope Adrian IV, as well as a multitude of others. The advent of antibiotics not only reduced the incidence of deep neck space infections, but improved the historically dismal prognosis.

Despite the improvement in patient outcomes resulting from the development of effective medical therapy, life-threatening complications, such as descending mediastinitis, carotid artery rupture, septic shock, disseminated intravascular coagulation, and airway obstruction, still occur, and are associated with high mortality. Rapid recognition and appropriate intervention remains essential to avert these complications and avoid the associated morbidity. Deep neck space infections remain medical and surgical emergencies.

Deep neck infections occur within the fascial spaces of the head and neck and spread along fascial planes. They are typically bacterial in origin [3, 4]. In the pre-antibiotic era, tonsillar and pharyngeal infections were common sources of infection [5]. Today, however, odontogenic infections are the most common source in adults [5–7], although pharyngeal etiologies still play a role. Other sources include pharyngeal trauma, swallowed foreign bodies, direct extension from skin infections, intravenous (IV) drug injection into neck veins, salivary gland infections, and Bezold's abscess from mastoiditis [8, 9]. Huang et al. found that the most common antecedent illness in their series of 52 pediatric patients was upper respiratory tract infection (30.8%) followed by dental infection (15.4%) and congenital anomalies (15.4%) [10]. A significant portion of deep neck space infections in both adults and children have no identifiable source [8].

Sites of infection reflect the common underlying portals of entry. Submandibular space infections are common in both the adult and pediatric populations. However, adults are significantly more likely to experience infections of the peritonsillar and parotid spaces, while children are more likely to experience infections of the parapharyngeal or retropharyngeal spaces [11]. Suppurative retropharyngeal nodes are found in

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_27

increased numbers in children, which likely underlies the increased propensity for retropharyngeal abscesses in this population [12].

The incidence across age groups is reported at 9–15/100,000/year [3, 11], although the incidence, clinical presentation, and disease course differ in the pediatric and adult populations. The incidence in children has been estimated at 1.37 per 10,000 and appears to have increased over the past two decades, largely due to an increase in retropharyngeal infections [8, 11].

Deep Neck Spaces

Familiarity with the anatomy of the deep fascial planes of the head and neck is important for understanding the behavior, progression, and management of deep neck space infections.

The cervical fascia consists of a superficial layer and a deep layer. The superficial layer lies under the skin and encloses the platysma. The deep layer is subdivided into three layers (superficial, middle, and deep). The superficial layer of the deep cervical fascia (investing layer) completely encircles the neck and divides to enclose the trapezius and sternocleidomastoid muscles. The middle layer is divided into a muscular and visceral layer. The muscular layer surrounds the strap muscles, while the visceral layer contains the esophagus, trachea, larynx, and thyroid gland. The visceral layer also contributes to the buccopharyngeal fascia, which lies posterior to the esophagus and forms the anterior boundary of the retropharyngeal space. The deep layer of the deep cervical fascia comprises the alar fascia and the prevertebral fascia. The prevertebral fascia encloses the prevertebral space, including the prevertebral muscles and the cervical vertebrae. The alar fascia lies anterior to the prevertebral fascia and posterior to the buccopharyngeal fascia.

These fascial planes form several potential and real neck spaces which can be categorized based on their locations (Figs. 27.1 and 27.2) [5]. Above the hyoid bone, the parapharyngeal, parotid, masticator, peritonsillar, sublingual, and submandibular spaces are found. The retropharyngeal space, danger space, and prevertebral space extend the entire length of the neck. Below the hyoid bone, the isolated anterior visceral and suprasternal spaces are found. Deep neck infections can occur in any of these locations, and are described in terms of the space(s) they occupy.

Infections can spread to and between deep neck spaces via multiple routes, including direct extension along fascial planes, penetrating trauma, and lymphatic and vascular extension. While infections may be isolated to a single space, extension to adjacent spaces is common.

Parapharyngeal (Lateral Pharyngeal, Pharyngomaxillary) Space Infections

The parapharyngeal space is classically described as an inverted pyramid, extending from the skull base superiorly to the hyoid inferiorly, and from the pre-tracheal layer of the deep cervical fascia medially to the investing fascia of the deep lobe of the parotid gland laterally. The anterior boundary is formed by the fascia of the pterygoid muscles, and the posterior boundary by the prevertebral layer of the deep cervical fascia. The parapharyngeal space is contiguous with multiple other spaces including the retropharyngeal space posteriorly, the masticator space laterally, the submandibular space inferiorly, and the carotid space as it travels through the parapharyngeal space. Infections of the parapharyngeal space are unlikely to spread to the mediastinum without first penetrating the posterior neck spaces.

Epidemiology

Parapharyngeal abscesses are most likely to occur in adults, adolescents, and older children (>8 years old) [10, 13]. These abscesses develop most often from dental infections or peritonsillar abscesses, but rarely may arise from otitis media, mastoiditis, or parotitis [13].

Presentation

Adults typically present with odynophagia, neck pain, and dysphagia. Common signs include neck swelling, fever, and trismus [7]. The presentation is more variable in children and often more sub-

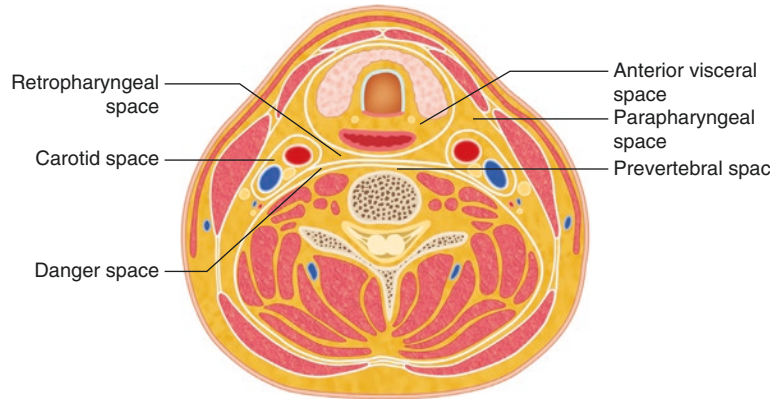

Fig. 27.1 Axial view of the neck illustrating deep neck spaces

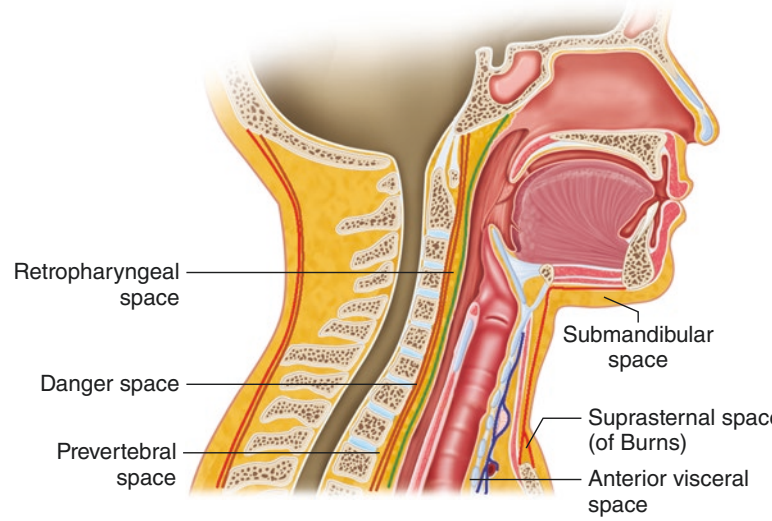

Fig. 27.2 Sagittal view of the neck illustrating deep neck spaces

tle. Children may initially exhibit decreased oral intake or irritability. Symptoms may progress to include anorexia, dysphagia, odynophagia, and neck pain [10]. The most common clinical sign is neck swelling or a neck mass. Other common findings include fever, torticollis, trismus, and cervical lymphadenopathy [10, 14]. Dyspnea, stridor, and drooling are late signs suggestive of impending airway obstruction and indicate the need for immediate intervention.

Palpation of the neck may reveal areas of tenderness, fullness, or fluctuance. Examination of the ears is essential to rule out an otogenic source. Flexible nasopharyngoscopy is an essential adjunct that can be performed at the bedside in most cases. It is valuable in the assessment of the airway for stability, and it may reveal fullness of the lateral pharyngeal wall. However, children have a low ventilatory reserve and a propensity to decompensate quickly. If there is concern about the stability of the airway in a child, endoscopy should be deferred until it can be performed in a controlled environment, such as the operating room, with full preparations in place to obtain a safe airway.

Consideration of comorbid risk factors is essential in the diagnosis and management of deep neck infections [8, 11]. Immunosuppression, including chronic corticosteroid use, and diabetes mellitus can blunt the clinical findings of deep neck infections. Intravenous drug use and immunosuppression increase the likelihood of unusual

pathogens, emphasizing the importance of obtaining appropriate cultures and the need for rapid and aggressive therapy.

Imaging

Prior to the advent of computed tomography (CT), parapharyngeal infections were difficult to diagnose and often presented at a late stage [15]. Today, radiographic imaging permits early diagnosis and treatment. Kalmovich et al. noted that the clinical presentation did not significantly differ in patients with an abscess and those who had cellulitis or phlegmon, reinforcing the essential role of imaging [16].

Contrast-enhanced CT of the neck (from skull base to tracheal bifurcation) is considered the standard imaging modality to assess for the presence of a parapharyngeal abscess [17]. A fluid collection with peripheral rim enhancement is the classic appearance of a deep neck space abscess (Figs. 27.3 and 27.4). However, a drainable collection may be present without rim enhancement. According to Miller et al., a discrete hypodensity with a volume greater than 2 ml may be more predictive than rim enhancement [18]. Overall, this study demonstrated an accuracy of 77% when assessing 44 adult patients with deep neck space infections using this criterion on CT, with a sensitivity of 95% and a specificity of 53%. When contrast-enhanced CT and clinical examination were combined, the accuracy in identifying a drainable collection was 89% [17, 18]. Reports suggest lower reliability in the pediatric population, with Vural and colleagues reporting an accuracy of 63% [19]. Nonetheless, CT is the most reliable imaging modality currently available. In addition to its diagnostic function, CT is essential for assessing extension to adjacent spaces prior to operative drainage, in order to avoid leaving a contiguous collection undrained.

Interventional radiology may be important for image-guided needle drainage of small abscesses. Needle aspirations can be performed either transorally or transcervially and with the assistance of either ultrasound or CT [16, 20].

Magnetic resonance imaging (MRI) is used less often than CT at most centers to diagnose parapharyngeal abscesses, but MRI may be useful in detecting vascular complications such as sigmoid sinus thrombosis or thrombophlebitis of the internal jugular vein.

Sharma et al. found that only 18% of patients with cervicofacial infections underwent CT prior to surgical drainage, illustrating that patients with an obvious abscess may not require imaging prior

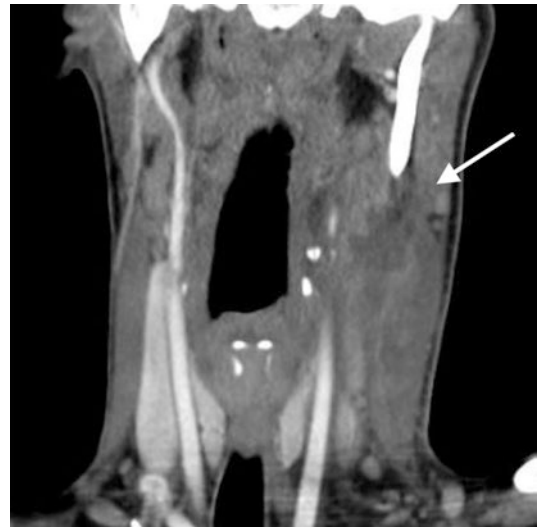

Fig. 27.3 Coronal CT images reveal a large parapharyngeal abscess

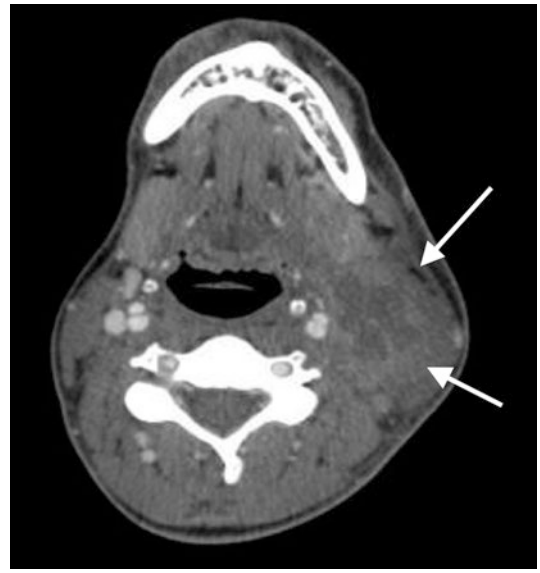

Fig. 27.4 Axial CT images reveal a large parapharyngeal abscess

to intervention [21]. However, in cases of diagnostic uncertainty, imaging is helpful in differentiating phlegmon from abscess. It can also delineate the extent of infection, and rule out spread to adjacent spaces and other complications.

Microbiology

Parapharyngeal abscesses are typically polymicrobial, and both aerobes and anaerobes are common [10, 13]. Common anaerobic organisms include *Prevotella, Porphyromonas*, *Fusobacterium*, *and Peptopstreptococcus* species, while common aerobes include viridans streptococci (including *S. anginosis* group), group A *Streptococcus* (*Streptococcus pyogenes*), *Staphylococcus aureus*, and *Haemophilus influenzae* [13]. The majority of abscesses contain beta-lactamase-producing organisms [10, 14].

Initial empiric antibiotic therapy should provide broad-spectrum coverage of the organisms noted above [8]. While no randomized trials have been performed to identify optimal regimens, possible regimens in immunocompetent hosts include ampicillin-sulbactam, ceftriaxone plus metronidazole, or clindamycin plus cefuroxime. Vancomycin may be added for patients at increased risk of methicillin-resistant *S. aureus* (MRSA) or those who present with severe infection [22]. In an immunocompromised host, pathogens may include more resistant Gram-negative bacilli (e.g., *Pseudomonas* or resistant enteric bacilli) as well as MRSA, so potential regimens include vancomycin plus either imipenem, meropenem, or pipericillin-tazobactam, or vancomycin plus metronidazole plus either cefepime or ceftazidime. Fungal causes should also be considered in immunocompromised hosts, particularly if the patient does not respond to initial broad-spectrum antibiotic therapy [22]. Blood cultures in addition to throat or abscess drainage cultures should be obtained. Cultures should be used to subsequently narrow and optimize antibiotic therapy [8].

Management

The initial management of parapharyngeal infections focuses on the assessment of the airway and stabilization if necessary. Patients exhibiting signs of impending airway collapse such as stridor, drooling, or orthopnea require immediate airway intervention, with awake fiberoptic intubation or awake tracheotomy. Patients without airway symptoms may be assessed with nasopharyngoscopy to determine airway patency and the need for intervention. Patients who do not require immediate airway intervention may warrant close observation in an intensive care setting due to the risk of clinical deterioration.

In patients with a clinically stable airway, the cornerstones of management include appropriate antibiotic therapy, effective source control, and management of underlying causes, such as immunosuppression and diabetes mellitus. Broad-spectrum antibiotic therapy should be initiated immediately upon diagnosis, before definitive cultures results become available. A brief course of IV corticosteroids in bacterial parapharyngeal infections can rapidly improve symptoms, such as pain and trismus [23, 24], and may help to control airway edema.

Surgical drainage of parapharyngeal abscesses has been advocated for decades as an essential component of initial management. However, more recently, several studies have advocated for initial treatment with IV antibiotics, with surgical drainage reserved for non-responders [14, 15, 25–27]. Outcomes using this approach have shown significant variability. De Marie et al. treated eight patients non-surgically, six of whom also underwent drainage through needle aspiration or diagnostic puncture, and obtained a high proportion of complications, including four cases of mediastinitis [14, 27]. In contrast, Sichel et al. reported on seven cases of parapharyngeal infections treated with IV antibiotics alone. Six of the seven were young children (age 10 months to 4.5 years) and the last patient was 24 years old. All had their diagnoses confirmed with CT imaging and none had extension to other deep neck spaces, septic shock, or airway compromise. All were treated with IV amoxicillin-clavulanic acid without surgical drainage or puncture, and resolution was obtained in all the cases, with no complications and an average duration of hospitalization of 11 days [14]. McClay et al. treated 11 children with CT evidence of parapharyngeal and/or retropharyngeal abscess.

Ten children (91%) responded to IV antibiotics alone and all of these began to improve clinically within 48 h of initiation of treatment [28]. The variability in outcomes appears to depend on the size of the abscess and the presence of extension into adjacent spaces [14, 15, 27].

While an initial course of IV antibiotics alone may be considered in a relatively mild infection limited to the parapharyngeal space, surgical exploration and drainage should be performed in the presence of airway obstruction, systemic toxicity, or when the clinical presentation or imaging is suggestive of a large abscess or one extending into adjacent spaces. An external, transcervical approach is the most straightforward, affording sufficient access to allow thorough drainage and separation of potential loculations. Adequate drainage of all affected spaces is critical for success. Select cases may be drained with an intraoral approach if the carotid sheath structures are adequately and safely lateralized. When operative cultures become available, antibiotic therapy should be narrowed to target the cultured pathogens. Repeat drainage may be required.

Even in the antibiotic era, complication rates remain relatively high. In a study by Huang et al., three of 22 children (13.6%) developed a complication of parapharyngeal abscess [10]. Life-threatening complications include local spread of infection causing mediastinitis or airway obstruction, spontaneous rupture of abscess into the airway causing obstruction or aspiration, and extension to major blood vessels causing rupture and hemorrhage or thrombophlebitis [13]. Aggressive medical and surgical management and frequent reassessment is warranted.

Recurrence of infection after appropriate treatment should alert the clinician to the possibility of underlying anomalies including congenital malformations (such as branchial cleft cyst) or malignancy [10].

Retropharyngeal Space Infections

The retropharyngeal space lies between the alar and visceral fascia and extends superiorly from the skull base to the tracheal bifurcation in the superior mediastinum. It is laterally contiguous with the parapharyngeal space. Retropharyngeal lymph nodes reside within the space and are a potential source of infection. A midline raphe causes abscesses in this space to occur slightly lateral of the midline. This helps to distinguish retropharyngeal abscesses from infections of the danger space or prevertebral space which are more likely to occur in the midline. Infections of this space can extend into the adjacent parapharyngeal space, or posteriorly into the danger space.

Epidemiology

Retropharyngeal abscesses occur most frequently in young children, with a peak incidence between the ages of 2 and 4 [13, 29]. In children, these infections are most likely to result from suppurative adenitis in retropharyngeal lymph nodes, and are noted to occur more frequently in the winter or spring when precipitating infections are more common [30]. In adults, direct extension from adjacent deep neck spaces is a common cause [15]. In a recent analysis of adults with peritonsillar abscess, 1.0% had a concurrent retropharyngeal abscess [29]. Adult retropharyngeal abscesses also occur more frequently in immunocompromised patients or as a complication of trauma related to foreign body ingestion [31].

The incidence of retropharyngeal abscesses in children appears to be increasing. A recent study illustrated an increase in incidence from 0.10 cases per 10,000 children in 2000 to 0.22 cases per 10,000 in 2009 [29, 32]. The cause for this increase is unclear, although the widespread use of antibiotics contributing to an increase in drug-resistant bacteria in normal oropharyngeal flora has been identified as a likely contributor. This is supported by the increase in MRSA as an isolate in deep neck space infections [32]. Other potential causes include improved diagnostic ability due to improved access to radiography [32].

Presentation

Adults may present with fever, odynophagia, torticollis, trismus, and throat or neck pain [31]. A history of previous spine surgery and hardware placement should be considered a risk factor.

Initial symptoms in children are often vague, including decreased oral intake or irritability. Symptoms progressively worsen to include fever and localizing neck complaints such as neck stiffness or pain [10, 12, 15].

The clinical exam can be more challenging in children, but neck swelling is frequently seen and fullness or a discrete mass may be palpated. Abnormal neck posturing with hyperextension is a common sign [8, 13]. Dyspnea, stridor, and drooling are late signs suggestive of impending airway obstruction and indicate the need for immediate intervention.

Bedside nasopharyngoscopy may reveal bulging of the posterior pharyngeal wall and provides valuable information about airway stability. As in parapharyngeal abscesses, if there is clinical concern about the stability of an airway, particularly in a child, nasopharyngoscopy should be performed in a controlled environment with preparations for airway management in place.

Imaging

Computed tomography is the gold standard for the radiographic assessment of retropharyngeal infections [8]. An abscess will typically appear as a homogeneous hypodense area, which classically exhibits ring enhancement with contrast (Figs. 27.5 and 27.6). Cellulitis or phlegmon will exhibit soft tissue swelling, with loss of well-defined fat planes. Two studies have previously assessed the sensitivity and specificity of CT in diagnosing retropharyngeal abscess. Boucher et al. obtained a sensitivity of 100% and a specificity of 45%, while Stone et al. obtained a sensitivity of 80.8% and a specificity of 62.5% [33, 34]. Both of these studies, however, were published in the 1990s, and significant advancements in CT imaging have been made since that time [8]. Computed tomography offers good visualization of both bone and soft tissue structures, is widely and rapidly available, and carries a relatively low cost [10]. It also has the benefits of short imaging time, important in children who may require sedation or general anesthesia for a longer study. If anesthesia is required for CT in a young or uncooperative child, a plan should be

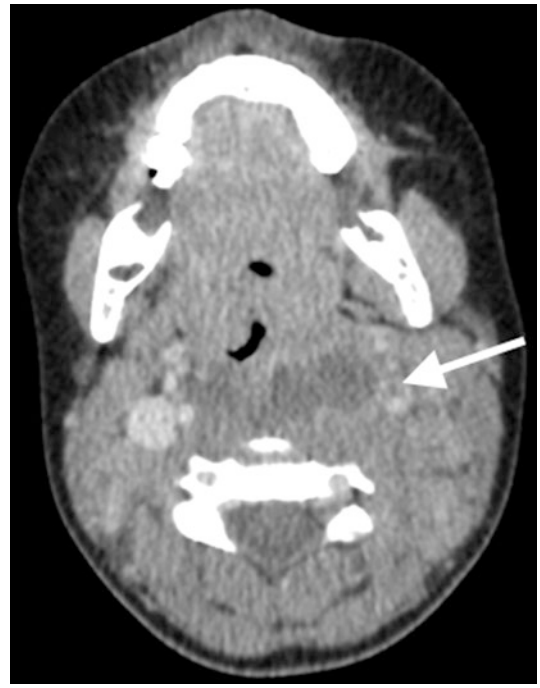

Fig. 27.5 Axial CT illustrating the classic appearance of a retropharyngeal abscess

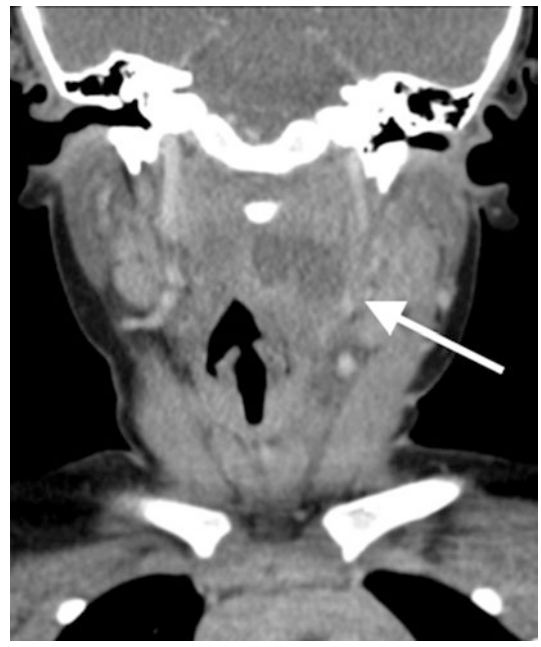

Fig. 27.6 Coronal CT illustrating the classic appearance of a retropharyngeal abscess

made to transport the patient directly from the radiology suite to the operating room, avoiding the need for multiple anesthetics.

Lateral soft tissue neck X-rays may be considered a rapid, simple alternative, particularly when the clinical suspicion is low. These are suggestive of a retropharyngeal infection when the width between the cervical vertebrae and the airway at the C2 level is greater than 7 mm, or greater than 14 mm at C6 in children or 22 mm in adults (Fig. 27.7) [8, 12]. While lateral neck X-rays have been reported to have a specificity of 100% and a sensitivity of 80% [33], the reliability is impaired by multiple confounders. The patient must be in a true lateral position, with the head extended, and at the end of inspiration. If these conditions are not met the space between the vertebrae and the airway will appear falsely widened [12, 35]. Crying, swallowing, respiration, and flexion of the neck can all result in false positives [12, 35]. Moreover, it is difficult to differentiate abscess from cellulitis on X-ray, requiring further imaging with CT following a positive X-ray [35].

Microbiology

Retropharyngeal abscesses are typically polymicrobial [8, 10], and both aerobes and anaerobes are common [3]. In an assessment of 103 patients by Rega et al., an average of 2.6 isolates were obtained per patient [3], while Brook et al. reported an average of 5 isolates per patient [13]. Common anaerobic isolates include *Provetella*, *Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus* species, while common aerobic species include viridans streptococci, group A *Streptococcus*, *S. aureus* and *H. influenzae* [3, 13]. Viridans streptococci, also called alpha streptococci due to their "alpha hemolysis" (greening of blood agar under colonies), are part of the normal oral flora but may contribute to serious head and neck infections. *Streptococcus anginosis* group members (formerly called *S. milleri*) are types of viridans streptococci particularly associated with abscesses in the head and neck, although they may not be specifically identified other than as viridans streptococci by the microbiology laboratory.

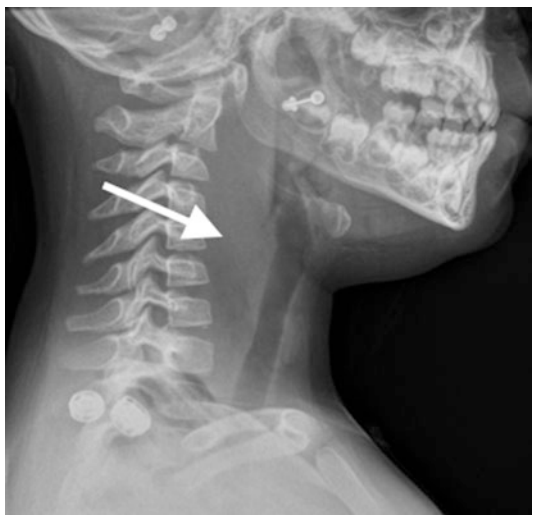

Fig. 27.7 Lateral neck X-ray revealing widened retropharyngeal space

Similar pathogens are seen in children, including groups A and B streptococci, viridans streptococci, *S. aureus*, and *H. influenzae* [8, 13]. Predominant anaerobes include *Bacteroides*, *Peptostreptococcus*, and *Fusobacterium* [36]. Beta-lactamase production is seen in the majority of patients [13].

Initial empiric antibiotics should provide broad-spectrum coverage for gram-positive cocci, gram-negative bacilli such as *H. influenzae*, and anaerobes [8]. Options include ampicillin-sulbactam, ceftriaxone with metronidazole, and clindamycin with cefuroxime. Vancomycin should be added in patients at increased risk of MRSA or those who are severely ill [22]. In immunocompromised patients, broader-spectrum coverage is indicated and possible regimens include vancomycin plus either imipenem, meropenem, or pipericillin-tazobactam, or vancomycin plus metronidazole plus cefepime. or ceftazidime. Unusual pathogens, such as fungi or *Mycobacterium tuberculosis* (e.g., from tuberculosis involving the cervical spine), should also be considered in hosts who are immunocompromised or who fail to respond to initial therapy [22]. Following initiation of broad-spectrum antibiotics, cultures should be used to narrow and optimize antibiotic treatment [8].

Management

Initial management focuses on the assessment of the airway and stabilization if necessary. Patients exhibiting signs of impending airway collapse such as stridor, drooling, or orthopnea require immediate airway intervention, with awake fiberoptic intubation or awake tracheotomy. Particular vigilance is required in children, where airway decompensation can occur quickly.

Patients who are not showing signs of airway distress should be assessed with bedside nasopharyngoscopy to determine airway patency. Patients who do not require immediate airway intervention may warrant close observation in an intensive care setting due to the risk of clinical deterioration.

Broad-spectrum antibiotic therapy should be initiated immediately upon diagnosis, before definitive cultures results become available. A brief course of IV corticosteroids may be helpful to reduce airway edema. If cultures become available from operative drainage, antibiotic therapy should be narrowed to target the cultured pathogens.

Surgical drainage has been the usual initial treatment for abscesses. This can be undertaken transorally, transcervically, or in combination, depending on the extent and location of the infection. However, some authors now advocate for an increased role for non-surgical management of retropharyngeal (or parapharyngeal) abscess in pediatric patients [15, 26, 37, 38]. Johnston et al. suggest that immediate drainage was important historically due to delayed diagnoses [15]. The combination of limited access to, and quality of, radiographic imaging and poor access to care resulted in delayed presentation, with patients presenting at a more advanced disease stage. Today, early diagnosis and improved antibiotic therapy make medical management more successful [15]. According to a meta-analysis by Carbone and colleagues, the pooled success rate of avoiding surgical intervention in children presenting with clear CT evidence of a deep neck space abscess (rim-enhancing hypodensity) was 52% (95% confidence interval, 33–70%) [37]. This data has largely been accrued in the pediatric population, and a study by Cramer et al. suggests that delaying incision and drainage in adults presenting with retropharyngeal or parapharyngeal abscesses results in a significant increase in abscess-specific morbidity, including septic shock, unplanned intubation, and prolonged ventilation [38]. In contrast, children who underwent delayed drainage showed no difference in complication rates relative to children who underwent immediate drainage. This suggests that a trial of medical management in some children, as detailed later, may be a safe option, as even those children who fail and undergo delayed drainage will not be at an increased risk of significant complications [38].

Kirse et al. have pointed out the difference in etiology between adult and pediatric retropharyngeal abscesses [39]. As adult infections are more likely to occur from direct extension from adjacent regions or from trauma, the infections are located along a fascial plane and have immediate potential to spread vertically. In children, the infections typically represent suppurative changes in a lymph node after an upper respiratory tract, sinus or ear infection, and tend to be confined to a lymph node, spreading only after rupture of the node [39].

Several studies have attempted to delineate which children are most likely to obtain success with medical management alone, and have identified smaller abscess size (<2.2 cm) and a lack of fluctuance as predictive factors. Although some authors report success with medical management in young children, Sauer et al. report an increased likelihood of an infection necessitating surgical drainage in children less than 4 years old, and Cheng et al. report an increased risk of failure of medical therapy in children less than 51 months of age [38, 40, 41]. Overall, although evidence is still being accrued, a trial of medical management may be appropriate for select children in stable medical condition, without systemic symptoms, and in the setting of careful monitoring.

Complications of inadequate treatment include local spread of infection causing mediastinitis or airway obstruction, extension to major blood vessels causing rupture and hemorrhage or thrombophlebitis, or rupture into the airway resulting in obstruction or aspiration [13].

Medical management should be limited to children without severe symptoms or systemic toxicity, and careful monitoring and frequent reassessment are warranted.

Parotid Space Infections

This space is created by the superficial layer of the deep cervical fascia as it envelops the parotid gland. It contains the parotid gland, peri-parotid lymph nodes, facial nerve, and the external carotid artery. Infections of this area can spread to the adjacent parapharyngeal space.

Epidemiology

Parotid abscesses generally occur as rare complications of bacterial parotitis [42]. Bacterial parotitis is discussed in further detail in Chap. 24. Risk factors include immunocompromise, poor oral hygiene, dehydration, malnutrition, neoplasms of the oral cavity, and medications that decrease salivary production such as antihistamines and diuretics [42–45].

Acute bacterial parotitis may affect patients of any age [44], but two noteworthy populations are the elderly and neonates. Infected first branchial arch remnants can also present as peri-parotid or intra-parotid abscesses depending on the subtype.

Presentation

Acute parotid infection presents with unilateral warm, tender, erythematous swelling of the cheek. Patients report unilateral cheek pain and often exhibit fever and leukocytosis. Milking of the parotid duct may cause extrusion of pus. Palpation of the cheek may reveal fluctuance, although the gland may remain firm due to its dense fibrous capsule [45].

Imaging

Ultrasound is the initial modality of choice when a parotid abscess is suspected [42]. It is effective at differentiating hypertrophy or generalized edema of the gland from focal abscess formation, and can also be used to guide needle aspiration of pus. Computed tomography is an alternate modality that can be used to detect suppuration or identify the extent of disease, and to rule out extension to adjacent spaces or other complications [45].

Microbiology

Staphylococcus aureus is the predominant pathogen in suppurative parotitis, causing over 50% of cases in most series; some are due to MRSA [44]. Parotid abscess has a similar microbiology. Other aerobic isolates include beta-hemolytic streptococci, viridans streptococci, and the respiratory pathogens, *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis.* Gram-negative bacilli such as *Escherichia coli* have also been reported but are rare. Less frequent isolates include *Klebsiella pneumoniae*, *Salmonella*, and *Pseudomonas aeruginosa*; mycobacterial infections such as *M. tuberculosis* are rare [42, 45, 46].

Brook et al. examined 32 aspirates of pus from acute suppurative parotitis, and recovered anaerobes from 41% of specimens, aerobes or facultative bacteria from 34%, and a combination of aerobic and anaerobic species from 25% of specimens. Approximately 1.7 isolates were recovered per specimen. The predominant aerobes were *S. aureus* and *H. influenzae*, and the predominant anaerobes were *Prevotella, Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus* species [45].

Appropriate initial empiric antibiotic choices include broad-spectrum agents that include coverage of staphylococci, anaerobes, and *H. influenzae* among other organisms, with tailoring of therapy based on culture results. Patients with parotid abscess nearly always require hospitalization and IV therapy. Initial therapy with an antibiotic such as IV ampicillin-sulbactam or piperacillin-tazobactam is appropriate for children (non-neonates) and adults who present from the community. Neonates with parotid infections should be treated with broad-spectrum therapy to cover *S. aureus*, MRSA, streptococci, and Gram-negative bacilli.

Patients with hospital-acquired infection or who are immunocompromised should be given

more broad-spectrum coverage initially since they may have oral flora colonization with MRSA and Gram-negative bacilli (e.g., Enterobacteriaceae, *Pseudomonas*) in addition to normal oral flora. In such patients, an initial broad-spectrum regimen might include vancomycin plus piperacillin-tazobactam, vancomycin plus a carbapenem (e.g., meropenem), or the combination of vancomycin, metronidazole, and ceftazidime or cefepime [45]. Needle aspiration can be used to identify the causative organism and appropriately narrow antibiotic therapy [45].

Management

The cornerstones of management include maintenance of adequate hydration and parenteral antibiotic therapy, as well as source control with needle aspiration or surgical drainage [45].

Ultrasound-guided needle drainage is effective for small abscesses. Larger abscesses, particularly those exhibiting extension to adjacent spaces, require conventional operative drainage [47]. Abscesses can be approached transfacially/transcervically or transorally, and the specific approach will be determined by the size and specific location of the collection.

Potential complications include facial nerve injury, spontaneous rupture into the external auditory canal or through pre-auricular skin, salivary fistula, and rarely, temporal lobe abscess [42, 48–51]. Patients should be admitted to hospital and monitored carefully for improvement. Clinical deterioration should prompt repeat imaging and consideration of a persistent collection requiring repeat drainage.

Masticator Space Infections

This space contains the muscles of mastication, including the masseter and the pterygoid muscles, as well the body and ramus of the mandible, the buccal fat pad, and the inferior alveolar vessels and nerves. It can be subdivided into the masseteric space, which is found between the masseter muscle and the mandibular ramus, and the pterygoid space, which is located deep to the temporal space and anterior and lateral to the parapharyngeal space. Infections of this space can extend to involve the parapharyngeal space.

Epidemiology

Infections of the masticator space typically result from the spread of odontogenic infections and most commonly occur following a dental procedure. The source of infection is most commonly pericoronitis associated with the third molar [52]. Masticator space abscesses occurring without a precipitating dental cause are uncommon, but may be seen in infants [53].

Presentation

Infections of the masticator space typically present with pain and tender swelling in the region of the ramus of the mandible or the buccal fat pad. Severe trismus reflects involvement of the masseter muscle. Young children are less likely to exhibit trismus, but present with fever, agitation, dysphagia, drooling, and poor oral intake. In infants, poor suckling, irritability, fever, and dehydration may be seen. Leukocytosis may be evident [52, 53].

Imaging

CT is the modality of choice to differentiate phlegmon from abscess and delineate the extent of the infection. Ultrasound may be useful in guiding needle aspiration, but may not reveal the full extent of abscess spread due to its inability to penetrate through the mandible.

Microbiology

Odontogenic infections of the head and neck are usually polymicrobial, including both aerobes and anaerobes. Common isolates include viridans streptococci, staphylococci, and anaerobes such as *Peptostreptococcus* and *Prevotella* [3]. Antibiotic therapy with ampicillin-sulbactam is appropriate; vancomycin may be added in patients at risk for MRSA colonization [53]. Penicillin remains a common empiric choice in odontogenic infections but is not sufficiently broad-spectrum for initial therapy of serious deep neck infections, since many organisms in the oral flora are resistant, and *S. aureus* and Gram-negative bacteria will not be susceptible [3, 54].

Management

The cornerstones of management include source control with image-guided needle aspiration or open surgical drainage and IV antibiotic therapy. Incision and drainage is typically via an intraoral incision, with dissection along the anterior border of the ramus of the mandible to enter the masticator space [52].

The most important surgical consideration is airway obstruction during induction of anesthesia, resulting from severe trismus. Fiberoptic nasal intubation may be required [52].

Peritonsillar Space Infections

This space is located between the tonsillar capsule medially and the superior constrictor muscle laterally. It is bounded by the palatoglossus anteriorly and the palatopharyneus posteriorly. Infections of this area can extend to the parapharyngeal space.

A full description of peritonsillar abscess and its diagnosis and management can be found in Chap. 17.

Sublingual and Submandibular Space Infections

The superior boundary of the sublingual space is the floor of mouth, and the inferior boundary is the mylohyoid. Anteriorly and laterally it is bounded by the mandible and posteriorly by the base of tongue. The sublingual space is contiguous with the submandibular space and infections spread freely between these two spaces. The submandibular space is located inferior to the mylohyoid, but connects with the sublingual space around the lateral edges of the muscle. The inferior border is the hyoid.

Epidemiology

Abscesses of the sublingual or submandibular spaces may be preceded by viral upper respiratory tract infections, trauma or salivary duct stenosis or calculus. Odontogenic infections are thought to be the most common source of infection [55–57].

Presentation

Infections of the submandibular and sublingual spaces may present with jaw or oral pain, dysphagia, odynophagia, and neck pain. Clinical signs include fever, tachypnea, and drooling. There may be a firm, tender swelling in the submental and submandibular regions [55, 58].

Ludwig's angina is an extensive and severe sublingual, submandibular, and submental space cellulitis. This edema displaces the tongue posteriorly, resulting in airway obstruction. Although rare, it may result in rapid airway compromise and should be considered a medical and surgical emergency [55, 57, 58].

Imaging

As in other deep neck spaces, ultrasound and CT are useful imaging modalities. Ultrasound is effective at differentiating cellulitis from abscess and may be used to guide needle drainage. Deeper abscesses and those involving multiple spaces are better assessed with CT.

Microbiology

Common causative organisms include streptococci, staphylococci, and anaerobies (*Prevotella, Peptostreptococcus* and *Bacteroides*) [56]. Infections of odontogenic origin are typically polymicrobial, with both anaerobic and aerobic organisms. Streptococcal species are the most common isolate [59]. Treatment with agents that adequately cover staphylococci and oral flora, such as ampicillin-sulbactam, is appropriate [59–61]. Vancomycin can be added if MRSA is a consideration, and broader-spectrum agents that include additional Gram-negative coverage should be considered in hospitalized patients who develop this infection.

Management

Infections of the submandibular and sublingual spaces can rapidly progress to cause airway obstruction and death. The initial management priority is assessment of the airway with intubation or tracheotomy if required. In most cases, intubation should be performed in the operating room with preparations for a surgical airway if needed. The cornerstones of management include intravenous administration of broad-spectrum

antibiotics, careful monitoring, and early surgical drainage [57]. Cellulitis, including Ludwig's angina, will often resolve with antibiotic therapy alone. However, infections that organize into an abscess require drainage. Computed tomography should be used to evaluate for the presence of abscess if not clinically obvious. Surgical techniques include intraoral and transcervical approaches [61]. Intravenous steroids decrease edema and may prevent the need for more aggressive airway interventions [61].

Danger Space Infections

The danger space lies between the alar fascia and the prevertebral fascia, and extends from the skull base to the level of the diaphragm. The loose tissue of this space provides minimal obstruction to the spread of infection from the pharynx to the mediastinum.

Epidemiology

Infections of the danger space result from contiguous spread from adjacent spaces, including the parapharyngeal, retropharyngeal, and prevertebral spaces [5, 22]. Infections of the danger space can spread to the posterior mediastinum, pericardium, and retroperitoneum. Mortality with mediastinal extension may be as high as 33% [22, 62, 63].

Presentation

Symptoms associated with danger space infections include odynophagia, dysphagia, dyspnea, and neck stiffness with abnormal positioning of the head [22]. Edema and anterior displacement of the posterior pharyngeal wall can result in respiratory distress progressing to airway obstruction [22].

Flexible nasopharyngoscopy may reveal bulging or fullness of the posterior pharyngeal wall. Care must be exercised as rupture of the lesion can lead to aspiration of pus or asphyxiation. Pleuritic chest pain may represent mediastinal extension of the infection [22].

Imaging

Computed tomography is the most common modality used to assess this space. It can effectively delineate the extent of infection as well as spread to adjacent spaces, and can also provide information regarding airway patency. In some cases, MRI may exhibit greater sensitivity and should be considered if symptoms persist in the setting of absent CT findings [64]. MRI may also be used to assess for complications such as extension to the adjacent prevertebral space and involvement of the epidural space or spinal cord.

Microbiology

Common isolates in the danger space include gram-positive cocci such as *S. aureus* and streptococci, and oral anaerobes. Gram-negative bacteria may also play a role. Antibiotics that provide coverage for these microbes include ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam. However, danger space infections have the potential to be highly morbid and rapidly progressive, therefore broader-spectrum coverage, including coverage for MRSA, may be the most appropriate initial management. Such regimens include vancomycin plus piperacillin-tazobactam, vancomycin plus metronidazole plus either ceftazidime or cefepime, or vancomycin plus meropenem (or a similar carbapenem). If extension of infection to the central nervous system is a consideration, then antibiotics that cross the blood-brain barrier (e.g., vancomycin plus metronidazole plus ceftazidime) should be used.

Management

Danger space abscesses carry a significant risk of morbidity and mortality. Early diagnosis and aggressive intervention are essential. Danger space infections without mediastinal extension may respond to intravenous antibiotic therapy alone if the antibiotics are initiated prior to the development of abscess. When a purulent collection has developed, source control is essential. Success has been reported with a minimally invasive approach comprised of catheter drainage and irrigation [22, 65]. In the setting of mediastinal

extension, surgical debridement of necrotic tissue and drainage of collections are necessary. However, even with aggressive medical and surgical therapy, mortality remains high [22].

Prevertebral Space Infections

The prevertebral space extends from the skull base superiorly to the coccyx inferiorly. It contains dense areolar tissue that is more effective at obstructing the spread of infection than the looser tissue of the danger space. It encloses the vertebrae, prevertebral and paraspinal muscles, brachial plexus and phrenic nerve.

Epidemiology

Infections of this space are primarily caused by cervical discitis, or as complications of surgical or accidental trauma [57]. Risk factors for prevertebral space infections include intravenous drug use, immunosuppression, alcoholism, diabetes mellitus, and a history of spine surgery, particularly with hardware insertion [22]. Tuberculous spondylitis (Pott's disease) must also be considered, particularly in developing nations.

Presentation

Misdiagnosis is common in prevertebral space infections due to the nonspecific presentation. Approximately 75% of patients report back or neck pain. Fever occurs in half of all patients, and one-third exhibit neurologic deficits such as neuropathic pain or paralysis [22]. Collections can ultimately cause cord compression and may result in irreversible paralysis, or can spread to the vertebrae or disc causing local destruction and spinal instability [22].

Imaging

Unlike the adjacent spaces, MRI is the preferred modality for imaging of the prevertebral space. It is essential to assess for involvement of the epidural space and spinal cord [57]. Plain radiographs can be used to assess for foreign bodies, particularly in a history of trauma. In the lateral plane, the thickness of the prevertebral soft tissues can also be assessed. However, the differential diagnosis of a widened prevertebral space is broad and the specificity of plain radiography is not adequate for use as a sole modality [66]. Multi-detector computed tomography (MDCT) provides better contrast resolution than traditional CT, allowing for detection of more subtle changes. In limited studies it also appears to provide accurate diagnosis of prevertebral space infections and may be more sensitive in detecting vertebral erosion [66, 67].

Microbiology

Prevertebral space infections exhibit microbiology different from that of the other deep neck spaces. These infections often occur due to extension of cervical spine osteomyelitis or discitis, which may result from bacteremic seeding or as a complication of cervical spine surgery. Other sources include trauma from local instrumentation of the trachea of esophagus leading to a posterior perforation. Prevertebral abscess has also been described occurring 6 weeks after tonsillectomy [68].

There are few studies that specifically examine the microbiology of prevertebral space infections; most reviews cite studies of spinal epidural abscesses, which may be similar if osteomyelitis is the cause of prevertebral infection [22]. However, the microbiology will vary depending on the etiology, and whether community-acquired or hospital-acquired bacteria are involved. If the prevertebral infection arises from the extension of a cervical osteomyelitis that arose from community-acquired bacteremia, then *S. aureus* will be the most likely etiology, although Gram-negative bacilli such as *E. coli* are also considerations. Tuberculosis may also present with cervical osteomyelitis and extension into the prevertebral space, so this should be considered in the appropriate patient. If the prevertebral infection developed as a complication of cervical spinal surgery, then MRSA and hospital-acquired Gram-negative bacilli (such as *Pseudomonas*) are potential pathogens. If the prevertebral infection arose from a perforation of the esophagus, then oral flora organisms and *Candida* species, in addition to *S. aureus*, must be considered. A broader spectrum of pathogens should be covered

if the patient acquired the esophageal defect in the hospital or has been on prolonged antibiotics [22, 69].

Management

A prevertebral space infection is potentially life-threatening. If an abscess is present, this should be drained as soon as possible and samples sent for culture. Blood cultures should be obtained in all patients on presentation, even if they are afebrile. Empiric therapy with broad-spectrum antibiotics that cover *S. aureus* (usually also MRSA), anaerobes, and Gram-negative bacilli should be given while awaiting culture results. If the prevertebral space infection is associated with a spinal epidural abscess, presumably due to cervical osteomyelitis or discitis, then the spinal epidural abscess will also require drainage. According to Curry et al., patients with spinal epidural abscesses treated without early surgery were more likely to suffer unfavorable outcomes such as clinical deterioration or death [70]. In most cases, early surgical intervention, in conjunction with aggressive antibiotic therapy, close monitoring, and medical management of contributing comorbidities is the most appropriate approach to management [22]. Operative intervention should be performed with an experienced spine surgeon.

Carotid Space Infections

This space is enclosed by the carotid sheath and extends from the skull base superiorly to the thorax inferiorly. It contains the internal jugular vein, carotid artery, vagus nerve, and sympathetic plexus.

Epidemiology

Infections of the carotid space generally occur due to spread from the adjacent parapharyngeal space. Other causes include intravenous drug use and penetrating trauma [5].

Presentation

Symptoms of infection include fever, tenderness, torticollis, and induration of the neck deep to the sternocleidomastoid muscle. Due to the robust nature of the carotid sheath, infections tend to remain localized. However, the accumulation of pressure can result in neural compression causing Horner's syndrome or vagus nerve dysfunction [71].

Septicemia, lethargy, and severe headaches should cause consideration of septic jugular vein thrombosis (Lemierre's syndrome). Fundoscopy should be performed frequently to assess for retinal thrombosis and other signs of diminished intracranial circulation [71]. Spiking fevers are suggestive of seeding into the bloodstream.

Erosion of the carotid artery can result in fatal hemorrhage. Small quantity bleeding into the pharynx or ear is suggestive of erosive aneurysm and should be viewed with great caution [71].

Imaging

Computed tomography with contrast is a useful modality for diagnosing carotid space infection and assessing for internal jugular vein thrombosis. Ultrasound may be more sensitive in detecting suppurative thrombophlebitis [72]. Angiography may be necessary if the diagnosis is unclear [71].

Microbiology

Broad antimicrobial therapy should be initiated to cover both anaerobes and aerobes, including *S. aureus,* streptococci, and oral anaerobes such as *Prevotella*, *Porphyromonas* and *Fusobacterium* [72]. Initial therapy should typically cover for MRSA, given the serious nature of these infections. Examples of possible antibiotic regimens include vancomycin plus either ampicillin-sulbactam or, piperacillin-tazobactam, or vancomycin plus metronidazole plus ceftriaxone or ceftazidime.

Management

The cornerstones of management include broad-spectrum IV antibiotic therapy and supportive management. The management of Lemierre's syndrome, or thrombophlebitis of the internal jugular vein, is described in detail in Chap. 18, including the use of anticoagulation and operative intervention. Most thrombophlebitis will

resolve with resolution of the endovascular collection, and ligation of the internal jugular vein is rarely required [72].

Carotid space infections that do not show improvement in clinical condition after 24–48 h of medical therapy should be treated with neck exploration and drainage of collections. Carotid space infections with obvious abscess should be drained on an emergency basis.

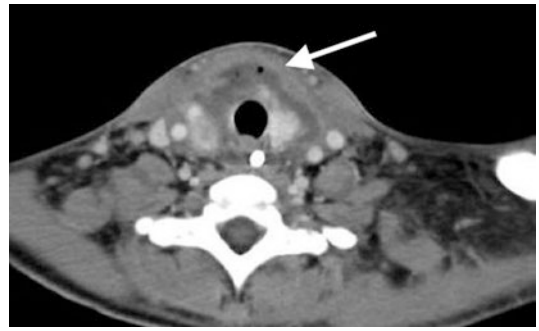

Fig. 27.8 Axial CT showing visceral space abscess

Anterior Visceral Space Infections

This space is bounded by the thyroid cartilage superiorly and the fourth thoracic vertebrae inferiorly. It encloses the pharynx, esophagus, larynx, trachea, and thyroid gland. Infections of the anterior visceral space are rare, and little has been published on management.

Epidemiology

Infections of this space can occur due to esophageal perforation by instrumentation or foreign bodies, iatrogenic or accidental trauma, or thyroiditis. Thyroglossal duct cysts may also lie within this space and act as a source of infection [5, 71, 73]. Similarly, third and fourth branchial cleft anomalies can track within the this space, causing recurring infections.

Presentation

Early signs of anterior visceral space involvement include hoarseness or muffled voice due to laryngeal edema. Dysphagia results from constrictor edema. Tenderness over the larynx may occur. Pitting edema over the larynx is suggestive of abscess. Mirror exam or flexible nasopharyngoscopy may reveal swelling of the hypopharynx, supraglottis, and glottis. Dyspnea may occur and symptoms can rapidly progress to acute airway obstruction [71, 72].

Imaging

Imaging is important due to the insidious initial course of infection, and the potential for rapid progression. Computed tomography is the preferred modality, providing information on the extent of disease and involved neck spaces. Contrast is helpful in differentiating abscess from phlegmon [74]. An example of a visceral space abscess can be viewed in Fig. 27.8.

Microbiology

Limited research has been done on the microbiology of the anterior visceral space. Extrapolating from other deep neck spaces, antibiotic therapy should cover both aerobic and anaerobic bacteria, including beta-lactamase producing organisms [8]. Appropriate initial regimens may include ampicillin-sulbactam, ceftriaxone plus metronidazole, or clindamycin plus cefuroxime. Vancomycin may be added for patients at increased risk of MRSA or those with significant toxicity [22]. In an immunocompromised host, potential regimens include vancomycin plus a carbapenem (e.g., imipenem, meropenem), or vancomycin plus pipericillin-tazobactam. Cultures should subsequently be used to narrow and optimize antibiotic therapy [8].

Management

The first priority is assessment of the airway and awake fiberoptic intubation or awake tracheotomy if required. In patients presenting with a stable airway, careful monitoring remains essential as decompensation can occur rapidly. Parenteral antibiotics should be initiated immediately. A short course of intravenous steroids may be necessary to reduce airway edema. Surgical drainage can be performed via an incision anterior to the sternocleidomastoid muscle and should be performed promptly to avoid mediastinal extension. In cases of recurrent infection, an underlying congenital anomaly should be considered [71, 72].

Conclusion

Deep neck space infections may be life-threatening if not diagnosed and treated promptly. Changing patterns of resistance, including the proliferation of antibiotic-resistant organisms, will continue to challenge clinicians. However, the foundations of treatment, including airway management, antibiotic therapy, and surgical drainage, have remained unchanged for decades. Using these principles, a previously devastating affliction has been transformed into a curable infection from which most patients fully recover.

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Human Papillomavirus and Head and Neck Cancer

28

Farhoud Faraji and Carole Fakhry

Introduction

Human papillomavirus is a common sexually transmitted virus [1] and a major infectious cause of cancer worldwide [2]. Global estimates indicate that human papillomavirus (HPV) is an etiologic factor in 4.6% of all malignancies and in 29% of cancers attributed to infection [2]. Although the clear majority of HPV-related cancers worldwide arise from the uterine cervix, HPV also causes cancers of the vagina, vulva, anus, penis, and upper aerodigestive tract, primarily in the oropharynx [2, 3]. Infection and subsequent neoplastic transformation of the squamous epithelia overlying the palatine tonsils, base of tongue, and other lymphoreticular structures of the oropharynx [4] by HPV is the cause of a unique subtype of head and neck squamous cell carcinoma (HNSCC) known as HPV-related oropharyngeal squamous cell carcinoma (HPV-OPC) [5].

HPV-OPC differs from HPV-negative HNSCC in its pathophysiology [6], epidemiology [7], and clinical course [8, 9]. The presence of oral infection by certain high-risk HPV types precedes the development of HPV-OPC [10, 11]. The primary risk factors for HPV-OPC relate to sexual behaviors that increase oral exposure to HPV [5]. In contrast, HPV-negative HNSCC most commonly results from chemical carcinogens associated with alcohol and tobacco use [12]. Trends in exposure to these distinct risk factors have led to a divergence in incidence trends of HPV-OPC and HPV-negative HNSCC [7, 13].

Over the past decades, increased public awareness of the dangers of smoking and drinking has contributed to declines in HPV-negative HNSCC and other tobacco-related tumors [13, 14]. Meanwhile, the incidence of HPV-OPC has steadily grown [7, 15, 16], recently surpassing the incidence of uterine cervical squamous cell carcinoma in the United States [17]. This rise in HPV-OPC has been attributed to societal trends in sexual behaviors that increase the transmission of oncogenic HPV infection.

The most clinically relevant feature of HPV-OPC is its effect on survival. Patients with HPV-OPC tend to present with small primary tumors and numerous lymph nodes [9]. Yet, HPV-positive tumor status at the time of diagnosis is an indicator of improved treatment response and

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_28

confers a significant survival advantage [8, 18]. The divergent influences of tumor and nodal stages on survival of HPV-OPC compared to HPV-negative HNSCC, combined with the generally favorable prognosis of HPV-OPC have led the American Joint Committee on Cancer to adopt a separate staging system specific to HPV-OPC [19].

While intensive investigation is clarifying the clinical behavior, risk assessment, and treatment strategies for HPV-OPC, the natural history of carcinogenic HPV infection in HNSCC remains incompletely understood. Persistent oral HPV infection is thought to precede HPV-OPC, a finding that has been established in cervical cancer [20]. However, unlike other HPV-related tumors, no precursor lesion has been identified for HPV-OPC. Furthermore, key elements of oral HPV infection—including potential routes of oral infection and determinants of persistent infection, latency, reactivation, and viral clearance—remain understudied. Answers to these questions will help provide a more complete understanding of the factors leading to HPV-OPC that could inform public health efforts, patient counseling, and the design of novel screening strategies. This chapter will provide an overview of carcinogenic HPV infection and the epidemiology of oral HPV infection.

Human Papillomavirus-Related Carcinogenesis

Human papillomavirus encompasses a family of small, non-enveloped DNA viruses that infect keratinocyte progenitors in the basal layer of stratified squamous epithelia [21]. Although most HPV infections are subclinical and cleared without detection, specific HPV types can cause papilloma, condyloma, or carcinoma [22, 23]. Approximately 200 distinct HPV genotypes ("types") have been described based on peptide sequence diversity of the viral L1 capsid protein [24]. Human papillomavirus type 16 is detected in approximately 90% of HPV-OPC and 70% of HPV-positive non-oropharyngeal HNSCC [25–27]. The remainder of HPV-related HNSCC is caused by other oncogenic ("high-risk") HPV types detected in HNSCC, including types 18, 31, 33, 45, 51, 52, 56, 58, 59, and 68 [17, 25, 28–30]. Notably, HPV types are also clinically relevant with respect to serologic response to L1 capsid-based vaccines, which confer strong type-specific immunity, but limited cross-type immunity even between highly related HPV types [31, 32].

Human papillomavirus infection is established through routes that provide virus access to basal keratinocyte progenitors. In the epidermis and anogenital tract, HPV infects basal cells through micro-abrasions sustained upon sexual or other direct physical contacts [33]. In the aerodigestive tract, HPV tropism for lymphoreticular structures of the oropharynx may be partially explained by the specialized reticulated squamous epithelium overlying tonsillar crypts. Reticulated epithelia are infiltrated with lymphoid tissue that interrupt epithelial barriers allowing HPV to access basal cells without requiring traumatic interruption of the surface epithelium [34].

Elements of the HPV viral life cycle are intimately linked with its carcinogenic potential. Infection of basal keratinocytes is followed by transport of the HPV genome into the host cell nucleus, where viral genes are expressed in a pattern dictated by keratinocyte differentiation [35]. The HPV life cycle typically progresses with the circular viral genome maintained in the nucleus as an "episome," or a genetic element separate from the host genome [36]. Interestingly, in HPV-OPC and other HPV-related tumors, the circular HPV genome is often found linearized and inserted, or "integrated," into the host genome [37]. Integration of the viral genome more often occurs with oncogenic HPV types [36], results in stable, upregulated expression of viral oncogenes [38], and may promote HPV-related carcinogenesis [39].

High-risk HPV types encode versions of two viral oncoproteins that mediate viral oncogenic potential by disrupting keratinocyte differentiation, promoting cell cycle progression, and facilitating keratinocyte immortalization [40]. Human papillomavirus oncoprotein E6 binds and targets p53 for proteolytic degradation [41]. P53 is the protein product of the *TP53* gene, a master orchestrator of the DNA-damage response [42],

regulator of the G_2/M (Growth phase G2 to Mitotic phase) cell cycle transition [43], and the most commonly mutated tumor suppressor gene in all cancer [44]. Human papillomavirus oncoprotein E7 facilitates the proteolytic destruction of another tumor suppressor protein, Retinoblastoma (Rb) [45]. Degradation of Rb releases E2F family mitogenic transcription factors into the nucleus and activates proliferative transcriptional programs [46, 47]. These molecular perturbations set the stage for genome instability and unregulated proliferation, tipping infected squamous cells toward malignant transformation [48].

Diversity in the biochemical properties of E6 and E7 accounts for differences in the oncogenic potential of various HPV types. For example, only E6 alleles from high-risk HPV types bind p53. Moreover, the strength with which high-risk E6 binds p53 is correlated with that HPV type's oncogenic potential. For example HPV16, which is responsible for more HPV-related cancers than HPV18 [49], possesses an E6 allele that binds p53 with twice the affinity of the HPV18 E6 allele [50]. Analogously, although low-risk E7 can bind Rb, it does so at a lower affinity than E7 from high-risk HPV types [51]. As such, the affinity of low-risk E7 for Rb is insufficient to promote neoplastic transformation [52].

In addition, the action of oncogenic E7 in diminishing Rb levels induces compensatory upregulation of, $p16^{INK4A}$ (p16), a downstream tumor suppressor of the Rb pathway [53]. Overexpression of p16 forms the basis for p16 immunohistochemistry as one strategy for designating OPC as HPV-related. Indeed, approximately 90% of diffusely, intensely p16-positive OPC are HPV-positive, and nearly 100% of HPV-OPC are p16 positive [54, 55].

Beyond circumventing cell cycle checkpoints and impairing genomic stability, HPV also evades host immunity through several mechanisms. Human papillomavirus oncoproteins disrupt signaling through interferons (IFNs), cytokines secreted by infected host cells that mediate the antiviral immune response [56]. Both E6 and E7 impair type I IFN signaling and the expression of IFN-responsive genes, thereby altering host resistance to infection and evading the cell-mediated immune response [57]. In addition to disrupting the interferon response, HPV diminishes immunostimulatory cytokine expression while enhancing production of immunosuppressive cytokines, impeding an effective immune response to HPV-infected cells and the clearance of nascent tumors [58, 59].

In summary, HPV-related carcinogenesis is initiated through the co-option and disruption of host cell intrinsic molecular pathways and propagated through viral modulation of the immune microenvironment permitting persistent infection. Longitudinal cohort analyses [60, 61] and genome-wide association studies [62] support the central role of cell-mediated immunity in the risk of oral HPV infection and susceptibility to HPV-OPC.

Risk Factors for HPV-Related Oropharyngeal Carcinoma

High-risk sexual behaviors are the most consistent and significant risk factors described in HPV-OPC. Suggesting a route for viral transmission, a high number of lifetime oral and vaginal sexual partners is the most specific risk factor for HPV-OPC [5, 11]. Analysis of multinational case-control data from the International Head and Neck Cancer Epidemiology (INHANCE) consortium demonstrated that history of ≥4 lifetime oral sex partners increased the risk of OPC (odds ratio, OR, 2.25 versus 0–1 partners) [63]. Younger age (≤18 years) at first sexual encounter (OR 1.10), more than one lifetime vaginal sexual partner (OR 1.63 for two partners, 1.25 for ≥6 partners), history of oral-anal contact (OR 1.31), and same-sex sexual contact among men (OR 1.02) also increased risk for OPC [63]. This pooled analysis confirmed previous findings linking sexual behavior with risk of HPV-positive HNSCC [5, 11]. The reproducible relationship between sexual behaviors and HPV-OPC indicates that, like anogenital HPV infection, oral HPV infection is sexually transmitted and likely precedes HPV-OPC. Consistent with this notion, oral HPV infection is associated with a 53-fold greater risk of HPV-OPC [5].

Tobacco use can modify risk for and the disease course of HPV-OPC. Although patients with HPV-OPC are less likely to report a history of heavy tobacco use than those with HPV-negative HNSCC [5], smoking has been identified as an independent risk factor in HPV-OPC [64]. Compared to never smokers, current smokers were at a 6.8-fold higher risk of OPC. The combined effects of smoking and HPV seropositivity were consistent with an additive interaction [64]. Consistently, incidence of HPV-OPC was higher in ever-smokers and current smokers than never-smokers in the United States [65]. Beyond increasing susceptibility to HPV-OPC, a history of smoking has been associated with a poor prognosis. Patients with a history of smoking presenting with HPV-OPC exhibit poorer survival and significantly greater risk of recurrence than never smokers with HPV-OPC [54, 66].

Trends in the Management of HPV-Related Oropharyngeal Cancer

The unique clinical features of HPV-OPC have resulted in a paradigm shift in the treatment of this subset of HNSCC. HPV-OPC is more responsive to treatment than HPV-negative HNSCC and HPV-positive tumor status confers a significant survival advantage [8, 54]. Although concurrent chemoradiotherapy has long been implemented as a therapeutic strategy for HPV-OPC, multimodality therapy of OPC may include various combinations of surgery, radiotherapy, and chemotherapy. These therapeutic regimens were developed prior to the recognition of HPV-OPC as a distinct HNSCC subtype with a significant survival advantage [8, 54, 67–70]. High treatment response rates that are independent of therapeutic modality have raised concerns that a subset of HPV-OPC patients may be over-treated. These patients may be subjected to unnecessarily intense therapeutic regimens associated with increased toxicity and no further improvements in survival [71]. Long-term treatment-related toxicities include life-altering dysphagia, esophageal fibrosis, sensorineural hearing loss, and osteoradionecrosis [72]. Various ongoing clinical trials focus on de-intensifying each of the three components of multimodality therapy—including the adjustment of radiation or chemotherapy doses, the elimination of chemotherapy, and the use of minimally invasive surgical innovations such as transoral robotic surgery (TORS)—with the goal of mitigating therapeutic toxicity while maintaining high response rates [71].

Epidemiology of Oral HPV Infection

The absence of a reliable in vitro or animal model system has impeded the understanding of the natural history of oral HPV infection. To date, cross-sectional and longitudinal cohort analyses represent the primary methods for understanding the natural history of oral HPV infection. In these studies, sloughed oral epithelial tissue is isolated by oral rinse and gargle and/or oropharyngeal or buccal swab. Tissue DNA is extracted and oral HPV infection ascertained through type-specific HPV nucleic acid testing via polymerase chain reaction in conjunction with a control gene, such as beta-globin, to ensure sample integrity.

Cross-sectional studies can only determine the prevalence of oral HPV infection. Prevalent oral infection is defined as a baseline positive test for oral HPV and represents the intersection of the incidence, persistence, latency, and clearance rates of oral HPV infection (Fig. 28.1). Although often complicated by loss of subjects to follow up and limited in temporal resolution by length of sampling intervals, longitudinal cohort studies can determine incidence, persistence, and clearance rates. Incidence is defined as an oral sample positive for HPV following one or more negative baseline samples. Clearance is defined as one or more oral samples negative for HPV following a positive sample. Persistence is defined as persistently positive oral samples after incident or prevalent infection (Fig. 28.2). These definitions may be complicated by the possibility for latent infection and reactivation, which manifest as intermittently positive and negative oral samples. Although evidence suggestive of latent HPV infection followed by reactivation has been described [73–75], to our knowledge no direct evidence of latent oral HPV infection exists.

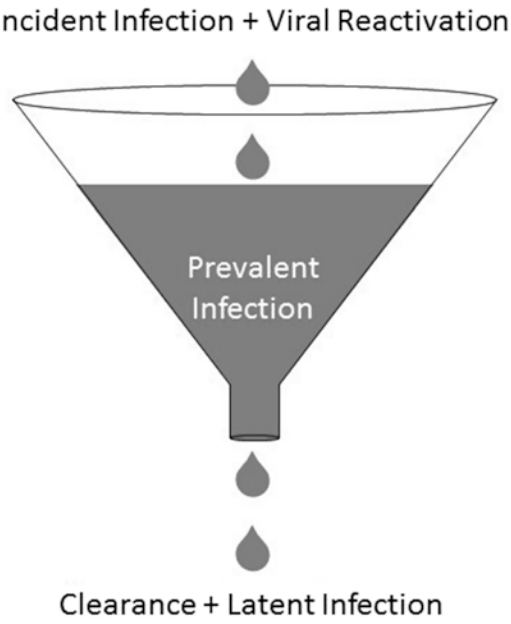

Fig. 28.1 The relationship between incidence, prevalence, and clearance in the context of human papillomavirus (HPV) infection. Incidence is the acquisition of new oral HPV infection. In this schematic of a funnel, the rates of incident infection and viral reactivation, which are positively related to infection prevalence, are represented by liquid droplets entering the funnel. Conversely, the rates of viral clearance and latent conversion are negatively related to infection prevalence and therefore represented as liquid droplets leaving the funnel

Prevalence of Oral HPV Infection

A cross-sectional study of a large, statistically representative sample of American men and women aged 14–69 years performed as part of the National Health and Nutrition Examination Survey (NHANES) 2009–2010 ($n = 5579$) found that the prevalence of any oral HPV infection was 6.9% [76]. At a prevalence of 1%, HPV16 represented the most prevalent type-specific oral HPV infection, accounting for 27% of high-risk types and 15% of all detected oral infections. Interestingly, a bimodal distribution was observed for oral HPV prevalence with respect to age in men but not women, with a minor peak at ages 30–34 years (peak prevalence = 7.3%) and a major peak at ages 60–64 (peak prevalence = 11.4%) [76]. In addition, men were found to have 2.8-fold higher prevalence of oral HPV infection of any type (10.1% vs. 3.6%) and 5.4-fold higher HPV16 infection (1.6% vs. 0.3%) than women [76]. These results are consistent with the disproportionately increased risk of HPV-OPC among men.

The NHANES 2009–2010 study supported a strong, dose-response relationship between sexual exposure and prevalent oral HPV infection [76]. Individuals who had ever had any sex, ever performed oral sex, or ever had vaginal sex were at a respective 8.7-, 2.2-, or 5.4-fold greater risk of oral HPV infection. Dose-response relationships were observed with respect to the number of lifetime oral, vaginal, or any type of sex partners as well as for number of lifetime oral, vaginal, or any type of sex partners in the past 12 months [76].

In addition, analysis of NHANES 2009–2010 also found a dose-response relationship between smoking and prevalent oral HPV infection that was more pronounced in women than men [76]. Compared to never smokers, current women smokers of greater than 20 cigarettes per day had a 5.9-fold increased risk of oral HPV infection, while men who smoked at similar rates only showed a 1.6-fold increased risk of oral HPV infection [76].

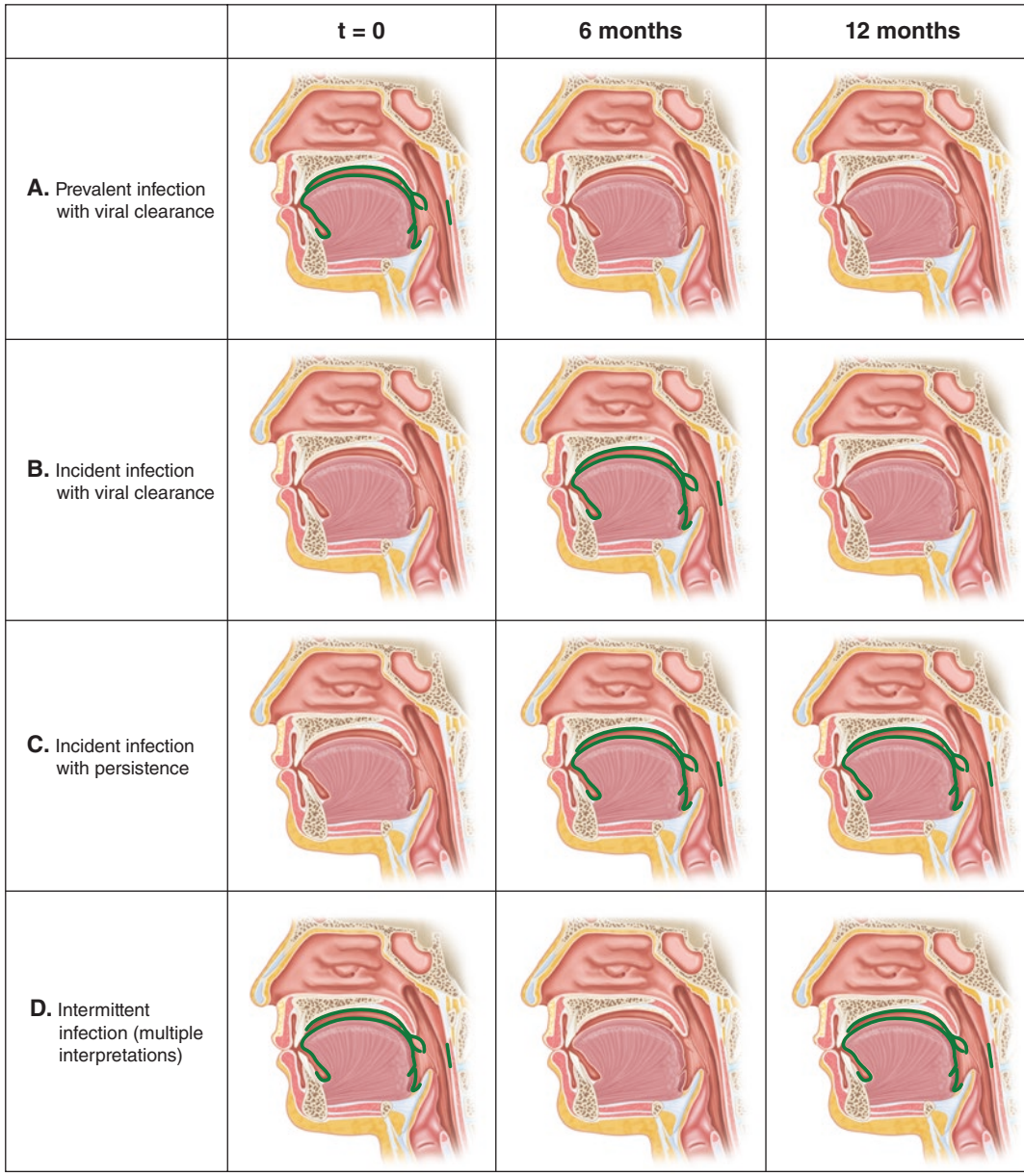

Fig. 28.2 Definitions of oral human papillomavirus (HPV) infections in the context of longitudinal cohort studies. Green lines represent HPV infection of the oral and oropharyngeal mucosa. $t = 0$ represents the baseline. (**a**) Prevalent infection is defined as a positive oral sample at baseline. (**b**) Incident infection is defined as a negative baseline oral sample followed by a positive oral sample. (**c**) Persistent infection is defined as a positive oral sample that remains positive; this can occur in either the context of an incident infection (as shown) or a prevalent infection. (**d**) Intermittently positive oral samples can represent multiple phenomena including: (1) prevalent infection followed by clearance and then reinfection, (2) prevalent infection followed by viral latency and reactivation, or (3) persistent infection with a spurious false negative test result

Observations that current smoking increases risk of infection have been independently confirmed and extended. Compared to never and former smokers, current smokers are three-fold more likely to have oral HPV16 infection [77]. Dose-response relationships have been observed for serum and urinary levels of tobacco-related metabolites, objective biomarkers of tobacco use, and an increasing risk of HPV16 infection [77]. Heavy alcohol consumption has also been associated with increased risk of oral HPV infection. Greater than 21 drinks per week were associated with 19-fold greater risk of oral HPV infection [78].

A recent analysis of NHANES data from 2009 to 2012 identified factors associated with male predominance of oral HPV infection [79]. Gender-stratified analyses demonstrated that, compared to women, a significantly higher proportion of men were heavy cigarette smokers (10.4% vs. 7.1%, >10 cigarettes/day), current cannabis users (16.4% vs. 10%), and heavy alcohol drinkers (11% vs. 2.6%, >14 drinks/week) [79]. On average, men also reported greater than two-fold higher numbers of lifetime sex partners for any sex (18 vs. 7), oral sex (9 vs. 4), and vaginal sex (16 vs. 7). Although age, current smoking, and number of lifetime sexual partners were identified as independent risk factors for oral HPV infection in both men and women, these risk factors exhibited significantly stronger associations in men than in women. For example, while no difference was observed between oral HPV prevalence in men and women with one lifetime sexual partner, the difference in prevalence of oral HPV infection between men and women reached 9.3% for individuals with 20 or more lifetime partners [79]. These findings suggest that behavioral and gender-specific biological effects contribute to higher rates of oral HPV infection in men. The male predominance of oral HPV infection is partially a result of higher rates of high-risk sexual behaviors, smoking, and alcohol use in men. In addition, men also exhibit disproportionately stronger associations between oral HPV infection and sexual behaviors, implying an underlying biological susceptibility specific to men. The higher prevalence of oral HPV infection in men may partially explain the male predominance of HPV-OPC.

Incident Oral Infection

Longitudinal studies investigating the natural history of subclinical oral HPV infection in men have observed annual incidence rates ranging from 4.4% to 12.3% [80–82]. Type-specific annual incidence of oral HPV16 infection ranged from 0.6% to 0.8% [80, 81]. Differences in study methodology and population likely account for reported variations in incidence rates. Edelstein et al., who found the highest incidence of oral HPV infection at 12.3% ($n = 212$), collected oral samples by both oropharyngeal swab and oral rinse and gargle [81]. Studies solely collecting samples by oral rinse and gargle, found lower rates of 4.4% ($n = 1626$) [80] and 6.3% ($n = 1000$) [82]. Indeed, Edelstein et al. found incidence rate of 6.8% by oral rinse and gargle alone, which was more concordant with other reported incidence rates.

Further differences in incidence rates across these studies may be explained by differences in ages in each cohort. Kreimer et al. [80], who reported the lowest incidence rates, analyzed subjects ranging in age from 18 to 73 years from three countries (United States, Mexico, and Brazil) enrolled in the HPV in Men (HIM) study. Studies by Edelstein [81] and Pickard [82] enrolled younger subjects (aged 18–24 and 18–30 years, respectively) restricted to the United States. Of note, the Pickard cohort consisted entirely of college students at The Ohio State University [82]. These younger cohorts fall within age ranges corresponding to peak prevalence of oral HPV infection [79], which may be related to higher rates of exposure to HPV and consequently higher rates incident oral HPV infection. As a result, the report by Kreimer et al. likely captures the most generalizable population-based findings on oral HPV infection to date. Consistent with this notion, a recent meta-analysis of nine studies ($n = 3762$) estimated annual incidence of oral HPV at approximately 5% [83].

Kreimer et al. identified status as a current or former smoker and being single, divorced, or widowed as independent risk factors for acquisition of oncogenic HPV infection [80]. Although marital status may implicate propensity for high-risk sexual behaviors, no significant associations

were identified between oral HPV infection and any specific sexual behavior [80]. Specifically, factors relating to oral sex (history of ever having had oral sex, or having had oral sex within the previous 6 months, or high recent number of oral sex encounters) did not increase the risk of HPV acquisition. Conversely, Edelstein et al. found that performance of oral sex on a woman more than once per week or frequent open-mouth kissing of a woman (≥31 times per month) in the last 4 months, and recent anal sex with men significantly increased risk of acquiring oral HPV infection of any HPV type [81]. Supporting the possibility of oral autoinoculation, Edelstein et al. also found current type-concordant genital and hyponychial HPV infections to increase risk of incident oral HPV infection [81]. Among college students, Pickard et al. found only recent open-mouth kissing and black race to increase risk of incident oral HPV infection [82]. Taken together, these discordant results highlight the need for further studies to clarify risk factors associated with incident oral HPV infection.

Longitudinal analysis of HIV-positive and -negative patients has shed some light into immune factors related to incident oral HPV infection. Beachler et al. collected oral rinse samples from 761 HIV-positive and 469 HIV-negative but at-risk men and women from several U.S. cities at 6-month intervals for a median of 24 months [60]. Of note, HIV-positive participants were more likely to be black, not current alcohol consumers, and to have fewer recent oral sex partners. HIV-positive individuals displayed nearly two-fold higher rates of oral HPV infection than their HIV-negative counterparts. HPV-positive and HIV-negative individuals exhibited 2-year cumulative incidences of 34% versus 19% for any oral HPV infection, 18% versus 10% for oral oncogenic HPV infection, and 4.5% versus 2.3% for oral HPV16 infection [60]. In this study, the risk of incident oral HPV was independently associated with oral sex, oral-anal contact, HIV infection, and reduced CD4-cell count. Interestingly, risk of incident oral HPV infection increased with number of *recent* oral sex partners in HIV-negative participants while risk in HIV-positive participants increased with the number of *lifetime* oral sex partners. The total number of recent or lifetime vaginal sexual partners for either HIV-positive or HIV-negative participants was not assessed in this study. The association of recent oral sex partners in HIV-negative participants may suggest that the primary contributor to incident oral HPV infection in these individuals is the acquisition of new viral infection. Conversely, that lifetime oral sex partners increased risk in HIV-positive participants may suggest that reactivation of previously acquired "latent" HPV infection contributed to the higher incidence rates observed in immune suppressed individuals [60].

Viral Latency and Reactivation

Specific HPV types have been demonstrated to exist in "latent" states, in which HPV DNA is present in basal cells without the occurrence of detectable virus production. Viral latency has also been defined less strictly as the presence of viral DNA in normal appearing tissue free of virus-related lesions—a definition indistinguishable from subclinical HPV infection. Such variability in definitions complicates interpretations designating HPV infections as latent.

Indirect evidence considered suggestive of a potential latent HPV state derives from the detection of viral DNA in unaffected sites of patients with laryngeal papillomata [84] or genital condylomata [85], and the persistent reappearance of these lesions after resection. Further support for latent HPV infection includes the rapid appearance of HPV-related lesions in immunosuppressed patients, which may represent reactivation of latent infection [73–75]. In the oropharynx, the observations by Beachler and colleagues discussed above demonstrating subtle differences in risk factors represent the only suggestions of a potentially latent oral HPV infection [60]. Understanding of the natural history of HPV infection, including objective determinants of viral clearance, would benefit greatly from establishing the role and significance of HPV latency (Fig. 28.3).

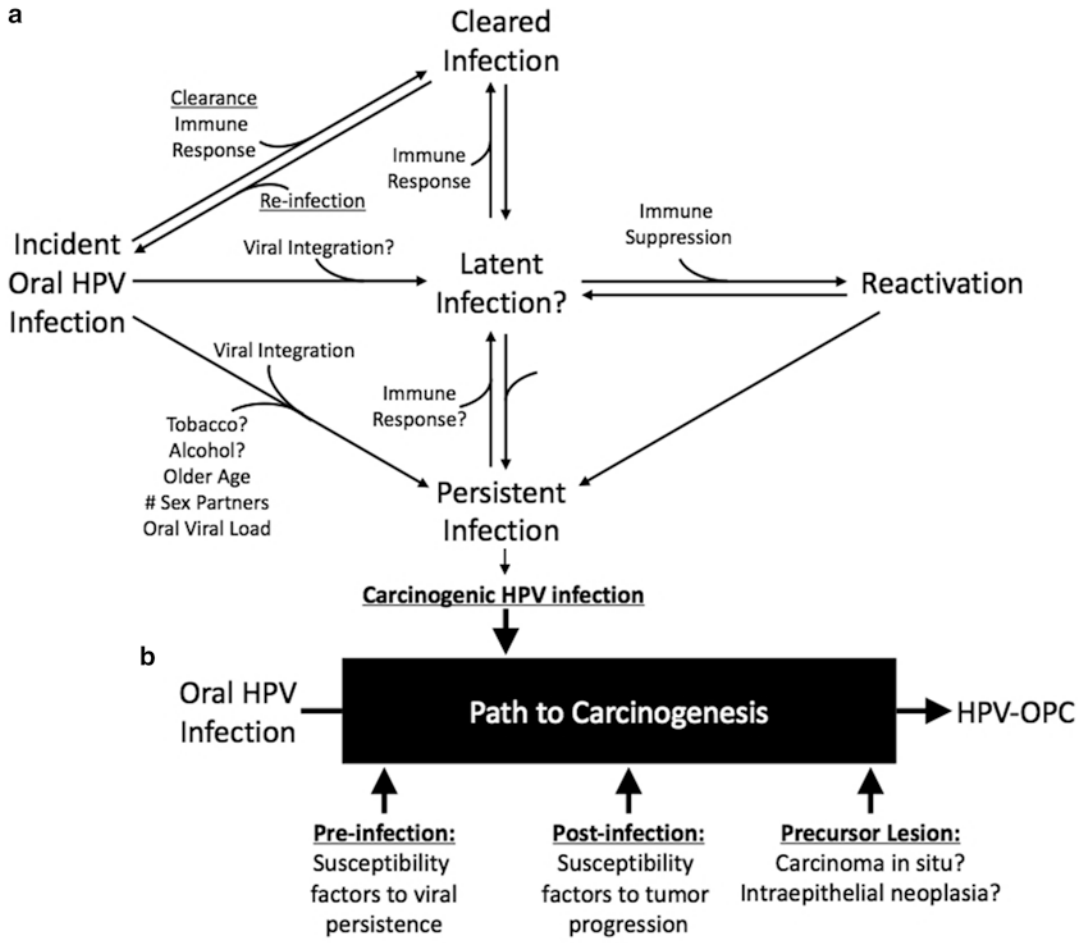

Fig. 28.3 Model of carcinogenic oral human papillomavirus (HPV) infection and oropharyngeal (OPC) tumor progression. (**a**) An incident oral HPV infection may undergo clearance, latency, or persistence. Viral clearance is hypothesized to be promoted by immune response, while immunosuppression, immunoscenescence (diminishing immunity resulting from old age or poor overall health), tobacco use, alcohol use, increased number of sexual partners, viral integration, and high viral load contribute to persistent oral HPV infection. Latent infection is theoretically promoted by viral integration. Latent infections may undergo reactivation secondary to immunosuppression, immunosenescence, tobacco use, and alcohol use. Reactivated infections may be either cleared or become persistent. (**b**) Oral HPV-related tumor progression model. In chronological order, individuals may possess genetic and environmental susceptibility factors to incident and persistent oral HPV infection. Persistent oral HPV infection represents the first step toward tumorigenesis, which is promoted by post-infection genetic and environmental susceptibility factors (including tobacco use), leading to a hypothetical precursor lesion and eventually to frank HPV-related oropharyngeal carcinoma (HPV-OPC). Bold arrows represent well-established steps in oral HPV infection. Thin arrows represent hypothetical or indirectly demonstrated phenomena in oral HPV infection

Viral Clearance and Persistent Oral Infection

Persistent oral HPV infection is thought to precede HPV-OPC, yet most incident HPV infections are not detectable within 1 year of acquisition [60, 80, 81]. Kreimer et al. reported median duration of infection between 6 and 7 months for any HPV, oncogenic HPV types, and HPV16 infection [80]. However, clearance rates can vary dramatically depending on how viral clearance is defined. For example, Beachler

et al. found that 83% of incident infections cleared within 1 year when a clearance was defined by a single negative test [60]. However, defining clearance by two consecutively negative tests significantly diminished the 1-year clearance rate to 53%. In both cases, clearance rates of incident oral HPV infection were similar among oncogenic and non-oncogenic type-specific infections [60].

Prevalent infections, on the other hand, exhibit much lower 1-year clearance rates of 51% with a single negative test and 35% with two consecutive negative tests, suggesting that a large portion of prevalent oral HPV infections are persistent [60]. Indeed, only 7% of incident infections in the Beachler study persisted for two years compared to 35% of prevalent infections [60]. These findings are consistent with a longitudinal analysis of 23 oral HPV16-positive HIM cohort participants by the Kaplan-Meier method [86]. Of 13 incident infections captured in this study, 70% cleared in 1 year, 90% in 2 years, and none persisted greater than 3 years. However, for ten prevalent infections the 1-, 2-, and 3-year clearance rates were 10%, 20%, and 43%, with 60% of prevalent infections persisting greater than 4 years [86]. In addition to prevalent infection, both studies found male sex and older age increased risk of persistence while only Beachler et al. identified smoking as a risk factor for persistence [60, 86].

Recent reports have begun to parse the biological determinants of infection. Analysis of the Persistent Oral Papillomavirus Study (POPS) cohort identified that oral viral load predicts persistent oral HPV infection [87]. In 35 incident and 53 prevalent oral HPV16-positive POPS participants, median viral copy number was greater than 20-fold higher in prevalent than in incident infection and greater than 10-fold higher in participants 55 and older than those younger than 45 years old [87]. Importantly, participants with viral loads in the highest tertile showed a significantly lower 2-year clearance rate (41%) than those in the lowest tertile (94%) [87]. Interestingly, smoking status, male sex, recent oral sex partners, CD4 cell count, and HIV status did not significantly correlate with oral HPV viral load.

That higher oral HPV16 viral loads in men correlated with persistence was independently confirmed in the Finnish Family HPV Study cohort [88]. Beyond demonstrating a relationship between viral load and persistence, comparison of 21 patients with persistent infection and 54 participants who cleared infection found that the physical state of the HPV genome was related to persistence. While the HPV16 genome remained episomal in all men and 66% of women who cleared HPV infection, it was found to be either totally or partially integrated into the host genome in 79% and 71% of men and women with persistent infection [88]. Taken together, associations between HPV integration with persistent oral infection and HPV-OPC suggest that genomic integration of HPV may represent a molecular link between persistent infection and HPV-related oropharyngeal squamous cell carcinoma.

The Role of Prophylactic HPV Vaccination in Oral HPV Infection

Three FDA-approved prophylactic HPV vaccines are currently available. These vaccines are based on virus-like particles of HPV L1 capsid proteins and protect at minimum against HPV-16 and -18, the two most commonly detected type-specific infections [89]. The efficacy of HPV vaccines was established for the prevention of cervical HPV infection and cancer through a series of large, multinational clinical trials performed in young women [90–92]. These studies demonstrated high vaccine efficacy in preventing premalignant HPV-associated cervical lesions in women without previous exposure to HPV (efficacy: 98–100%) [90–92]. Prophylactic HPV vaccination also exhibits high efficacy in preventing genital HPV-related lesions in men (efficacy: 90%) [93]. Although no data is currently available on the efficacy of HPV vaccination in preventing HPV-OPC, a significant increase in the prevalence of oral antibody has been observed after vaccination [94]. Moreover, oral titers correlated with serum antibody titers, suggesting that HPV vaccination may reduce oral oncogenic HPV infection (estimated efficacy for oral HPV: 93%) [94, 95].

Notably, in patients with genital infection vaccine efficacy was significantly lower in analyses that included patients with previous evidence of HPV infection [96, 97]. In addition, vaccination did not accelerate clearance of prevalent cervical infection [98]. These findings demonstrate that vaccination plays no current role after infection. Furthermore, these data collectively support the vaccination of both males and females prior to sexual debut, when the risk of exposure to HPV becomes significant [90–93, 96, 98]. As a result, prophylactic vaccination is currently not recommended for spouses/partners of patients with HPV-OPC. Finally, beyond the theoretical benefit of preventing oral HPV infection, HPV vaccination currently plays no therapeutic role for HPV-OPC.

Summary

Human papillomavirus-related oropharyngeal squamous cell carcinoma (HPV-OPC) is growing in incidence worldwide. Accumulating evidence links the rise of HPV-OPC to sexual behaviors that increase the risk of oral HPV infection. While correlates of oral HPV infection are beginning to emerge, much remains to be understood about its epidemiology and whether oral HPV infection is causally linked to oropharyngeal carcinogenesis. As large, consortium-based collaborations elucidate the molecular underpinnings of HPV-related oropharyngeal carcinogenesis, international prospective cohort studies continue to refine our understanding of oral HPV infection. Large leaps in our understanding of HPV-related oropharyngeal carcinogenesis are likely to arise from integrating increasingly sophisticated epidemiological analyses with insights offered by big data biology.

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Recurrent Respiratory Papillomatosis and Human Papillomavirus

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Introduction

Recurrent respiratory papillomatosis (RRP) is a disease that is characterized by recurrent growth of exophytic wart-like lesions throughout the respiratory tract. The disease is mainly associated with human papillomavirus (HPV) types 6 and 11 [1]. RRP has an unpredictable and recurrent disease course. Patients generally experience voice problems. Without treatment, patients eventually develop a compromised airway [2]. Although many therapies have been tried, there is no curative treatment for RRP. Owing to the recurrent character of RRP, patients depend on repeated surgical removal of the lesions (called papillomas or papillomata) to keep the voice functional and airway patent [3]. A single patient might need dozens of surgical interventions for the removal of papillomas: there are even reports of over 150 interventions in single patients [4, 5].

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Human Papillomavirus

The human papillomavirus (HPV) is a highly prevalent virus, which has a great specificity for tissues and species [6]. It is a small double-stranded non-enveloped DNA virus existing of 7900 base pairs. It belongs to the Papillomaviridae virus family. It infects the stem cells in the basal layer of mucosa or skin [7]. By 2015, more than 120 HPV types and approximately 200 subtypes had been identified [8].

Human papillomavirus types are generally categorized as "low-risk" HPV or "high-risk" HPV, which describes the ability of the virus to transform healthy cells into malignant cells [9]. Low-risk HPV types can cause cutaneous warts, anogenital warts, low-grade intraepithelial neoplasia, and RRP [1, 10]. Recurrent respiratory papillomatosis is primarily associated with the low-risk HPV types HPV6 and HPV11 (in 83–100% of cases). Other HPV types such as HPV16, HPV18, HPV31, HPV33, HPV35, and HPV45 have been associated with RRP to a lesser extent [11]. These HPV types are called high-risk viruses. Malignant transformation has been described in 1.6–4% of RRP cases [12, 13].

The average lifetime probability of acquiring HPV is between 50 and 100% [14]. It is unclear why only a fraction of HPV-exposed individuals develops an HPV-related disease [14].

M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_29

The genome of HPV consists of nine multifunctional genes [9]. Seven of these genes are early expressing (E prefix) and two are late expressing (L prefix) in the viral life cycle [9]. Pathogenesis of the virus is caused by the E-genes. These are responsible for the replication of the virus, but more importantly for the interaction with the host cell, interaction with oncogenes, and other cell transforming factors [9]. The L-genes encode for structural proteins of the virus [9, 10]. Differences in E6 and E7 genes between high-risk and low-risk viruses are suspected to be responsible for the difference in malignant transformation [15].

The human papillomavirus initially enters the epithelium by invading the stem cells of the basal layer through micro-lesions of the epithelium [16]. The virus can induce immune regression and latency followed by persistence with low-level viral gene expression [16]. Human papillomavirus can therefore evade the systemic immune response for years [10]. During cell division, HPV DNA is multiplied and distributed into the new cells in the same manner as the host's DNA [9]. Newly formed host cells with HPV DNA then migrate to the upper epithelial layers, while differentiating [9] and producing virions [17]. Transformation of the virions can generate an exophytic wart-like lesion [10].

Recurrent Respiratory Papillomatosis

Etiology

Patients with RRP present with benign squamous lesions—papillomas—throughout the respiratory tract. Papillomas can appear from the nasal vestibule to the lungs. However, the vocal folds are the most common location [18, 19]. The papillomas often spread during the course of the disease [1].

Human papillomavirus-negative papilloma in RRP patients is rare and occurs in approximately 5% of patients. Omland et al. used polymerase chain reaction (PCR) to analyze formalin-fixed, paraffin-embedded biopsy samples from 221 RRP patients and detected HPV in 94%, all due to HPV6 or HPV11, or both [11]. They applied metagenomic sequencing to the 14 HPV-negative samples and detected HPV8 in one sample, but no virus in the remaining 13 (6%) samples. Although the authors noted that a false-negative result for HPV is possible for various reasons (e.g., low viral load or loss of the L1 region when HPV is integrated into the human genome), they suspected some cases of RRP are truly HPV-negative. In the Omland study, HPV-negativity occurred more often in adult onset than in juvenile onset RRP cases (7% vs 2%), and was associated with a high relative risk of laryngeal neoplasia or carcinoma in the respiratory tract [11].

The etiology of RRP depends on the age group of the patient. The first peak of RRP onset, at age 4 years, is most likely caused by vertical transmission through an HPV-infected birth canal [20, 21]. The greatest risk factor is having a mother with condylomata acuminata, a disease caused by the same viruses as RRP. Children of mothers with condylomata acuminata have a more than 200-fold increased chance of acquiring RRP [22]. Most children with RRP were vaginally delivered, had a longer than average delivery, and had young primigravida mothers at the time of delivery [22, 23]. A longer delivery time and therefore a more prolonged exposure to the virus during delivery may play a causative role [24]. A small number of children with RRP are thought to have acquired the virus in utero because they were born by caesarean section [22, 25].

The second peak of RRP onset occurs around the age of 34 years and has been attributed to acquisition of HPV through sexual contact. Several studies have noted that adults with RRP report a higher number of lifetime sexual partners than do non-RRP patients [23, 26, 27]. An association between oral sex and RRP is unclear, however. A 1992 study reported an association between RRP and a higher number of lifetime oral sex partners [23] but a 2014 study found no such association [27]. It should be noted that patients with RRP are not considered contagious, and there have been no reports of horizontal transmission. Gerein et al. found that none of the sexual partners or children of 38 RRP patients developed RRP over a 15-year observational period [28].

The third peak of RRP onset occurs between ages 60 and 64. One hypothesis is that this peak is due to reactivation of latent HPV infection in the setting of loss of immunity through aging [29–31].

Immunology

Most of the cellular and immunological pathways that cause RRP are not yet elucidated. It has been shown that RRP patients lack an effective immune response to HPV, although most RRP patients do not have evidence of other immunological deficiencies and have effective immune responses to other viruses [32]. The balance between the necessary T helper cell 1 (Th1) response and the less effective T helper cell 2 (Th2) response is shifted toward Th2 in RRP patients [32]. The Th1 response is needed for cell-mediated immunity and necessary to clear HPV from the already infected epithelial cells [33]. The predominant Th2 response in RRP patients is a humoral response and therefore ineffective in RRP, which is a disease due to intracellular HPV [33]. The immune tolerance of HPV appears to be site specific and confined to the airways [32]. A change in the concentration of Th2-like chemokines may correlate with disease severity, with lower levels of these chemokines correlating with clinical remission [34]. Unfortunately, there is still no treatment that would invert the ineffective Th1/Th2 ratio in RRP patients.

Histology

The clinical diagnosis of RRP must be histologically confirmed by a pathologist. Recurrent respiratory papillomatosis is characterized by exophytic, pedunculated proliferations with fingerlike projections of non-keratinized stratified squamous epithelium with a core of centrally fibrovascularized connective tissue (Fig. 29.1) [35]. Furthermore, an RRP papilloma has basal cell hyperplasia, increased mitoses in the basal layers of the epithelium, koilocytotic changes, nucleomegaly, and dyskeratotic cells [36].

Most of the healthy upper respiratory tract is covered with ciliated columnar epithelium, whereas the vocal folds are covered with stratified

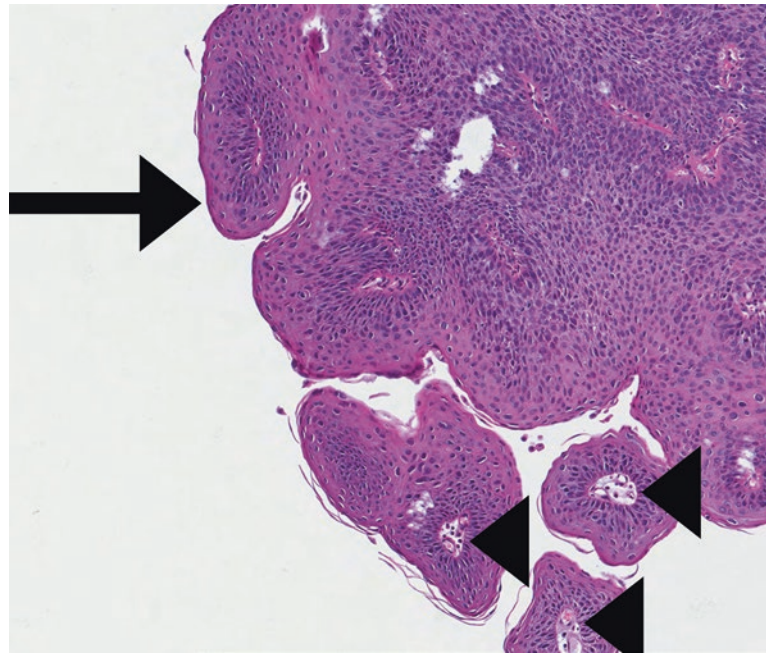

Fig. 29.1 Histology of recurrent respiratory papillomatosis (magnification 100×). Fingerlike projections of nonkeratinized squamous epithelium (arrow) and central fibrovascular tissue (arrow heads) (Reprinted from Tjon Pian Gi et al. [66] with permission from John Wiley and Sons)

squamous epithelium. HPV-associated lesions appear mostly at sites in which ciliated and squamous epithelia are juxtaposed [37]. The epithelial transition zone could be a preferential location, comparable to the histologic transition zone in the cervix uteri [38].

This juxtaposition can also occur when ciliated epithelium is exposed to repeated trauma, for instance a tracheostomy. The epithelium then undergoes squamous metaplasia, is replaced with non-ciliated epithelium, and acts as a new iatrogenic squamociliary junction [35].

Epidemiology

Recurrent respiratory papillomatosis can appear at every age: the age of onset has been described from 1 day to 90 years old [4, 31]. Traditionally, two distinct forms of RRP are juvenile onset recurrent respiratory papillomatosis (JoRRP) and adult onset recurrent respiratory papillomatosis (AoRRP) [39]. The distinction between these two types is based on age of onset, usually set at 18 years. Histologically, there is no difference between these entities, which raises the question of whether or not there is a real difference. The European incidences of JoRRP and AoRRP are 0.17 per 100,000 and 0.54 per 100,000 respectively [39], There is an equal distribution between genders in JoRRP, whereas AoRRP is seen twice as often in males as in females [39–41]. San Giorgi et al. demonstrated that there is a trimodal distribution in the age of onset of RRP, rather than a bimodal distribution as previously reported [31].

Clinical Presentation

The clinical course of RRP is highly variable. The clinical presentation depends on the anatomical location of the papilloma. Most papillomas occur in the glottic region (Fig. 29.2) [19]. Therefore, RRP patients mostly experience dysphonia [2]. In less developed countries, stridor and respiratory distress can be the presenting symptom [42]. In later stages of the disease course, or if the papillomas are situated elsewhere in the airways, the patients may suffer from dyspnea, stridor or respiratory distress, failure to thrive, chronic cough, recurrent pneumonia, and dysphagia [2, 43]. Between 16% and 25% of all patients develop subglottic and more distally located papillomas [2, 18, 40]. No incidence figures are available for involvement of the trachea alone. Approximately 3% of patients develop RRP in their lungs [44]. Sixteen percent of these patients develop a pulmonary malignancy, which generally has a very poor

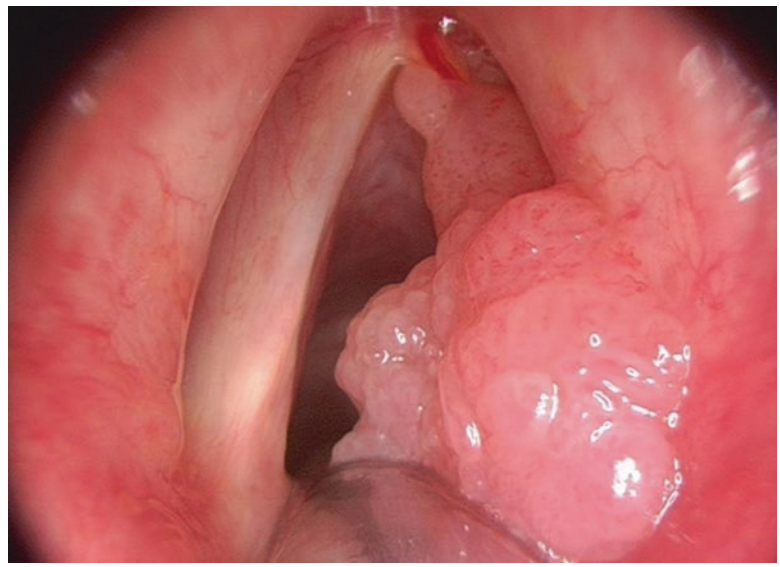

Fig. 29.2 Recurrent respiratory papillomatosis over the full length of the right vocal fold, expanding to the right false vocal cord. Ventilation tube in situ

prognosis [44]. All of the reported cases of RRP involving the lungs have had tracheal involvement as well.

Recurrent respiratory papillomatosis patients have been reported to require between 1 and more than 150 surgical interventions to clear the papillomas [5]. It is unclear when the disease goes into remission and what causes the remission. However, the disease can always recur: cases with an inter-operative interval of 32 years have been described [5]. Many factors have been associated with a severe clinical course. First, HPV type seems to have an influence on the disease course. Many studies have associated HPV11 with a worse clinical course [5, 41, 45–47]. In contrast, one study reported a worse clinical course in patients with HPV6 [48]. Second, younger age of onset appears to correlate with more severe disease [18, 40, 49]. It has been postulated that the frequency of RRP recurrences diminishes naturally during the disease course [2, 18, 50]. This hypothesis has been confirmed clinically [5].

The association of gastroesophageal reflux disease (GERD) and asthma with the clinical course of disease in RRP patients has been investigated [51, 52]. A systematic review found no evidence that GERD aggravates the clinical course or tissue properties of RRP [53]. Nevertheless, many otolaryngologists use anti-reflux medication in the treatment of RRP [54]. The influence of asthma on RRP is still uncertain [55].

Possible consequences of RRP are the need for a tracheostomy and malignant transformation. Between 4% and 21% of RRP patients eventually require a tracheostomy to secure the airway [1].

It is known that voice problems have a negative effect on the quality of life of patients [56]. Therefore, RRP patients may experience multiple psychosocial complaints, apart from their clinical symptoms. Recurrent respiratory papillomatosis patients find their voice insufficient and suffer from voice problems in normal life [57–61]. They have a lower perception of their general health [60]. Owing to these complaints, patients report a lower health-related quality of life [57, 59–62]. Quality of life and distress (an unpleasant emotional experience of a psychological, social, or spiritual nature [63]) are important aspects of patient care in chronic disease [64]. It is therefore important to know which factors cause distress or a lower quality of life. Although the number of surgeries or the duration of disease are often used to describe the clinical severity of disease, these two factors do not predict patient distress [60]. As expected, both voice problems and the fear for a worsening voice are predictors of a lower quality of life in RRP patients [61]. It is also important to optimize information for patients and their families [61]. Ensuring that the patient's partner has sufficient information about the disease is of utmost importance for the patient's quality of life, and both patient and partner benefit from understanding the disease [61, 65].

Diagnosis

The evaluation of a patient with possible RRP includes obtaining a history of any voice or respiratory problems followed by visual inspection with video laryngostroboscopy of the glottic region [43]. As noted earlier, RRP is diagnosed by suspension microlaryngoscopy and has to be histologically confirmed by a pathologist. A biopsy can be performed in the office in some cases. Recently, a new visualization modality was introduced in laryngology, Narrow Band Imaging, which facilitates the recognition of RRP lesions by their vascular formation [66]. Pulmonary involvement by RRP can be diagnosed by a computed tomography scan of the lungs [44]. The first intraoperative inspection should include the entire airway from nasal vestibule to lungs, as papillomas may involve any part of the airway. The first intervention should therefore take place under general anesthesia, as opposed to a biopsy in the office, to allow for this complete inspection. Inspections during subsequent surgical interventions can be limited to the larynx, trachea, and other sites where papillomas were previously found. An experienced pathologist should analyze the tissue to confirm the diagnosis and to rule out malignancy or premalignancy, even if the tissue clinically looks like RRP.

Table 29.1 The Dikkers RRP scoring system for recurrent respiratory papillomatosis in the larynx [67]

Grade 1	Sessile papilloma, unifocal or multifocal
Grade 2	Exophytic papilloma, unifocal
Grade 3	Exophytic papilloma, multifocal

Spread and extension of the disease are often described by two different scoring systems, in both daily practice and clinical research. The Dikkers score (Table 29.1) describes anatomical spread and volume of a lesion restricted to the larynx [67]. The Derkay/Coltrera score (Fig. 29.3) describes the anatomical spread and volume of RRP in the entire respiratory tract, in combination with a functional score [49].

Prevention and Treatment

Development of RRP occurs through a combination of infection with HPV and genetic and immunologic susceptibility. As disease susceptibility is not yet a modifiable factor, prevention of HPV acquisition through vaccination is the focus of efforts to reduce and ultimately eliminate RRP [55]. All HPV vaccines target HPV16 and HPV18, the high-risk HPV types associated with 70% of cervical cancers [68], and a significant proportion of anal, oropharyngeal, vulvar, vaginal, and penile cancers. Cervarix® (GlaxoSmithKline, Brentford, London, U.K.), a bivalent vaccine targeting HPV16 and HPV18, is part of several national vaccination programs but does not prevent HPV6 and HPV11 acquisition. Gardasil® (Merck, Darmstadt, Germany and Merck & Co, Kenilworth, NJ, U.S.) is a quadrivalent vaccine that targets HPV6 and HPV11 in addition to HPV16 and HPV18. Gardasil-9® (Merck & Co, Kenilworth, NJ, U.S.) was introduced in 2014 in the U.S. and targets 9 HPV types (types 6, 11, 16, 18, 31, 33, 45, 52, 58), five types in addition to those covered by Gardasil®. Gardasil-9®has been the only HPV vaccine available in the U.S. since mid-2017. Gardasil® is typically given to both boys and girls between ages 9 and 26. In the U.S., two doses of Gardasil-9® at least 6 months apart are now recommended for children ages 11–12.

Gardasil® was developed for the prevention of cervical carcinoma and other high-risk HPV16 and HPV18 and low-risk HPV6 and HPV11 associated diseases [69]. Introduction of this vaccine in Australia led to a highly significant decrease in genital disease caused by low-risk HPV [70]. It is thought that Gardasil® will also lead to a decrease in the incidence of RRP [71, 72].

As it is improbable that HPV vaccination programs can be fully implemented in the near future, especially outside industrialized nations, RRP will probably not vanish. Recurrent respiratory papillomatosis is also a problem in developing countries [42, 73]. The preventative efficacy of the quadrivalent vaccine against condylomata is 96–100% in the first 4 years after vaccination [74]. Because condylomata are HPV6- and HPV11-correlated like RRP, the expectation is that the incidence of RRP will decline in countries where the quadrivalent vaccine is part of the national vaccination program.

Multiple treatments for RRP have been tried over the years. Surgery is the mainstay of RRP treatment. The most common surgical treatment is physical removal of the papillomas with "cold" instruments (forceps and scissors), microdebrider, or by laser surgery [3].

Choice of surgical method depends on the surgeon's preference [75]. Surgery with cold instruments was historically performed by many surgeons and is still popular [5]. Since the 1970s, the carbon dioxide (CO_2) laser has been used in the treatment of RRP [5]. Some surgeons report that the CO_2 laser reduces surgical bleeding and has higher accuracy [75]. On the other hand, the CO_2 laser may cause a higher incidence of respiratory tract burns and tracheal stenosis or scarring [75]. The CO_2 laser is the most commonly used type of laser for RRP, but some prefer the potassium titanyl phosphate (KTP) laser as it is more angiolytic [76]. The microdebrider has been used more frequently since the 1990s, as it is a relatively cheap, fast, and efficient way to eradicate papilloma [5, 75, 77]. The microdebrider may render histopathological examination of the tissue harder as it cuts the tissue in little pieces. Currently, the use of office-based surgery

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS:____ DATE OF SURGERY:____ SURGEON:____
PATIENT ID #:____ INSTITUTION: ____

1. How long since the last papilloma surgery? ____days, ____weeks, ____months, ____years, ____don't know, ____1st surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months? ____
3. Describe the patient's voice today: ____aphonic, ____ abnormal, ____normal, ____other
4. Describe the patient's stridor today: ____absent, ____ present with activity, ____ present at rest, ____don't know
5. Describe the urgency of today's intervention: ____scheduled, ____urgent, ____emergent

FOR EACH SITE, SCORE AS: 0 = none, 1 = suface lesion, 2 = raised lesion, 3 = bulky lesion

LARYNX

Epiglottis
Lingual surface _____ **Laryngeal surface** _____
Aryepiglottic folds: **Right** ____ **Left** ____
False vocal cords: **Right** ____ **Left** ____
True vocal cords: **Right** ____ **Left** ____
Arytenoids: **Right** ____ **Left** ____
Anterior commisure _____ **Posterior commisure** _____
Subglottis _____

TRACHEA:

Upper one-third _____
Middle one-third _____
Lower one-third _____
Bronchi: **Right** _____ **Left**_____
Tracheotomy stoma _____

OTHER:

Nose _____
Palate _____
Pharynx _____
Esophagus _____
Lungs _____
Other _____

TOTAL SCORE ALL SITES:_____

Fig. 29.3 The Derkay/Coltrera RRP scoring system for recurrent respiratory papillomatosis (From Derkay et al. [49], reproduced with permission from Elsevier)

(mostly in combination with laser surgery) is increasing as it is very cost-effective in comparison with operation room surgery [78].

It is common practice to only initiate surgery when patients have significant voice or dyspnea problems or when papillomas are exophytic and could compromise the airway. Owing to the recurrent character of RRP, patients may have to undergo dozens of surgical interventions.

Multiple adjuvant therapies have been and are being used. Interferon therapy, photodynamic therapy, indole-3-carbinol, ribavirin, bevacizumab [79] intralesional cidofovir, and acyclovir have been tried [43, 80]. Bevacizumab, an anti-vascular endothelial growth factor agent, has been used for intralesional injections or systemic therapy. Two small series of pediatric patients found that intralesional bevacizumab injections decreased the frequency of surgical procedures and repeat injections [81, 82]. Three to 16 courses of systemic bevacizumab were given to four patients with refractory RRP (and one case with inverted papilloma) and this decreased the subsequent frequency of required interventions [79]. It will remain unclear however, what part of improvement is due to the natural course of disease [5]. A report of a single case describes a 12-year-old child with lifelong severe RRP, including tracheostomy and pulmonary involvement at age 1, who had a dramatic response to systemic bevacizumab, including resolution of laryngeal and pulmonary lesions [83]. The true efficacy of systemic bevacizumab is still uncertain.

A distinction is made between therapeutic and preventive medication. Since 1988, intralesional cidofovir has been one of the most widely used additional therapeutic treatments of RRP [84]. Cidofovir is an antiviral drug primarily used for the treatment of cytomegalovirus retinitis in patients with advanced human immunodeficiency virus (HIV). Cidofovir is a cytosine nucleotide analogue with antiviral activity [85]. It is used to diminish HPV activity in infected epithelial cells and thus reduces the growth of papillomas. While systemic cidofovir can have significant toxicities, intralesional use of cidofovir appears to be safe [86]. An international retrospective study by Tjon Pian Gi et al. of 635 RRP cases in 11 countries included 275 patients who received intralesional cidofovir (median 3 injections per patient) [86]. The authors found no statistical difference in the incidence of nephrotoxicity, neutropenia, or laryngeal malignancy between the cidofovir and non-cidofovir groups. The effect of intralesional cidofovir on the clinical course of RRP remains to be elucidated [87].

Therapeutic use of Gardasil® in RRP patients may be beneficial. A case report found that a 2-year-old boy with aggressive RRP did not need further surgeries in the 10 months following vaccination [88]. In a series of six RRP patients, vaccination led to a reduction in the number of surgeries during follow-up (median time 4 years) [89]. It should be noted that the clinical response described in that article was only used for a power analysis for a future randomized controlled trial. Its sample size was too small to analyze the clinical course and to correct for the natural clinical course and other therapies (e.g., cidofovir) [89]. Vaccination of these RRP patients with Gardasil® led to a reactivation of the humoral immune response, even though the patients already had active disease [89]. It is thought that reactivating the immune system could help in preventing further spread of the papillomas into uninfected epithelium [89]. Although a beneficial effect was seen on the clinical course in these studies, they lacked the power to make firm conclusions about the effect of Gardasil® on the clinical course [88, 89].

Cost of Disease

The costs of a JoRRP patient in the USA were estimated at around $60,000 per year in 2000 [90]. The total cost of the whole disease course of a single RRP patient was estimated at around $200,000 in 2012 [90, 91].

Conclusion

Recurrent respiratory papillomatosis is a virus-induced, debilitating, predominantly laryngeal disease for which there is currently no cure available. Surgical treatment remains the main-

stay of therapy. Morbidity of this disease is high, as dozens of surgical interventions may be necessary to temporarily eradicate disease. Research on the effect of vaccination against HPV is ongoing.

Acknowledgement Note: this chapter is partly based on work done for the PhD theses of Dr. R.E.A. Tjon Pian Gi (*Recurrent respiratory papillomatosis—from diagnosis to treatment*. Rijksuniversiteit Groningen, the Netherlands, defended October 12, 2016) and Dr. M.R.M. San Giorgi (*Recurrent Respiratory Papillomatosis—clinical course and psychosocial aspects*. Rijksuniversiteit Groningen, the Netherlands, defended July 5, 2017).

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Preventing Surgical Site Infections in Otolaryngology

30

Marlene L. Durand

Introduction

Surgical site infections (SSIs) cause patient morbidity and mortality, increase length of hospital stay, and increase costs. An SSI is associated with an average mortality rate of 3%, and 75% of these deaths are attributable to the SSI [1]. The cost of each SSI is estimated at $10,000–25,000 but can be much higher; costs may exceed $90,000, for example, in SSIs involving a prosthetic joint [2].

The possibility of preventing all SSIs is unlikely because most occur from colonizing bacteria present at the site of incision. These sites cannot be sterilized. The numbers and diversity of the human microbiome are high; there are more bacterial cells residing on or in the human body than human cells (3.8×10^{13} bacterial cells vs 3.0×10^{13} human cells) [3]. Fortunately only a few pathogens are commonly associated with SSIs, and various measures can reduce the likelihood that these bacteria will contaminate or infect the surgical wound. The number and diversity of bacterial pathogens is lower on the skin than in the upper respiratory tract and gastrointestinal tract, and skin is easier to "disinfect" than mucosal surfaces. It is not surprising, therefore, that surgery involving skin only ("clean" surgery) has a lower SSI rate than surgery involving a mucosal surface (clean-contaminated surgery). The SSI risk is higher still if surgery is considered contaminated (e.g., from breach in sterile technique or bowel rupture intraoperatively), or if the surgery involves a site of active infection (dirty/infected class surgery). Table 30.1 notes the surgical wound class definitions listed by the Centers for Disease Control and Prevention (CDC) [1].

Measures that may reduce SSIs include general measures unrelated to antibiotics, such as ensuring adequate perioperative glycemic control, good tissue oxygenation, and normothermia, as well as surgical antibiotic prophylaxis. A common point of confusion is what constitutes antibiotic prophylaxis. Surgical antibiotic prophylaxis refers only to clean or clean-contaminated surgeries, because wounds classified as contaminated or dirty/infected require antibiotics for *treatment*, not surgical prophylaxis.

Surgical Site Infection Definition

To determine SSI risk factors and compare the efficacy of preventative measures, it is important to use the same definition of SSI. Multiple definitions have previously existed: a study of 90 trials

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1_30

Table 30.1 The U.S. Centers for Disease Control and Prevention (CDC) surgical wound classification [1]

Class	Definition (quoted from the CDC [1])
Clean	"An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria"
Clean-contaminated	"Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered"
Contaminated	"Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered including necrotic tissue without evidence of purulent drainage (e.g., dry gangrene) are included in this category"
Dirty or infected	"Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation"

published in the 1990s found that 41 different SSI definitions were used [4]. The definition that has been used by hospital infection control departments in the U.S. for many years is the one by the CDC, detailed in Table 30.2 [1]. This definition, or one similar to it, is also used by multiple institutions around the world. Three points about the CDC definition are worth highlighting: (1) SSIs are categorized as superficial, deep, or organ space; (2) cellulitis alone does not constitute a SSI; and (3) the SSI follow-up period is 30 days postoperatively (90 days for some surgeries such as cardiac, craniotomy, joint prosthesis, as noted in Table 30.2 footnotes). The 90-day SSI follow-up for some surgeries involving implants is a recent change. Previously, any surgery involving an implant had a follow-up period of 1 year.

The SSI definitions used by the European Centre for Disease Prevention and Control (ECDC) are also widely used worldwide. These definitions are almost exactly the same as the CDC's except that the ECDC does not specify the exclusion of cases of cellulitis alone [5].

It is difficult to compare publications in the ear, nose, and throat (ENT) literature that use different SSI definitions or, in some cases, no definition. Of nine recent series that reported SSI incidence after head and neck free flap surgeries, for example, only two (22%) used the CDC SSI definition and 30-day follow-up interval, while others listed a minimal definition ("purulent discharge"), no definition, or a shorter follow-up interval (hospital discharge) [6]. The follow-up interval affects reported SSI rates, since approximately half of SSIs following major head and neck free flap surgeries occur after hospital discharge [7]. Studies of other types of surgeries have found that 20–70% of SSIs occur post-discharge [8, 9].

General Recommendations

The most recent U.S. guidelines for reducing SSIs were published by the CDC in 2017 [2], the American College of Surgeons and Surgical Infection Society (ACS/SIS) in 2016 [10], and the Society for Healthcare Epidemiology of American (SHEA) in 2014 [11]. The first worldwide guidelines for preventing SSIs were published by the World Health Organization (WHO) in November 2016 [12]. These four guidelines are compared in Table 30.3, and their recommendations are summarized later.

Screening and Decolonization for *Staphylococcus aureus*

Staphylococcus aureus is the most important cause of SSIs in clean surgery and the most important cause of SSIs overall in most countries.

Table 30.2 The definition of surgical site infections (SSI) by the U.S. Centers for Disease Control and Prevention (CDC)

Type of SSI	Criteria
Superficial incisional	Infection involves only skin and subcutaneous tissue AND has at least *one* of the following: • Purulent drainage from incision • Organisms identified from a culture (or non-culture-based method) which is performed for purposes of diagnosis and treatment • Incision is deliberately opened by surgeon (or attending physician, or designee) and culture is not performed, AND patient has at least *one* of the following: pain or tenderness, swelling, redness, heat • Diagnosis of superficial incisional SSI by surgeon (or attending physician, or designee). Neither cellulitis alone (i.e., no drainage) nor a stitch abscess meet this criterion
Deep incisional	Infection involves deep soft tissues (e.g., fascial and muscle layers) AND has at least *one* of the following: • Purulent drainage from incision • Incision spontaneously dehisces or is deliberately opened by surgeon (or attending physician, or designee) AND patient has at least one of the following: fever >38 °C; or localized pain or tenderness • Abscess or other evidence of infection involving the deep incision and detected on gross anatomical exam, or histopathology, or imaging
Organ or organ space	Infection involves any part of the body deeper than the fascial and muscle layers and that is manipulated during surgery AND patient has at least *one* of the following: • Purulent drainage from a drain placed in the organ or organ space • Organisms identified from culture (or non-culture-based method) of an aseptically obtained fluid or tissue in the organ/space • Abscess or other evidence of infection involving the organ or organ space that is detected on gross anatomical exam, or histopathology, or imaging

The follow up interval or "inclusion criterion" for SSIs is 30 days following surgery, except as noted below. This 30-day time frame applies to all ENT surgeries (ear, nose, throat specialty) except for those involving a craniotomy. A 90-day SSI follow up interval applies to breast surgery, cardiac surgery, craniotomy, spinal fusion, open reduction of fracture, herniorrhaphy, hip or knee prosthesis, pacemaker, peripheral vascular bypass surgery, and ventricular shunt [1]

In the U.S., *S. aureus* is the single most common SSI pathogen and causes 30% of all SSIs, with 44% of these *S. aureus* SSIs due to methicillin-resistant *S. aureus* (MRSA) [12, 13]. The role of *S. aureus* in SSIs is not surprising since this organism colonizes 20–30% of the general population at any one time. *Staphylococcus aureus*, and especially MRSA, has intrinsic virulence factors that allow it to evade host defenses and cause infection once it breaches the skin or mucosal barrier. Preoperative prophylactic antibiotics can decrease the rate of *S. aureus* SSIs, but standard prophylaxis with antibiotics such as cefazolin or ampicillin-sulbactam is ineffective against MRSA. Vancomycin is effective against all strains of *S. aureus* including MRSA, but vancomycin takes longer than beta-lactam antibiotics to kill methicillin-susceptible *S. aureus* (MSSA). As a consequence, vancomycin is not recommended for surgical prophylaxis except in MRSA-colonized patients.

Should all surgical patients be screened prior to surgery to detect if they are colonized with MRSA or even methicillin-sensitive *S. aureus* (MSSA)? If colonized, should they be decolonized? What is the optimal protocol for such decolonization? The answers to these questions are still unknown. Guidelines recognize that the answers partly depend on the incidence of MRSA in a population, the importance of MSSA or MRSA as causes of SSIs for a particular type of surgery, evidence that preoperative decolonization reduces SSI rates, and a given country's resources. Screening programs are expensive.

The rate of MRSA colonization in a surgical population varies by region and country; MRSA has been more common in the U.S. than in most European countries, for example. Risk factors for MRSA colonization include recent hospitalization, residence in a long-term care facility, and antibiotic use. Colonization with MRSA may be acquired in the hospital or in the community, and MRSA strains have spread worldwide [14]. A U.S. study found that patients who were MRSA-colonized at the time of admission were ten times more likely to develop an invasive MRSA infection in the ensuing 15 months than non-colonized patients [15]. Another study

Table 30.3 Recommendations for perioperative measures to prevent surgical site infections

Topic	WHO 2016 [12]	CDC 2017 [2]	ACS/SIS 2016 [10]	SHEA 2014 [11]
Decolonization for *Staphylococcus aureus* (or MRSA)	Yes for colonized patients undergoing orthopedic or cardiac procedures	Not evaluated[a]	No recommendation[a]	Yes for "high-risk" procedures (some orthopedic or cardiac)
Preoperative bathing with soap	Yes	Yes	Not evaluated	Not evaluated
Preoperative bathing with chlorhexidine	No recommendation	No recommendation	No recommendation	No recommendation
Hair removal at surgical site	Avoid; if necessary, use clippers	Not evaluated	Avoid; if necessary, use clippers	Avoid; if necessary, use clippers
Skin preparation at surgical site[b]	Alcohol-based	Alcohol-based	Alcohol-based	Alcohol-based
Oxygenation in intubated patients	80% FiO_2 intraoperatively and 2–6 h postoperatively	"Increased FiO_2", target not specified	80% FiO_2 intraoperatively and immediately postoperatively	"increased FiO_2", target not specified
Maintain normothermia	Yes	Yes	Yes	Yes
Maintain normovolemia	Yes	Yes	Not evaluated	Yes
Glucose control	Yes, target not specified	Yes, <200 mg/dl	Yes, 110–150 mg/dl (<180 in cardiac)	Yes (≤180 mg/dl)
Prophylactic antibiotics				
• Start	≤120 min before incision	"Before incision" (target range not specified)	≤60 min before incision (≤120 min for V or FQ)	≤60 min before incision (≤120 min for V or FQ)
• Redose intraoperatively	No recommendation	No recommendation	Redose based on antibiotic half-life, or for >1500 ml blood loss	Redose at 2 half-lives of the antibiotic, or for "excessive" blood loss
• Stop[c]	End of surgery	End of surgery	End of surgery	≤24 h postoperatively

WHO World Health Organization, *CDC* Centers for Disease Control and Prevention, *ACS/SIS* American College of Surgeons and the Surgical Infection Society, *SHEA* Society for Healthcare Epidemiology of America, *MRSA* methicillin-resistant *Staphylococcus aureus*, *mg/dl* milligrams per deciliter, *V* vancomycin, *FQ* fluoroquinolones

[a]"No recommendation" means that the organization evaluated the topic but determined there was insufficient data on which to make a recommendation. "Not evaluated" means that the organization did not mention the topic in their guidelines

[b]All endorse alcohol-based solutions for skin preparation, except when contraindicated (e.g., eyes, mucosal surfaces, neonates). Alcohol-based chlorhexidine solutions are specified by the WHO, but alcohol-based chlorhexidine or alcohol-iodine solutions are considered equivalent by ACS/SIS and SHEA

[c]Includes cases in which a drain is placed. The ACS/SIS guidelines state that antibiotics should stop at the end of surgery except that optimal timing is unknown for three types of surgeries: cardiac, breast implant, and joint arthroplasty

found that MRSA-colonized surgical patients were nine times more likely to develop a MRSA SSI than non-colonized patients [16].

Screening for MRSA colonization is usually done by culture or molecular diagnostic tests of a nasal swab sample. Screening at additional sites such as the throat, axilla, and groin increases the rate of detection but also increases cost. However, a single nasal swab detects only two-thirds of MRSA-colonized patients, compared with multi-site screening [17].

Risk factors may have a significant influence on MRSA colonization rates. In a prospective study of patients admitted to a U.S. Veterans Administration hospital, the MRSA colonization rate was nearly three times higher in patients with a history of antibiotic use in the preceding year than in patients without such a

history (15% vs 5.6%) [18]. Colonization with MRSA can persist for years unless decolonization attempts are made. A review of the literature found that the median time to spontaneous clearance of MRSA colonization was 1.7 years [19]. Another study found that nearly 50% of MRSA-colonized patients were still colonized 1 year later and 21% were still colonized 4 years later [20]. Decolonization protocols are usually effective for a brief period of time in a majority of patients, so programs that choose to screen and decolonize surgical patients preoperatively must do so within a short period of time prior to surgery. Long-term eradication of MRSA cannot be assumed in patients who are successfully decolonized in the immediate preoperative period. Even short-term success was achieved in only one-third of patients after the first decolonization attempt in one study [21]. The most commonly used decolonization protocols include intranasal application of mupiricin 2% ointment, usually twice daily for 5–7 days preoperatively, with or without a daily bath with chlorhexidine. Decolonization methods for MRSA are also effective for MSSA, and MSSA is a more common cause of SSIs than MRSA in most studies.

The impact of *S. aureus* screening and decolonization protocols on SSI incidence has been variable, with the most convincing data provided by trials in cardiothoracic and orthopedic patients. The WHO guidelines do not make recommendations as to which surgical patients should be screened, but state that patients known to be colonized with *S. aureus* should be decolonized with mupiricin (with or without a chlorhexidine bath) prior to cardiac or orthopedic procedures [12]. The WHO guidelines say that such decolonization should be "considered" for other types of surgeries. To avoid unnecessary treatment of non-colonized patients and selection of mupiricin-resistant staphylococci, the WHO strongly recommends against using empiric mupiricin treatment for all preoperative patients. In the U.S., the SHEA recommends screening and decolonization for *S. aureus* for "high-risk procedures, including some orthopedic and cardiothoracic procedures" [11].

Preoperative Bathing with Soap or Chlorhexidine

Bathing with soap is recommended by the CDC and WHO [2, 12]. The CDC states that patients should bathe or shower with soap, either antimicrobial or plain soap, or an antiseptic agent on at least the night before surgery [2]. The WHO also said it was "good clinical practice" for the patient to shower or bathe before surgery but noted that evidence was lacking as to whether this reduced SSIs [12]. Bathing with chlorhexidine solution or chlorhexidine-impregnated cloths was considered by the WHO to have uncertain benefit due to "limited and low-quality evidence," and the other organizations listed in Table 30.2 agreed.

Skin Preparation (Hair Removal, Topical Disinfectants)

All organizations, including the WHO and national organizations from the U.S. and the United Kingdom, recommend against hair removal at the surgical site unless necessary, and the use of clippers (no razors) when hair removal is necessary [12]. There is some evidence that shaving increases the risk of SSIs when compared with no hair removal or use of clippers [12, 22].

For skin preparation at the surgical site, all the organizations listed in Table 30.2 recommend an alcohol-based solution rather than an aqueous solution. Comparisons of alcohol-based chlorhexidine versus an aqueous solution of povidone-iodine have found that the former is associated with a lower SSI rate. A study from Texas, for example, randomized 849 patients undergoing clean-contaminated surgery to a chlorhexidine-alcohol versus povidone-iodine skin preparation solution and found that SSI rates were lower in the chlorhexidine-alcohol group (9.5% vs 16%) [23]. Iodophors may also be combined with alcohol-based solutions, and while the WHO favors a chlorhexidine-alcohol solution, the CDC, ACS/SIS, and SHEA either do not specify which alcohol-based solution is best, or note that there is no clear superiority of chlorhexidine-alcohol over iodine-alcohol [2, 10, 11].

Oxygenation

For adults undergoing surgery who are intubated and given general anesthesia, the WHO recommends 80% FiO_2 (fraction of inspired oxygen) during surgery and "if feasible" for 2–6 h postoperatively [12]. The WHO made this recommendation after performing a meta-analysis of the literature, but looking only at subgroups of patients who were intubated and had general anesthesia [12]. The WHO noted that their conclusion differs from that of a 2015 Cochrane review which found no benefit to administering high FiO_2 [24]. The WHO ascribed the discrepancy to the fact that the Cochrane review included all types of anesthesia, including face mask and nasal cannula, and not just the intubated subgroups.

Other groups, such as SHEA and the CDC, recommend optimizing tissue oxygenation in intubated patients by giving "supplemental oxygen" (without defining this) while also maintaining normothermia and giving appropriate volume replacement. Hypovolemia can jeopardize tissue oxygenation. The CDC 2017 guidelines note that "randomized controlled trial evidence suggested uncertain trade-offs between the benefits and harms of increased fraction of inspired oxygen (FiO_2) during only the intraoperative period in intubated patients with normal pulmonary function" [2]. The CDC recommended that patients with normal pulmonary function who are intubated and receive general anesthesia should, however, receive increased FiO_2 "intraoperatively and in the immediate postoperative period" [2]. The CDC did not specify how high this FiO_2 should be nor for how long it should be given postoperatively.

The WHO recommendation for administering 80% FiO_2 to intubated patients intraoperatively has been controversial among anesthesiologists [25–27]. Some anesthesiologists have noted that studies suggesting a lower SSI rate with high FiO_2 are in fact inconclusive, that performing a subgroup analysis after the fact may not be valid, and that there are risks with giving high FiO_2 such as promotion of atelectasis [27].

Normothermia and Normovolemia

Guidelines recommend maintaining perioperative normothermia and normovolemia, although measures to achieve this are not usually specified. For maintaining normovolemia, the WHO notes that "the optimal fluid (colloid or crystalloid) or strategy of fluid management" remains controversial. The CDC and SHEA recommend maintaining "adequate volume replacement" as part of the measures necessary to ensure good tissue oxygenation, but do not provide guidance on optimal ways to ensure normovolemia [2, 11].

Hypothermia is usually defined as a core body temperature of less than 36 °C (96.8 °F) [12], although SHEA defined hypothermia as <35.5 °C in their guidelines [11]. The surgical patient can become hypothermic because of exposure to a cold operating room in the setting of anesthesia-induced impairment of the patient's thermoregulatory control. A study from 1996 found that patients who received intraoperative care that was standard for that time (no warming) had a mean core body temperature of 34.7 °C [28]. The WHO notes that inadvertent, non-therapeutic perioperative hypothermia has been associated with impaired wound healing, cardiac events, coagulopathies, increased blood loss, and altered drug metabolism [12]. The association between hypothermia and increased SSI risk, however, has been based primarily on two randomized controlled trials [12]. The first trial was performed over 20 years ago and included 200 patients undergoing colorectal surgery [28]. Those who received intraoperative warming and were normothermic during surgery had a significantly lower SSI rate (6% vs 19%) than those who received "routine" care and were hypothermic. The second trial, reported in 2001, evaluated over 400 adults undergoing clean surgical procedures (breast, varicose vein, hernia) and found that the cohort who received preoperative warming for at least 30 min had a lower SSI rate (5% vs 14%) than those who received routine care without warming [29].

It is unknown whether preoperative or postoperative warming conveys additional benefit

over intraoperative warming alone. A small randomized controlled trial (103 patients) reported in 2007 warmed all trial patients intraoperatively during their major abdominal surgery to maintain normothermia, but half of the patients received additional warming for 2 h before and after surgery [30]. The additionally warmed cohort had a significantly lower blood loss than the control group, but the lower SSI rate (13% vs 27%) did not reach statistical significance. All guidelines recommend maintaining normothermia intraoperatively. Some guidelines (CDC, SHEA) state that normothermia should be maintained "perioperatively," but do not specify a time frame [2, 11]. The WHO states that "it was not possible to reach an agreement regarding the optimal pre- and postoperative time for warming" [12]. Devices to achieve warming are not specified by guidelines [2, 12].

Glycemic Control

Blood glucose levels increase during and after surgery due to surgical stress, and observational studies suggest that hyperglycemia increases SSI risk in both diabetic and nondiabetic patients [31–33]. As noted in Table 30.3, guidelines committees have differed on the quality of the evidence supporting tight glucose control as a means to reducing SSIs. There have been 15 randomized controlled trials in various types of surgery (eight cardiac, six major abdominal or other non-cardiac, one emergency cerebral aneurysm clipping) that have compared intensive glucose protocols versus conventional protocols [12]. However, these trials did not have SSI as a primary outcome, used different definitions of SSI, and used intensive glycemic control at different perioperative periods (two intraoperatively, eight intra- and postoperatively, five postoperatively). A recent meta-analysis of these 15 studies noted the same problems but concluded that the studies provided evidence that strict glycemic control lowered SSI risk [34].

The WHO panel reviewed these 15 studies, felt that the quality of evidence was "low," and recommended "protocols for intensive perioperative blood glucose control for both diabetic and non-diabetic adult patients" but said they could not specify target levels [12]. The CDC panel, in contrast, labeled the level of evidence as "high to moderate quality," and made a "strong" recommendation for "perioperative" glycemic control with blood glucose target levels of <200 mg/dl (perioperative was not defined) [2]. The SHEA panel recommended controlling blood glucose levels in the "immediate postoperative period" to 180 mg/dl or lower, and cautioned that targeting glucose levels to less than 110 mg/dl may lead to higher risk of adverse outcomes but without SSI reduction [11]. The ACS/SIS guidelines recommend "perioperative" target glucose levels of 110–150 mg/dl in non-cardiac patients and less than 180 mg/dl in cardiac patients (perioperative was not defined) [10]. Outside the U.S., 2011 guidelines from the United Kingdom recommend intraoperative glucose control (to <11 mmol/l, approximately 200 mg/dl) only for diabetic patients, stating that the benefit of tight glucose control in non-diabetic patients has not been proven [35]. In summary, there appears to be a lack of consensus on this topic.

Antibiotic Prophylaxis

Perioperative antibiotic prophylaxis refers to systemic antibiotics given in some clean and most clean-contaminated surgeries to reduce the rate of SSIs. In clean surgeries, randomized prospective trials require large numbers of patients in each arm of the study because the baseline SSI rate is less than 5% and often less than 1%. In most clean surgeries, prophylactic antibiotics do not reduce SSI rates further and are not recommended. In otolaryngology, antibiotics are recommended for clean-contaminated surgeries except for routine sinus surgery and tonsillectomy. As noted above, in contaminated or "dirty" surgeries, recommendations for antibiotic prophylaxis do not apply because antibiotics are necessary for treatment, not prophylaxis.

In 2013, guidelines for surgical prophylaxis were developed by the American Society of Health-System Pharmacists (ASHP), in conjunction with

the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), and SHEA [36]. Recommendations from this ASHP guideline have been adopted by many U.S. hospitals and some centers in other countries [37, 38]. The portions of the ASHP guidelines that pertain to otolaryngology are summarized in Table 30.4.

The ASHP guideline is the only recent major guideline to offer specific recommendations as to which surgeries require prophylaxis and for antibiotic choice. Other guidelines address timing of surgical antibiotic prophylaxis but sidestep these other points. The WHO guidelines state: "It is not within the scope of these guidelines to provide recommendations on what type of operations require surgical antibiotic prophylaxis and the antibiotics, doses and intraoperative redosing rules that should be used." [12] The CDC guidelines state: "Administer preoperative antimicrobial agents only when indicated based on published clinical practice guidelines and timed such that a bactericidal concentration of agents is established in the serum and tissues when the incision is made." [2] The ACS/SIS guidelines state: "Administer prophylactic antibiotics only when indicated. Choice of antibiotic prophylaxis should be dictated by the procedure and pathogens likely to cause SSI." [10]. The SHEA guidelines state: "Administer antimicrobial prophylaxis according to evidence-based standards and guidelines," citing the ASHP guidelines as the most recently published reference [11]. The American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) has not published guidelines for antibiotic prophylaxis in ENT surgeries other than tonsillectomy (no indication).

Which Surgeries Do Not Require Antibiotic Prophylaxis?

Clean ENT Surgeries

The ASHP guidelines do not recommend prophylactic antibiotics for clean ENT surgeries unless they involve an implant other than tympanostomy tubes [36]. The ASHP lists lymph node excision and thyroidectomy as examples of surgeries not requiring prophylaxis, and cites a multicenter prospective trial from Italy by Avenia et al. in support of the latter. This study randomized 500 patients undergoing thyroid cancer or goiter procedures to either a single dose of preoperative intravenous ampicillin-sulbactam or no antibiotic prophylaxis; SSI rates were not statistically different between the groups (0.8% vs 0.4%, respectively) [39]. Because of multiple exclusion criteria (e.g., diabetes, immunosuppression, severe obesity, concomitant lymph node excision, locally advanced cancer), the study authors considered the trial preliminary. All patients had drains placed at surgery and in 10%, these were removed later than postoperative day 1 but that did not affect SSI rate, nor did antibiotic prophylaxis affect SSI rates in this subgroup. A Cochrane review also found that the presence of drains in thyroid surgery did not affect SSI rates [40].

Tonsillectomy and Sinus Surgery

The ASHP guidelines recommend antibiotics for all clean-contaminated surgeries except tonsillectomy and functional endoscopic sinus surgery [36]. The AAO-HNS also recommends against antibiotic prophylaxis for tonsillectomy in children and adolescents [41].

Clean Head and Neck Surgery

The ASHP guidelines do not mention clean head and neck cancer surgery. A 2016 United Kingdom national guideline for head and neck cancer surgery states that "antibiotics are necessary for clean-contaminated surgery, but unnecessary for clean surgery." [42] However, the guideline goes on to say that "For surgery with malignant disease that is clean (e.g. neck dissection), antibiotic prophylaxis can be considered". This appears to be a contradiction. The guideline does not specify the antibiotic to be used in such clean surgeries, stating only that in clean-contaminated head and neck cancer surgery, the "choice of antibiotic should ensure broad-spectrum cover for aerobic and anaerobic organisms" [42].

Guidelines have also been published recently by the American Association of Plastic Surgeons (AAPS). The AAPS guideline panel found only 4 randomized trials of clean head and neck surgeries and these had "very serious" risk of bias, with

Table 30.4 The American Society of Health-System Pharmacists (ASHP) 2013 guidelines for antibiotic prophylaxis as they pertain to selected surgeries in otolaryngology [36]

Surgery	Give prophylaxis?	If yes, antibiotic[a]	Alternative if β-lactam allergy	Comments
Clean nasal or facial plastic surgery, no implant	No	N/A	N/A	ASHP
Clean nasal or facial plastic surgery, with implant	Yes ("consider")	Cefazolin, or ampicillin-sulbactam[a]	Clindamycin[b], or vancomycin[b]	ASHP
Thyroid surgery	No	N/A	N/A	ASHP
Lymph node excision	No	N/A	N/A	ASHP
Other clean surgery without implant	No	N/A	N/A	ASHP
Clean surgery with implant (excludes tympanostomy tubes)	Yes	Cefazolin, or cefuroxime	Clindamycin[b]	ASHP
Tonsillectomy	No	N/A	N/A	ASHP for all ages; AAO-HNS Guidelines agree for children and adolescents (no comment on adults)
Functional endoscopic sinus surgery	No	N/A	N/A	ASHP
Clean-contaminated surgery (except tonsillectomy or functional endoscopic sinus surgery)	Yes	Cefazolin (or cefuroxime) + metronidazole, or ampicillin-sulbactam[a]	Clindamycin[b]	ASHP
Clean-contaminated head and neck cancer surgery	Yes	Cefazolin (or cefuroxime) + metronidazole, or ampicillin-sulbactam[a] (see adjacent comment and text)	Clindamycin[b] (see adjacent comment and text; clindamycin alone has been associated with a higher risk of SSIs and is probably inadequate)	See the text. Some centers prefer piperacillin-tazobactam for non-allergic patients, and clindamycin plus a gram-negative agent (e.g., levofloxacin) for β-lactam-allergic patients. See the text for comments regarding MRSA-colonized patients
Craniotomy	Yes	Cefazolin[a]	Clindamycin[b], vancomycin[b]	ASHP

N/A not applicable, *ASHP* American Society of Health-System Pharmacists, *AAO-HNS* American Association of Otolaryngology—Head and Neck Surgery, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a]The ASHP guidelines state that for procedures in patients known to be colonized with MRSA, "it is reasonable to add a single preoperative dose of vancomycin to the recommended agent(s)" [33]

[b]The ASHP notes: "For procedures in which pathogens other than staphylococci and streptococci are likely, an additional agent with activity against those pathogens could be considered. For example, if there are surveillance data showing that gram-negative organisms are a cause of surgical site infections (SSIs) for the procedure, practitioners may consider combining clindamycin or vancomycin with another agent (cefazolin if the patient is not β-lactam allergic; aztreonam, gentamicin, or single dose fluoroquinolone if the patient is β-lactam allergic)" [33]

"very low" quality of evidence [43]. However, based on these studies, the AAPS concluded that there was no apparent benefit to surgical prophylaxis for these clean procedures.

ENT Plastic Surgery Procedures

The ASHP guidelines state that no antibiotics are necessary for clean facial or nasal procedures not involving an implant, but antibiotic prophylaxis "should be considered" if an implant is placed [36]. Recommendations for clean-contaminated surgeries are listed in Table 30.4. For septoplasty or rhinoplasty surgeries, the AAPS guideline states that trials of clean procedures do not exist since nearly all of these procedures are clean-contaminated [43]. For clean-contaminated septoplasty/rhinoplasty, the AAPS recommends antibiotic prophylaxis but says the strength of this recommendation is "weak" because the level of evidence is "low."

Which ENT Surgeries Require Prophylaxis?

Clean-Contaminated Surgeries, Clean Surgeries with Implants

Guidelines from the ASHP and others recommend that antibiotics should be given for clean-contaminated surgeries, except for tonsillectomy and endoscopic sinus surgery. Antibiotics should also be given or "considered" for clean surgeries requiring implants (other than tympanostomy tubes).

Craniotomy

In ENT surgery, craniotomy may be performed for acoustic neuroma surgery and skull base surgeries. The ASHP guidelines recommend antibiotic prophylaxis for all craniotomies, including clean procedures without implants, based on observational studies that have reported lower SSI rates in patients given prophylaxis. One of the largest studies with over 4500 cases (including 64 "neurinomas," presumably acoustic neuromas), evaluated SSI rates during time periods before and after a protocol was instituted to give antibiotic prophylaxis to all craniotomies [44]. The SSI rate was significantly lower after universal antibiotic prophylaxis was instituted, primarily because of the impact on SSI rates in "low SSI risk" craniotomies (4.6% SSI rate with vs 10% without prophylaxis).

Timing of Prophylaxis

It is now accepted practice in the U.S. and many other countries to start antibiotic prophylaxis within 1 h prior to incision (within 2 h for long-acting antibiotics). This is because of the nationwide implementation of the Surgical Care Improvement Project (SCIP), launched in the U.S. in 2003 based on the recommendations of a consortium of ten national organizations, including the CDC and the Centers for Medicare and Medicaid (CMS) [45]. Measures from SCIP influenced perioperative care protocols worldwide. The measure labeled "SCIP-1" required that the prophylactic antibiotic start within 60 min prior to the surgical incision ($\leq$120 min if using vancomycin or fluoroquinolones). Measures labeled SCIP-2 (appropriate choice of prophylactic antibiotic) and SCIP-3 (stop prophylactic antibiotics within 24 h postoperatively) were also part of SCIP. These three measures subsequently became incorporated in the ASHP guidelines, and became part of CMS pay-for-performance metrics for hospitals as well as public reporting of hospital quality. As a consequence, U.S. hospitals achieved very high compliance rates with required SCIP measures so CMS felt that mandatory reporting of compliance was no longer required as of January 2016.

Despite the importance of this topic, no randomized controlled trials have ever been performed to determine optimal timing of antibiotic prophylaxis. The SCIP measures and subsequent guideline recommendations are based on observational studies. The Classen study, published in 1992, was one of the earliest to call attention to the impact of the timing of the "on call" prophylactic dose of antibiotic on SSI rates [46]. This study retrospectively reviewed 2800 surgeries of various types and found that the lowest SSI rates occurred in patients who received antibiotic

prophylaxis within 2 h prior to incision [46]. A similar study of 4500 patients, reported by Steinberg et al. in 2009, found low rates of SSIs (2%) if antibiotics were given within 0–60 min prior to incision but a higher rate (5%) if prophylaxis was started after incision [47]. A 2017 study of Florida hospitals reported that compliance with SCIP-1 correlated with decreased wound complication rates, including SSIs [48]. In evaluating the data for the WHO guidelines, de Jonge et al. performed a meta-analysis of the literature and pooled the results of 14 papers, including over 54,500 patients, that met inclusion criteria [49]. The study's conclusion was that the lowest risk of SSI occurred if antibiotics were given 0–120 min before incision, but that there was no difference when antibiotics were started within that time frame (e.g., 60–120 vs 0–60 min). This is the basis for the WHO opinion that preoperative antibiotics may be started at any point within 2 h prior to incision. De Jonge et al. did find a five-fold increased risk of SSI if prophylactic antibiotics were given earlier than 2 h before incision and a two-fold increased risk if antibiotics were started after incision.

Because of the absence of randomized controlled trials, the 2017 CDC guidelines do not give a specific window of time in which to start antibiotics, stating only that they should be "timed such that a bactericidal concentration of the agents is established in the serum and tissues when the incision is made" [2]. Most U.S. hospitals continue to follow the SCIP guidelines of starting antibiotics within 60 min before incision (within 120 min for vancomycin or fluoroquinolones).

Dosing in Obesity, and Intraoperative Redosing

The value of increased antibiotic doses in heavier patients and short redosing intervals intraoperatively is presently unknown. The ASHP guidelines recommend cefazolin as a first-choice antibiotic for most types of surgeries requiring prophylaxis (cefazolin plus metronidazole, or ampicillin-sulbactam, for clean-contaminated ENT surgeries) [36]. The ASHP recommends a higher than usual dose of cefazolin: 2 g of cefazolin for adults weighing less than 120 kg (264 pounds), and 3 g for adults weighing 120 kg or more [36]. The ASHP also recommends intraoperative redosing of antibiotics at 2 half-lives, so every 4 h for cefazolin and every 2 h for ampicillin-sulbactam (or piperacillin-tazobactam). However, for prolonged head and neck cancer surgeries, the latter recommendation could be problematic as these cases can last 7–10 h. A case lasting just over 6 h would therefore be given a total of four doses of intravenous ampicillin-sulbactam (3 g each dose) within that time, counting the preoperative dose as time 0 (0, 2, 4, 6 h). This is a total dose of 12 g, the standard dose given for *treatment* of an infection during a *24-h* period of time. While high doses of cefazolin are usually well tolerated, potential toxicity (e.g., seizures from high-dose penicillins) might be a consideration for such frequent redosing of penicillins. The ASHP guidelines are based primarily on pharmacokinetic considerations and small or older observational trials rather than well-designed clinical trials. No randomized controlled trials have been performed. As a consequence of the inadequate data on which to base a recommendation, the CDC states that they can make no recommendations regarding either weight-based dosing or intraoperative redosing [2]. The WHO also says that no recommendation regarding redosing can be made, since "the reviewed studies have not addressed in surgical antibiotic prophylaxis protocols the duration of surgical procedures or re-dosing in relation to SSI." [12]

Choice of Antibiotic for Surgical Prophylaxis

Table 30.4 lists the antibiotics recommended by the ASHP for surgical prophylaxis for various types of ENT procedures, with comments about other regimens. The ASHP recommends cefazolin for clean procedures (when prophylaxis is indicated), cefazolin (or cefuroxime) plus metronidazole or ampicillin-sulbactam for clean-contaminated procedures, and clindamycin for patients with beta-lactam allergy. The ASHP

notes that if surveillance data indicate that SSIs are due to bacteria other than staphylococci and streptococci, such as Gram-negative bacilli, an additional antibiotic might be added to clindamycin to cover those pathogens. In MRSA-colonized patients, the ASHP recommends the addition of a single dose of intravenous vancomycin to the prophylactic regimen.

Clindamycin used as the sole prophylactic agent appears to be a risk factor for SSIs in major head and neck surgeries, based on several large retrospective studies [7, 50–52]. This may be due to the prominence of Gram-negative bacilli in these SSIs. One study reported that Gram-negative bacilli were pathogens in 44% of SSIs following major head and neck free flap surgeries [7]. The addition of a Gram-negative agent such as levofloxacin, ciprofloxacin, or aztreonam to clindamycin would provide broad-spectrum coverage in penicillin-allergic patients.

The choice of antibiotic prophylaxis is especially important in major clean-contaminated head and neck cancer surgeries involving flap reconstruction, as these procedures carry a much higher risk of SSI (usually 15–30%) than any other type of ENT surgery. The optimal prophylactic antibiotic regimen for these procedures is unknown, but should include activity against *S. aureus*, streptococci, anaerobes, and Gram-negative bacilli. Cefazolin and ampicillin-sulbactam have activity against some Gram-negative bacilli, but many Gram-negative bacilli such as *Pseudomonas* are resistant. One study found that only 15–26% of the Gram-negative bacilli cultured in SSIs after major free flap surgeries were susceptible to ampicillin-sulbactam or cefazolin, respectively [7]. Piperacillin-tazobactam, an agent with broader-spectrum Gram-negative activity than ampicillin-sulbactam, was a very effective prophylactic agent for clean-contaminated flap surgeries at one center [53]. As noted above, a single dose of vancomycin should be added to the preoperative prophylactic regimen in MRSA-colonized patients. However, outside the perioperative prophylaxis setting, the combination of vancomycin plus piperacillin-tazobactam given for ≥48 h has been associated with an increased risk of renal toxicity than vancomycin plus cefepime (or a similar Gram-negative agent) [54, 55]. The potential renal toxicity of a single dose of vancomycin added to piperacillin-tazobactam prophylaxis has not been assessed, but alternative regimens with a similar spectrum of activity include vancomycin plus metronidazole plus either cefepime or another Gram-negative agent (e.g., levofloxacin, ciprofloxacin, aztreonam).

Duration of Antibiotic Prophylaxis

Multiple randomized controlled trials have been performed to determine the optimal duration of antibiotic prophylaxis. None have demonstrated any benefit to continuing antibiotics beyond the end of surgery, including in cases with drains. For this reason, the ASHP and SHEA recommend stopping antibiotics within 24 h postoperatively, while the WHO and the CDC recommend stopping antibiotics at the end of surgery, regardless of the presence of a drain. The CDC guidelines were published more recently (2017) than ASHP and SHEA so likely supercede those earlier recommendations. The CDC guideline panel gave the recommendation to stop antibiotics at close of surgery their strongest endorsement, category 1A ("strong recommendation, high-quality evidence") [2]. The 2016 WHO guidelines also grade this as a "strong" recommendation, but with "moderate quality of evidence" [12].

The WHO panel performed a meta-analysis of the literature and found 69 randomized controlled trials (>21,000 patients) that evaluated optimal duration of prophylaxis in a variety of surgical procedures. The first dose was always given preoperatively but patients either received no postoperative antibiotics or received postoperative antibiotics for varying lengths of time (<24 h, <48 h, >48 h, etc.). The WHO panel concluded that "there is a moderate quality of evidence that prolonged [i.e., any] postoperative antibiotic prophylaxis has no benefit in reducing the SSI rate with compared to a single dose of antibiotic prophylaxis (OR: 0.89; 95% CI: 0.77–1.03)" [10]. Prolonging antibiotic prophylaxis is not benign. Prolonged antibiotics lead to the selection of

antibiotic-resistant bacteria and the risk of antibiotic side effects such as *Clostridium difficile* diarrhea and allergic reactions.

Conclusion

Surgical site infections may cause significant morbidity and mortality, as well as increased length of stay and cost of care. Several national and international panels have reviewed the literature and formulated guidelines for measures to prevent SSIs: these recommendations are summarized here. Measures that may reduce SSIs include avoidance of hair shaving, use of alcohol-based disinfectant for skin preparation of the surgical site, maintaining perioperative normothermia, normovolemia, and glycemic control, ensuring adequate tissue oxygenation, and the use of perioperative prophylactic antibiotics when such prophylaxis is indicated. Prophylactic antibiotics should be started in a short window of time prior to incision, and should stop at the end of surgery according to the most recent guidelines. Prolonging the course of prophylactic antibiotics carries a risk to the patient of antibiotic side effects and selection of resistant bacteria, but without any proven benefit.

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M. L. Durand, D. G. Deschler (eds.), *Infections of the Ears, Nose, Throat, and Sinuses*,
https://doi.org/10.1007/978-3-319-74835-1