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USE OF THE CLINICAL MICROBIOLOGY LABORATORY FOR THE DIAGNOSIS AND MANAGEMENT OF INFECTIOUS DISEASES RELATED TO THE ORAL CAVITY

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The oral cavity is one of the initial areas examined when a patient presents with complaints of cough, cold, or sore throat. An understanding of the infectious processes affecting this area and how to diagnose them accurately is important.¹⁷ Visits to physicians for symptomatic complaints related to possible infections of the oral cavity are a common occurrence. Not only is it important to accurately determine the entity causing an infectious syndrome so that appropriate therapy may be given, it is also important because these interactions with the healthcare system likely result in a large amount of unnecessary antibiotic prescribing. For example, a recent report by Mainous et al⁴¹ found that 60% of over 2000 patients seeking medical care were given at least one of 19 different antimicrobial agents for acute nasopharyngitis (the common cold). Less than 2% had an accompanying bacterial sinusitis or otitis.

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Because the symptomatic complaints the authors described are nearly all secondary to viral infections, such antibiotic prescribing is not beneficial. Similarly, although chronic cough is often treated with antimicrobial agents, 90% is caused by smoking, postnasal drip, asthma, gastroesophageal reflux, and chronic bronchitis.⁵⁰ None of these latter conditions are usually responsive to antimicrobial therapy. Data collected in the United States between 1980 and 1994 for persons presenting with a complaint of cough found that antibiotic prescription rose from 59% of visits in 1980 to 70% in 1994.⁴⁴ Interestingly, clinical characteristics did not appear to be the major influence in such prescriptions.⁴⁴

Infections related to the oral cavity are important from two very different perspectives. First, when they occur within the oral cavity, the result frequently is significant morbidity (pain), such as with pharyngitis, stomatitis, and even dental caries. The intraoral infectious syndromes and their management are diverse. For example, dental caries is a major medical and economic problem, typically associated with infection by *Streptococcus mutans*¹⁷; however, specific microbiologic evaluation is rarely done or needed for caries. Pharyngitis is also common, but only a very few inciting microbes require specific treatment. Other local infections, such as candidiasis (thrush), actinomycosis, and sexually transmitted diseases, occur less frequently, but all require therapy. Second, an infectious disease from mouth origin can present at a distant site, resulting in both morbidity and mortality. These range from sinusitis, where the connection to the oral cavity is direct, to infections like endocarditis, where oral microbes travel through the vascular system to reach their final site of infection.

The infectious diseases associated with the oral cavity have their own unique, often mixed, microbiology, making culture detection of a specific organism linked to a given episode of infection frequently complicated. Because infections in this area most often arise from normally resident flora, it is important to first understand what microbes are often found here. Nonhemolytic streptococci, coagulase-negative staphylococci, micrococci, *Corynebacterium* spp (aerobic diphtheroids), *Neisseria* spp (other than *N. meningitidis* or *N. gonorrhoeae*), spirochetes, *Lactobacillus*, and *Veillonella* spp are nonpathogenic organisms frequently present. Additionally, β -hemolytic streptococci, viridans streptococci, *Peptostreptococcus* spp, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *N. meningitidis*, *Corynebacterium diphtheriae*, *Mycoplasma* spp, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Fusobacterium* spp, *Mycobacterium* spp other than tuberculosis (MOTT), *Enterobacteriaceae*, *Acinetobacter* spp, *Pseudomonas* spp, *Klebsiella ozaenae*, *Eikenella corrodens*, *Bacteroides* spp, *Actinomyces* spp, herpes simplex virus (HSV), *Candida albicans*, filamentous fungi, and even *Cryptococcus neoformans* may be recovered from the oral cavity as pathogens or commensals. The best diagnostic approach is to begin with a careful history and physical examination, followed by specific laboratory testing, to detect the suspected pathogens. The purpose of this article is to highlight the likely pathogens responsible for oral cavity infections, and to suggest ways to

integrate the clinical and laboratory diagnosis to establish an accurate microbiologic diagnosis for these infectious diseases.

INFECTIONS IN THE ORAL CAVITY

Pharyngitis

Acute pharyngitis is a common illness that sends nearly 1% of all children and adults to seek care from physicians and emergency rooms each year. Searching for a specific organism, *Streptococcus pyogenes*, as the causative pathogen is the most common infectious disease diagnostic effort performed on the oral cavity. The primary cause of most microbial pharyngitis is a virus in most adults; however, *S. pyogenes*, also known as the group A β -hemolytic streptococcus (GABHS), is the most important organism to recognize. The inflammatory syndrome of the pharynx resulting from *S. pyogenes* infection is marked by a wide variety of signs and symptoms, and nearly always is accompanied by fever and sore throat.^{6, 35, 64} It is important for physicians to accurately diagnose which organism is causing the disease because infection with GABHS should be treated with antibiotics such as penicillin and erythromycin, whereas viruses do not respond to such therapy. *S. pyogenes* also causes suppurative infections of the tonsils, sinuses, and middle ear, or cellulitis as secondary sequelae after an episode of pharyngitis. Treatment of GABHS pharyngitis is crucial because this can shorten the duration of symptoms and prevent the spread of the organism to other patients. It will also prevent the potential damage that *S. pyogenes* may cause to the heart and kidneys from rheumatic fever and glomerulonephritis, respectively.

The gold standard diagnostic test for GABHS infection is the throat culture.⁶ Unfortunately, the culture takes 24 to 48 hours to complete. If the patient leaves their physician or healthcare facility with a prescription for antibiotics, the treatment would then begin before the microbial entity is known. In the age of emerging drug resistance, unnecessary antimicrobial agent use must be avoided. Because untreated GABHS infection may have serious consequences for the patient, rapid detection methods for *S. pyogenes* were developed to give nearly immediate results in order to make the diagnosis of streptococcal pharyngitis possible while the patient is still in the office or clinic. There are several manufacturers of rapid identification test kits for GABHS in the marketplace today.^{34, 47, 52} The Centers for Disease Control and Prevention (CDC) reviewed 25 published studies that examined the sensitivity of these rapid identification test kits.¹⁸ They found the sensitivity of these tests ranged from 62% to 100%. Within any one institution, the sensitivity of a single kit varied by as much as 20%. Assuming that a good diagnostic screening test should have a sensitivity of at least 95% (so almost all infected patients will be detected), this study showed that a negative rapid identification test for GABHS cannot accurately rule out infection, and that a corresponding culture also is needed.¹⁸

In a national survey, the College of American Pathologists (CAP) sent 2692 laboratories a swab seeded with *S. pyogenes* to perform a rapid detection test with the kit used at their institution. Fourteen different types of GABHS kits were assessed. The number of correct results ranged from 80% to 100%, with only three kits providing 100% accuracy for all participants. Those using these three kits comprised only 11% of the users. Based on this survey, and similar performance on previous CAP surveys, both the CAP and CDC recommend that a negative test result generated by a rapid identification test for GABHS must always be followed with a culture. This also is the current recommendation of the American Academy of Pediatrics. A useful approach is to collect two throat swabs, one for rapid testing and the other for culture. If the antigen test is positive, the second swab for culture is not needed. If the antigen test is negative, the second swab should be used to perform the culture. This approach can be an economic practice for an institution caring for a large number of children.

Adults with pharyngitis would more than likely have to have both a rapid screen and a culture performed, as studies have shown that the percentage of adult patients with GABHS disease is low (less than 10% of all cases). This is because streptococcal pharyngitis is nearly exclusively a disease of 5- to 15-year-olds.⁶ Therefore, the chance of having a true positive screen test in an adult population is very low. As previously noted, the rapid, direct tests for *S. pyogenes* have a reported sensitivity ranging from 62% to 100%, with an excellent specificity of at least 95%; however, with a low GABHS prevalence adult patient population ($\leq 5\%$), a full 50% of positive tests would be false-positive results, even with a test that was 100% sensitive and 95% specific (5 true-positive and 5 false-positive patients for each 100 tested). This leads to additional prescribing of unnecessary antibiotics for patients, with the risk of a serious adverse reaction in someone who did not need treatment. A study of 806 community patients with an overall 25.1% prevalence of GABHS recovered by culture, published in 1990, supports this concern.⁵² Using a direct "rapid" test did not add to a clinical evaluation, and compared to a well-done culture, it resulted in "delayed treatment, unnecessary treatment, and increased costs." Compared to culture, the rapid test only had a positive predictive value of 61% and a negative predictive value of 89%.

Susceptibility testing generally is not done on any GABHS isolated, as these bacteria have traditionally been susceptible to all agents usually employed for therapy. When a rapid screen is positive and no culture is done, there is also no viable organism available to perform such testing. In an era of emerging antibacterial drug resistance, this practice may need to change. At Northwestern Memorial Hospital, 66 strains of invasive *S. pyogenes* were tested for antibiotic susceptibility between 1995 and 1998. Of these, 5% were resistant to erythromycin, the usual first-line therapy for streptococcal pharyngitis.

Physicians can help maintain (or even improve) the sensitivity of the GABHS detection by clinically selecting which patients to culture

and then using proper specimen collection techniques. Adults with signs and symptoms of pharyngeal exudate, swollen anterior cervical lymph nodes, absence of cough, and documented fever of 38°C or more ($\geq 100.5^{\circ}\text{F}$) are three times more likely to have a positive culture for *S. pyogenes* than those with only two of these findings. With none of these signs or symptoms, only 2.5% of adults with pharyngitis will have a positive culture for GABHS. The optimal culture technique when streptococcal pharyngitis is considered likely is to thoroughly swab the palatine tonsils and oropharynx and avoid the tongue. Doing this, one can expect that within 48 hours a final culture result, with sensitivity and specificity approaching 100%, will be reported, and only those patients really requiring therapy will receive it.

Cases of pharyngitis caused by groups B, C, and G, and by nonhemolytic members of these groups of streptococci have been reported. Added to this list of uncommon causes of pharyngitis are mixed anaerobes (Vincent's angina, or gangrenous pharyngitis), *N. gonorrhoeae*, *C. diphtheria*, *Arcanobacterium haemolyticum* (accompanied by a scarlatini-form rash), *Yersinia enterocolitica*, *Yersinia pestis*, *Francisella tularensis* (pharyngeal tularemia), rhinovirus, coronavirus, adenovirus, HSV 1 and HSV 2, parainfluenza virus (croup), coxsackievirus A (herpangina), Epstein-Barr virus (EBV mononucleosis), cytomegalovirus (CMV mononucleosis), primary HIV infection, influenza A and B, *Mycoplasma pneumoniae*, *Chlamydia psittaci*, and *C. pneumoniae*.^{1, 6, 30} Although there are microbes other than *S. pyogenes* that may cause pharyngitis, it is important to remember that the other streptococci, most alternative bacteria, and the viruses are not known to benefit from specific antimicrobial therapy. The clinical laboratory does not routinely look for any of these other agents in throat swabs, except in unusual circumstances when specifically requested by the clinician involved.⁵⁹

Diphtheria

Although much less common than streptococcal pharyngitis, *C. diphtheriae* can still be isolated from patients with sore throat, as well as from those with a more serious systemic disease. Epidemic diphtheria re-emerged in the former Soviet Union beginning in 1990, resulting in approximately 125,000 cases and 4000 deaths between 1990 and 1995. Although the number of new cases began to decrease in 1996, following a World Health Organization (WHO) strategy to vaccinate 90% of persons aged 3 years or older, cases are still being exported to Europe and other parts of the world.⁴⁶ The introduction of new strains into the United States from exogenous reservoirs can cause outbreaks in homeless populations who are often in poor health and lack basic medical care.²⁵ The laboratory diagnosis of diphtheria includes appropriate processing of a throat or nasopharyngeal swab. It should be inoculated to blood agar designed to detect β -hemolytic streptococci, and to differential media for *C. diphtheriae*, such as tellurite agar and a Loeffler slant.⁵⁶

Colonies appearing on the Loeffler's slant are stained with methylene blue to detect typical cellular morphology. Gray to black colonies on tellurite agar are confirmed as *C. diphtheriae* by biochemical testing, and further referred to a public health laboratory for toxigenicity analysis. Other *Corynebacterium* spp (*C. ulcerans* and *C. pyogenes*) can cause pharyngitis, with or without membrane formation or associated rash, but such infections are rare.

Other Bacteria Causing Pharyngitis

A recently recognized pathogen, *Arcanobacterium haemolyticum*, may cause as many as 10% of pharyngotonsillitis in patients 10 to 30 years old. It is typically associated with a rash consisting of erythematous macules and petechiae. Vesicles may also appear with the rash. To detect this microbe, a laboratory needs to hold the routine throat culture for 72 hours, as the organism is very slowly hemolytic; or alternatively plate the throat swab on agar containing 5% human blood to enhance hemolysis at 24 hours.²⁰ *N. meningitidis*, too, occasionally can be recovered from the nasopharynx of carriers, although finding it here is not significant unless the patient has recently been exposed to a patient with *N. meningitidis* meningitis. *N. gonorrhoeae* can cause an exudative pharyngitis. In this setting, as well as in disseminated gonococcal disease, the organism may be isolated from throat cultures. *Neisseria* spp require special media for satisfactory cultivation in the laboratory, and therefore consulting with microbiology personnel should be done before collecting and submitting specimens for their detection (Table 1). Although *H. influenzae*, *S. aureus*, and *S. pneumoniae* are frequently isolated from nasopharyngeal and throat cultures, they have not been shown to cause pharyngitis.

Atypical Pathogens

Mycoplasma pneumoniae occasionally may cause pharyngitis, and can be isolated from nasopharyngeal aspirates or swabs, when specifically requested. The same specimens may also be the most easily collected sample for detection of *Chlamydia pneumoniae*, an important consideration in patients with chronic pharyngitis¹⁹; however, this organism can be difficult to grow in many laboratories, and newer polymerase chain reaction (PCR)-based tests will offer improved detection in the near future.^{30, 49, 61} As noted earlier, a number of viral infections can result in exudative pharyngitis, including rhinoviruses, adenoviruses, respiratory syncytial virus (RSV), influenza and parainfluenza viruses, coronavirus, coxsackieviruses, CMV, and EBV. These are generally not sought in routine diagnostic testing, but when detection is needed, nasopharyngeal washings or tracheal secretions are the specimens of choice for these cultures. Multiplex PCR assays may soon offer the ability to rapidly and reliably detect them.²³ A current exception is the need for diagnosis of EBV or CMV mononucleosis. This is most readily accomplished by use

of serologic testing for the presence of heterophile antibodies ("Mono-spot" test) to diagnose acute EBV infection, or detection of IgM antibody directed against CMV for diagnosis of CMV mononucleosis.⁵ Use of accurate, rapid diagnostic tools can limit empiric antimicrobial agent therapy for pharyngitis and help reduce unnecessary use of these agents.²³

Another rare but important oral infection presentation is oral hairy leukoplakia in persons infected with HIV.^{42, 68} This infection is best diagnosed by in situ hybridization for EBV from suspected lesions. Therapy is difficult and most responsive to control of the underlying disease.

Epiglottitis

Oral infection with *H. influenzae* can cause epiglottitis, leading to airway obstruction if not treated. The effects of combined oral cavity anaerobic flora may cause an exudative, gangrenous pharyngitis (Vincent's angina) with a membrane-type lesion that can mimic diphtheria and also occasionally lead to airway compromise. This may occur alone or in connection with a serious necrotizing ulcerative gingivitis (Vincent's gingivitis, or trench mouth) that is similar in pathogenesis to the pharyngitis bearing the same name. Although this is now a rare disease, it has occurred with increasing frequency in patients infected with HIV^{28, 67}; however, the foul odor noted in patients with Vincent's diseases may be useful in separating them from infection due to *H. influenzae*. Evidence suggests that *Fusobacterium necrophorum* is an important causative agent, but that other anaerobes are involved in this typically mixed infection.

Peritonsillar Abscess

The predominant organisms in peritonsillar abscess are nonspore-forming anaerobes, including *Fusobacterium* spp (especially *F. necrophorum*), various *Bacteroides* spp (including the *B. fragilis* group), *Prevotella* and *Porphyromonas* spp, and anaerobic cocci. *Streptococcus pyogenes* and viridans streptococci may also be involved. Culture is helpful in the case of peritonsillar abscess, such as those that frequently accompany Vincent's angina, as specific antimicrobial agent therapy appears beneficial.⁶⁸ Here, pus from the drained abscess should be sent to the laboratory for aerobic and anaerobic culture, with susceptibility testing done on isolated pathogens.

Infection in Immunosuppression

Immunosuppressed patients, including very young babies, may develop oral candidiasis, or thrush. Thrush can progress to produce esoph-

Table 1. LABORATORY DETECTION OF ORAL MICROBIAL PATHOGENS

Oral Infection Syndrome	Microbial Pathogens	Comments
Streptococcal pharyngitis Non-streptococcal pharyngitis	<i>S. pyogenes</i> (GABHS) <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , rhinoviruses, adenoviruses, respiratory syncytial virus (RSV), influenza and parainfluenza viruses, coronavirus, coxsackieviruses, CMV, EBV, <i>Bordetella</i> <i>diphtheriae</i> , <i>Neisseria gonorrhoeae</i>	Routine microbiology culture Contact the laboratory to ensure proper collection and culture materials are available. Tests for viral pharyngitis (other than EBV or CMV serology) are not usually performed. Some PCR assays are available for special diagnostic use. <i>C. diphtheriae</i> is enhanced by culturing both throat and nasopharynx, and special processing in the laboratory is required. PCR is recommended for <i>B. pertussis</i> . For culture of <i>B. pertussis</i> , inoculation of fresh media at the patient's bedside is optimal. <i>N. gonorrhoeae</i> is a routine test using special media. Culture is usually not performed, although pathogens can be recovered from a pharyngeal scraping or swab
With immune compromise	<i>Enterobacteriaceae</i> , <i>S. aureus</i> , or <i>Candida</i> sp	Routine microbiology culture Culture not usually helpful
Epiglottitis Vincent's angina and gingivitis	<i>Haemophilus influenzae</i> <i>Fusobacterium necrophorum</i> plus other mixed anaerobes (including <i>Bacteroides</i> sp)	For abscess, culture purulent scraping aerobically and anaerobically
With peritonsillar abscess	<i>Candida albicans</i> and other yeast	Scraping of exudate for fungal culture and smear Culture or DFA of scraping from the lesion for virus Culture not usually helpful
Thrush	HSV	Routine microbiology culture
Infectious stomatitis	Mixed oral flora	Routine microbiology culture
Purulent nasopharyngitis	<i>Klebsiella rhinoscleromatis</i>	Routine microbiology culture
Rhinoscleroma	<i>Klebsiella ozaena</i>	Routine microbiology culture
Ozaena		

Periodontitis	<i>Porphyromonas gingivalis</i> , <i>Bacteroides forsythus</i> , <i>Treponema denticola</i> , <i>Prevotella intermedia</i> , <i>Peptostreptococcus micros</i> , <i>Actinobacillus</i> <i>actinomycetemcomitans</i> , <i>Wolinella recta</i> , <i>Eikenella corrodens</i> , other spirochetes	Scraping of plaque shows numerous spirochetes. When antimicrobial therapy is considered for extensive disease, culture and susceptibility testing of subgingival plaque may be warranted.
Dental infections, including periapical abscess and osteomyelitis	<i>Peptostreptococcus</i> sp, <i>Veillonella</i> sp, <i>B. fragilis</i> group, <i>Prevotella</i> and <i>Porphyromonas</i> sp, and <i>Fusobacterium</i> sp	Routine anaerobic microbiology culture on abscess material
Actinomycosis, or "lumpy jaw"	<i>Actinomyces israelii</i>	Notify laboratory that condition suspected for optimal testing
Sialadenitis	<i>S. aureus</i>	Routine microbiology culture
Parotitis	Mumps virus, influenza virus, enteroviruses, <i>M. tuberculosis</i>	Viral culture and serology, or culture for <i>M.</i> <i>tuberculosis</i>
Acute sinusitis	<i>H. influenzae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>M. catarrhalis</i> , <i>P. acnes</i> , rhinovirus, influenza virus, and parainfluenza virus	Routine microbiology culture on purulent sinus material
Chronic sinusitis	Mixed oral flora anaerobes, <i>M. catarrhalis</i>	Routine microbiology culture on purulent sinus material
Deep space infections	<i>S. pyogenes</i> , <i>S. aureus</i> , <i>Peptostreptococcus</i> sp, <i>Bacteroides</i> , <i>Prevotella</i> , <i>Porphyromonas</i> sp, <i>Fusobacterium</i> sp, <i>Actinomyces israelii</i> , and viridans group streptococci	Routine microbiology culture on aspirated purulent material
Bacterial tracheitis	<i>S. aureus</i> and streptococci	Routine microbiology culture on aspirated purulent material

agitis, a common complication in AIDS and other immunosuppressed patients. Pharyngitis in the granulocytopenic patient may be associated with numerous unexpected microbes, including Enterobacteriaceae and *S. aureus*, as well as *Candida* spp. It is manifested by erythema and sore throat, and occasionally exudate. Additionally, in the current era of major advances in cancer treatment and transplantation, a new infectious complication of the oral cavity has emerged: mucositis. Recent work suggests that gram-negative bacilli colonizing or infecting the oral cavity play an important role in the severe forms of mucositis.⁶⁰ It is now added to the list of differential diagnoses in the febrile neutropenic patient. Other unusual oral flora microbes are associated with fever and bacteremia in the immunocompromised patient with mucositis. One of those recently recognized is bacteremia from *Capnocytophaga* spp.³⁷ Infection with herpes simplex virus (HSV) can cause painful lesions in the mouth and the oropharynx (stomatitis), another condition that is also prevalent among immunosuppressed patients, including those with HIV infection. Interestingly, stomatitis is a common manifestation of primary HSV infection for young children, and has even been reported as an employment-related infection for healthcare workers.² Oral hairy leukoplakia, as noted earlier, is increasingly seen as an EBV-related infection that is associated with HIV, manifesting itself as a lesion in the oral cavity.^{42, 68}

Vincent's angina is considered a necrotizing anaerobic tonsillitis with pseudomembrane formation on tonsillar surfaces. This infection is relatively rare today, but it is very serious when seen in immune deficiency because of complications including septic thrombophlebitis, bacteremia, and metastatic infection. Multiple anaerobes, especially *F. necrophorum*, are implicated in this syndrome. In a related infection, acute necrotizing ulcerative gingivitis (Vincent's gingivitis), a large spirochete seems to be a key pathogen; however, clinical microbiology laboratories are not asked to do cultural studies for diagnosis of this latter condition. A Gram stain of the lesion is often helpful if a high percentage of spirochetal forms are recognized.

Nasopharyngitis

In children, inflammatory involvement of the nasal passages frequently occurs with acute pharyngitis. This infection, purulent nasopharyngitis, is due to a mixture of aerobic and anaerobic organisms, consistent with the flora of the oral cavity.⁷ A rare form of chronic granulomatous infections of the nasal passages, encompassing the sinuses and occasionally the pharynx and larynx, is rhinoscleroma. Associated with *Klebsiella pneumoniae* subsp. *rhinoscleromatis*, the disease is characterized by nasal obstruction developing over a prolonged period, appearing as a tumor-like growth with local extension. Another gram-negative rod species, *K. ozaenae*, can also be recovered from upper respiratory tract infections. This organism may contribute to the infre-

quent condition, ozaena, characterized by a chronic, mucopurulent nasal discharge (often foul smelling) thought to be caused by a secondary mixed anaerobic infection.

Tooth-Associated Infection

Dental problems may stimulate requests for microbiologic assessment, with the most common being root canal infections, with or without periapical abscess, followed by orofacial odontogenic infections, with or without osteomyelitis of the jaw, and perimandibular space infections. The bacteriology is similar in all of these situations, involving primarily anaerobic bacteria and streptococci.^{9,54} A possible exception is perimandibular space infections that may also involve staphylococci and *Eikenella corrodens* in a relatively high percentage (15%) of patients. The streptococci are microaerophilic or facultative in growth requirements, and usually α -hemolytic. These are implicated in up to 30% of cases that are associated with a preceding dental infection. The *B. fragilis* group organisms are found in root canal infections, orofacial odontogenic infections, and bacteremia secondary to dental extraction in 5% to 10% of patients. Anaerobic cocci (both *Peptostreptococcus* and *Veillonella*), pigmented *Prevotella* and *Porphyromonas*, the *Prevotella oralis* group, and *Fusobacterium* spp are found in about 20% to 50% of these conditions. Oral bacteria are clearly important in other dental processes, such as caries and periodontitis, but clinical laboratories are not traditionally involved in culturing in such cases. Typically, periodontal infections have been managed by mechanical cleansing and empiric therapy. A better understanding of the pathogenesis of this disease process is leading to a greater recognition of the role of bacterial originating agents and the modifying role of host defenses.²¹ When periodontal disease develops, it appears that the local microflora are able to penetrate the gingival epithelium and bring about an inflammatory response. This inflammation significantly contributes to the subsequent destruction of the periodontium. Another recent report suggests that a direct smear of plaque taken from the subgingival area (showing numerous spirochetes), and even culture with susceptibility testing may be useful for a specific diagnosis and antimicrobial therapy.⁴⁰ Such an approach to specifically target the microbial plaque is consistent with the most recent understanding of disease pathogenesis. The common microbial species for this infection are given in Table 1. This new approach is advocated based upon the evidence that specific therapy of anaerobic infection can be important for improved healing and a reduced need for surgery in the management of periodontal disease.⁴⁰

Actinomycosis

Infection with *Actinomyces israelii* may complicate any intraoral surgery or trauma. This organism is part of the usual oral flora, and

therefore is not acquired from external sources. Infections usually present as an indolent swelling, abscess, or mass lesion.³⁶ When this organism is suspected, the laboratory should be notified, as it may be missed as part of an otherwise mixed infection unless the microbiology technologists are alerted to look specifically for this anaerobe. Submit pus with grains of "sulfur granules" in an anaerobic transport media for the highest recovery of this pathogen.

Suppurative Parotitis

Acute suppurative parotitis (sialadenitis) is seen in very ill patients, especially those that are dehydrated, malnourished, elderly, or recovering from surgery.⁵¹ It is associated with painful, tender swelling of the parotid gland. Purulent drainage may be evident at the opening of the duct of the gland in the mouth. *S. aureus* is the major pathogen, but on occasion viridans streptococci and oral anaerobes may play a role. A chronic bacterial parotitis has been described that also commonly involves *S. aureus*. Less often, other salivary glands may be involved with a bacterial infection, usually also because of ductal obstruction. The mumps virus is traditionally the major viral agent involved in parotitis; however, with prevalent childhood vaccination, infection with mumps virus is now rarely found. Influenza virus and enteroviruses occasionally cause parotitis. Diagnosis of viral infection is usually done serologically. Infrequently, *Mycobacterium tuberculosis* may involve the parotid gland in conjunction with pulmonary tuberculosis.

Acute Bacterial Sinusitis

Symptomatic acute sinusitis caused by bacterial infection usually develops during the course of a viral "cold."²⁴ When bacterial sinusitis develops, the infection typically is caused by the microbial flora of the oral cavity, from bacteria being trapped in the sinus cavity owing to inflammation and swelling of the ostiomeatal area mucosa from a viral infection, thus occluding normal drainage, or much less frequently (5% to 10%) by direct extension from a dental source of infection. Sinusitis tends to be self-limited, usually lasting 1 to 3 weeks, but is important because it affects approximately 2 million Americans each year. It not only results in direct morbidity and visits to physicians, but bacterial sinusitis is the most commonly recognized cause of subdural empyema, responsible for 56% of cases in a recent series.¹⁵ Other complications include local extension into the orbit and other bones of the skull, and development of chronic sinusitis. Most studies of the microbiology of acute sinusitis have dealt with maxillary infection because it is the most common type and the only one accessible for puncture and aspiration.⁶³ Bacterial cultures should be positive in nearly three fourths of patients with acute sinusitis. In a study involving young adults, *H. influenzae* was

recovered from 50% and *S. pneumoniae* from 19% of patients. *Streptococcus pyogenes* and *M. catarrhalis* were also found, in addition to normal skin flora such as *Propionibacterium acnes*. Anaerobes were considered pathogens in only 2% of cases of acute sinusitis. Among children, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* appear most common.^{33, 58} Rhinovirus can be found in 15% of patients, influenza virus in 5%, parainfluenza virus in 3%, and adenovirus in less than 1%.

An important clinical aspect is the differentiation between bacterial sinusitis and a viral upper respiratory tract infection, as only bacterial sinusitis will respond to antibiotic therapy. Clinical signs strongly suggesting bacterial infection include symptoms for more than 7 days, sinus pain, postnasal drainage, and a history of prior sinusitis.²⁹ Persistence of symptoms beyond 7 days may be the most important differentiating factor, especially for the consideration of bacterial sinusitis in children.¹¹ Presence of findings such as an abnormal lung exam, sore throat, and cough make the diagnosis of an upper respiratory tract infection other than bacterial sinusitis much more likely, and thus not likely to respond to antimicrobial agent therapy.²⁹

Other types of microbes, particularly anaerobes and fungi, are more frequently involved in chronic sinusitis in adults. Interestingly, a report by Tinkelman and Silk⁵⁸ has shown *M. catarrhalis* to be more associated with chronic sinusitis in children.

Neck Infections

Infections of the deep spaces of the neck are potentially serious because they may spread to critical structures, such as major vessels of the neck or to the mediastinum, leading to thrombosis, mediastinitis, purulent pericarditis, and pleural empyema.¹³ One of these infections, classically called Ludwig's angina, often occurs in the floor of the mouth as a bilateral brawny swelling of the sublingual and submandibular spaces, often following tooth extraction, which can lead to airway obstruction when not treated.⁶⁶ Another neck infection is peritonsillar abscess caused by mixed infection, of which GABHS and *S. aureus* seem to play important roles.¹⁰ Lateral and retropharyngeal abscess involves vital structures extending into the neck that may be life-threatening.⁶⁶ This infection is highly associated with anaerobes, often outnumbering aerobic bacteria 3:1, with an average of more than 7 bacterial species in the abscess material.^{8, 10} Perimandibular infection leading to suppuration in the lateral pharyngeal space caused by *F. nucleatum* frequently leads to sepsis and jugular vein thrombophlebitis (Lemierre's syndrome).⁵⁵ Accurate microbiologic diagnosis is difficult unless purulent material free of contaminating mouth flora can be obtained by needle aspiration or surgery and sent to the laboratory for both aerobic and anaerobic culture. As expected, the oral flora is responsible for many of these locally invasive infections. Accordingly, the predominant organisms are anaerobes, primarily represented by *Peptostreptococcus*; various *Bacteroi-*

des, *Prevotella*, *Porphyromonas*, *Fusobacterium*, and *Actinomyces* spp. Streptococci, chiefly of the viridans variety, also are important. When this infection develops in a hospitalized patient, *S. aureus* and various aerobic gram-negative bacilli are more likely the responsible pathogens.

Tracheitis

The airway infection bacterial tracheitis presents as unresponsive croup in children. It is a community-acquired infectious disease primarily due to *S. aureus* and streptococci that is recognized by the recovery of copious amounts of mucopus on tracheal suctioning from a child with croup that is unresponsive to usual therapy. The suctioned material shows the organism on Gram's stain and in culture.^{32, 39}

Specimen Acquisition

Regarding specimen collection, the main problem in obtaining oral or dental infection material is to avoid, or at least minimize, contamination with oral flora that is always present in abundance. To properly diagnose oral infections, either collecting purulent material from a biopsy or needle aspiration (preferred when possible) or material on swabs designed for transport of microbial cultures should be obtained. For collection of material from an intraoral abscess such as a root canal infection, the tooth can be isolated by means of a rubber dam. A sterile field is established, and the area is swabbed with disinfectant. The specimen is obtained and placed into nonnutritive anaerobic transport medium. Alternatively, needle aspiration can be used if sufficient purulent material is present. Completely defining the flora of many such infections is beyond the scope of routine clinical microbiology laboratories. Specimens from neck space infections usually are obtained with a syringe and needle or by biopsy during an operative procedure. Transport must be under anaerobic conditions, as so many of these infections are due to anaerobes. Any swab, even those with calcium alginate-tips, can be toxic to some organisms. Even for aerobic bacteria, if transport is to be prolonged beyond 4 hours, some type of transport medium for the swab must be used to maintain viability. Because the oral cavity contains an abundant microbial flora, special testing procedures are often required. Table 1 reviews the major oral cavity infection syndromes, the pathogens responsible, and suggestions for optimal microbial detection. Routine culture swabs are adequate for recovery of adenoviruses and herpesviruses, and most bacteria and yeasts including *C. diphtheriae*, *Mycoplasma*, *Candida* spp, and *Haemophilus* spp; however, many of these pathogens require special processing, and thus, prior laboratory notification before specimen collection is highly recommended for optimal microbial detection. Nasopharyngeal swabs are better suited for recovery of respiratory syncytial virus, parainfluenza

virus, *Bordetella pertussis*, *Neisseria* spp, and the viruses causing rhinitis.²² Modified Stuart's transport medium, as is often used in commercially produced swab systems, will preserve most viruses for a short time; however, nasopharyngeal swabs should ideally be transported in specially designed broth or other protein-containing fluid if they are not being cultured within a few hours. Recovery of *C. diphtheriae* is enhanced by culturing both throat and nasopharynx. Here, too, appropriate transport media should be used to preserve the microbe's viability. Aspirated nasopharyngeal secretions collected in a soft rubber bulb are the best specimens for *B. pertussis*. If this is impossible, transport for less than 2 hours in 1% casamino acid medium is acceptable.^{26, 31}

Specimen Processing

In the laboratory, a Gram's stain of material obtained from the oral cavity has a limited benefit in establishing a diagnosis of most superficial infections, such as pharyngitis. A few exceptions are that yeast-like cells can be identified, helpful in identifying thrush, and the characteristic pattern of fusiforms and spirochetes of Vincent's angina or gingivitis may be seen. Plain Gram's crystal violet can be used to identify the agents of Vincent's infection. Direct smears of exudate from membrane-like lesions, used to differentiate diphtheria from other causes of such membranes, are unreliable and not recommended. Fungal elements, including yeast cells and pseudohyphae, may be visualized with a 10% potassium hydroxide (KOH) preparation, with calcofluor white fluorescent stain, or with a periodic acid-Schiff stained slide. Direct examination of material obtained from the nasopharynx of suspected cases of whooping cough using a direct fluorescent antibody (DFA) stain has had some useful application, although PCR analysis is the most sensitive and specific test. DFA smears are also commercially available for detection of herpes simplex virus, influenza virus (rarely used), adenovirus, parainfluenza virus, and respiratory syncytial virus.^{27, 43} Particularly for RSV, DFA analysis has been shown to be superior to culture or enzyme immunologic assay methods when performed by an experienced laboratory technologist.

For pharyngitis, classically a throat swab is plated onto 5% sheep blood agar. This is done because sheep blood does not support growth of potentially confusing β -hemolytic bacteria like *Haemophilus haemolyticus* and *H. parahaemolyticus*. The use of a sheep blood agar plate for isolation of *S. pyogenes* needs overnight growth for adequate colony formation and then further manipulations of any β -hemolytic growth for definitive identification. If sufficient numbers of pure colonies are not available on the primary culture plate, a subculture requiring additional growing time is necessary. New selection agars have been developed that suppress the growth of almost all normal flora and β -hemolytic streptococci except for groups A and B, and *Arcanobacterium haemolyticum*.⁶² By placing a 0.04 unit differential bacitracin filter paper disk

directly on the area of initial inoculation, presumptive identification of *S. pyogenes* can be made after overnight incubation if heavy growth occurs. A probe test was released for commercial use in 1992 (Gen-Probe, Inc., San Diego, CA) that provides highly sensitive and specific results following a 4-hour incubation step in selective media. The cost of this genetic-based test is its primary drawback. Also, with the probe-based tests there is no organism recovered. Although not currently routine, susceptibility testing of a recovered *S. pyogenes* is likely to become more important in the future, as several areas are now recognizing increasing resistance to erythromycin in this important pathogen.

Cultures for *C. diphtheriae* should be plated onto sheep blood agar and onto special media for recovery of the agent, when diphtheria is suspected, as streptococcal pharyngitis is, in the differential diagnosis of diphtheria. The current detection method of choice for *B. pertussis* and *B. parapertussis* is PCR.³⁸ These assays are now both sensitive and specific. Culture is often difficult. To grow this organism, freshly prepared Bordet-Gengou agar is the medium of choice for isolation of *B. pertussis*, and therefore, prior notification of the laboratory is needed when a suspected case of either diphtheria or pertussis occurs, as they would not be recovered on routine media available in most US microbiology laboratories.⁴ Interestingly, a modified medium designed for isolation of *Legionella* spp, buffered charcoal yeast extract agar with 3 µg/mL lincomycin and 80 µg/mL anisomycin, has been shown to yield good recovery of *B. pertussis*. Jones and Kendrick³¹ have also reported excellent recovery on a blood-free medium containing charcoal, heart infusion base, 2% agar, and 0.3 U/mL penicillin. The charcoal medium developed for *Legionella* spp is more readily available and is thus a useful substitute for many clinical laboratories. Specimens should be plated directly onto media, if possible, because the organisms are extremely delicate. The yield of positive isolations from clinical cases of pertussis varies from 20% to 98%, depending on the stage of disease and laboratory techniques used.

Specimens received in the laboratory for isolation of *N. meningitidis* (for detection of carriers) or for *N. gonorrhoeae* should be plated to a selective medium, such as Thayer-Martin agar. The anaerobes involved that typically originate in the oral cavity and are often more delicate than anaerobes isolated from other clinical material; therefore, very careful attention must be paid to providing optimal techniques of anaerobic cultivation by the laboratory.¹⁶

For infections where purulent material is actually submitted, it should always be smeared and examined directly by Gram-stained smears or other appropriate techniques, and then cultured. Material aspirated from the maxillary sinus, from neck space infections, and from jaw infections should be examined directly for bacteria and fungi.

Optimal results from diagnostic tests are always dependent on the quality of the specimen obtained. This has been recently reviewed in detail by Thomson et al,⁵⁷ and specific information relating to collection,

transport, and processing of specimens for the laboratory diagnosis of a wide variety of infectious diseases are covered in that review.

DISTANT INFECTIONS FROM THE ORAL CAVITY MICROBIAL FLORA

Although not specifically part of the diagnostic techniques needed for determining the microbiologic origin of intraoral infections, it is important to realize that the pathophysiology of infectious diseases distant from the mouth still involves microbes whose origin is the oral cavity. Long ago, it was recognized that infectious endocarditis was associated with pathogenic bacteria that are often part of the normal flora of the human mouth.⁵³ Detection of bacteremia, including that associated with endocarditis, requires appropriate culture of blood. Published standards exist for optimal blood culture practices in adults. These indicate that 2 to 3 sets in a 24-hour period, each consisting of 20 to 30 mL (for a total of 60 mL), maximizes detection of bacteria in the blood stream.^{3, 12, 65} A recent review also found that oral infection can result in distant infection at several unexpected sites.⁴⁸ Not only did the authors find expected infections, such as brain abscess, osteomyelitis, and mediastinal abscess due to *Bacteroides* spp, *Fusobacterium* spp, streptococci, and *Peptostreptococcus* spp, but also hepatobiliary infection from *Actinomyces* spp, *Fusobacterium* spp, and oral streptococci.⁴⁸ In patients with solid tumors or leukemia, when fever develops in the presence of granulocytopenia (<100 granulocytes/mm³), oral lesions are present in a majority of the patients (>70%), and often this is the only source site of potential bacteremia recognized.⁴⁵ During and after immunosuppression, the microbial flora in the mouth can harbor such diverse pathogens as *C. albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *HSV*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *H. influenzae*, *Acinetobacter* spp, *S. aureus*, *S. epidermidis*, and *Streptococcus pneumoniae*. Thus, bacteremia and fungemia arising from the oral cavity can be very diverse and challenging.

SUMMARY

Our knowledge regarding the pathogenesis of infections relative to the oral cavity is rapidly expanding, similar to our overall understanding of how infectious diseases impact our daily lives. The complexity of the flora within the oral cavity is quite unique and often makes diagnosis difficult; however, it is becoming more apparent that accurate diagnostic testing is important from the standpoint of focusing appropriate therapy on pathogens within this crucial body site, and avoiding overuse of antimicrobial agents in settings of infection where they have no demonstrated benefit. New diagnostic methods are being developed to detect pathogens and rapidly delineate resistance patterns. Many will be based

on new genetic assays, but they must be cost effective, sensitive, and specific.¹⁴ Another growing challenge is to provide adequate lab support to outpatient offices and clinics, without compromising the specimen culture or turnaround times. So many patients are being seen away from hospital laboratories that we need ways to diagnose sinusitis, pharyngitis, abscess, and other infections of the oral cavity without killing the anaerobes and other significant facultative bacteria, and without ruining the direct stains by overgrowth or inflammatory cell degradation during specimen transport. These results need to be available quickly enough to give useful information for office diagnosis in order to effect therapy. To optimize both diagnosis and treatment, a key to the future will be better communication between the clinical practitioner and laboratory, with an increasing emphasis on training expertise in medical microbiology and infectious diseases.

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