12 | Non-Sexually Transmitted Infectious Diseases of the Oral, Nasal, and Vaginal Mucosae

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The skin and mucous membranes are the principal barriers to invasion of the body by microorganisms. Besides functioning as a mechanical barrier, the mucosae are endowed with an array of still poorly characterized specific and nonspecific host defense capabilities. These include the production of mucus, secretory immunoglobulin (IgA), lysozyme, lactoferrin, and alpha-antitrypsin, in conjunction with a low-grade exudation of leukocytes.[1] In addition, the mucosal surfaces of the upper respiratory, gastrointestinal, and lower vaginal and urinary tracts support a large number of "nonpathogenic" microorganisms that comprise the so-called "normal flora." This commensal flora plays an important and complex role in protecting the host from microbial invasion. Mechanisms for this protection likely include the following: (1) competition for the same nutrients (interference); (2) competition for the same receptors on host cells (tropism); (3) production of bacteriocins, that is, bacterial products that are toxic to other organisms, usually of the same species; and (4) stimulation of cross-protective immune factors such as the "natural antibodies."[1]

The "normal" flora is inconstant and may be altered by dietary factors, debilitation, hormonal events (such as menstruation, pregnancy, and possibly use of oral contraceptives), personal hygiene, medications, intercurrent infection, and probably many others. Antibiotic therapy and menstruation can have a profound effect on the composition of this group of microorganisms.[2] Disturbance of the delicate host–commensal relationship may cause a clinically significant infection due to these "nonpathogens." This may occur in response to the aforementioned factors (eg, pregnancy predisposing to vaginal candidiasis) or because of disruption of the anatomic barrier (eg, local mucosal infection at a site of trauma, or injury from cytotoxic drugs) or in association with exogenous infection (eg, rhinoviral infection leading to secondary bacterial otitis media). Invasion by "normal flora" may result in serious systemic illness. A clear example of the latter is the development of infective endocarditis caused by viridans streptococci following a dental procedure.

TABLE 1. Non-sexually Transmitted Infectious Diseases Of the Oral Mucosa

Viral	Bacterial	Fungal	Parasitic
Organisms That May Cause Prominent Pharyngeal Signs and Symptoms Usually With Minimal Or No Systemic Component			
Adenovirus[3]	*Actinomyces* species	*Aspergillus* species	—
Coronavirus[4]	Anaerobic species (mixed)[14]	*Candida* species (thrush)	
Coxsackie A[5-7]	(Vincent's angina or	Mucormycosis	
(Herpangina)	stomatitis)		
(Hand-foot-and-mouth-	(Noma)		
disease)	*Bacillus anthracis*		
Herpes simplex[8]	*Corynebacterium diphtheriae*[15]		
Influenza viruses[9]	*Corynebacterium hemolyti-*		
Molluscum contagiosum	*cium*[16]		
Parainfluenza viruses[10]	*Corynebacterium ulcerans*[17]		
Respiratory syncytial	*Francisella tularensis*[18]		
virus[11]	*Hemophilus influenzae*[19]		
Rhinoviruses[12,13]	*Mycoplasma pneumoniae*[20]		
	Streptococcus pyogenes		
	(GpA)[21]		
	Streptococcal species (Gp's		
	C,G)[22]		
	Yersinia enterocolitica[23]		
Organisms That Cause Systemic Disease Which May Have Prominent Pharyngeal Signs and Symptoms			
Cytomegalovirus	*Brucella* species[25]	*Coccidioides immitis*	*Leishmania*
Epstein-Barr[24]	*Listeria monocytogenes*[26]	*Cryptococcus neoformans*	species
(Infectious mononucle-	*Mycobacterium leprae*	*Blastomyces dermatitidis*	*Toxoplasma*
osis)	*Mycobacterium tuberculosis*	*Histoplasma capsulatum*	*gondii*
Lassa fever virus	*Neisseria meningitidis*	*Paracoccidioides*	
Rubella	*Coxiella burnetii*[27]	*brasiliensis*	
Rubeola	*Staphylococcus aureus*		
Varicella-zoster			

The majority of all human pathogens enter the body through a mucosal surface, at which point they may or may not cause local disease. Whether or not local mucosal infection is established on entry, the mucosae may still be affected secondarily as part of the systemic disease process. Consequently, it is far too ambitious a task to describe in detail every infection known to involve the mucosae, even excluding the sexually transmitted ones.

What must be considered an incomplete tabulation of those non-sexually transmitted infectious diseases with manifestations in the oral, nasal, or vaginal mucous membranes is given in Tables 1, 2, and 3.[3-27]

Instead, the focus of this chapter is to review the clinical features of an important and com-mon syndrome, pharyngitis, with particular reference to newer concepts regarding the relationship of this entity to that of the "normal flora."

Pharyngitis

Respiratory infections are the leading cause of acute illness in the United States, and sore throat is the third most common symptom seen in medical practice.[28,29] Despite years of experience with this condition, its management is far from a settled or secure issue, and questions being raised today are not the same as those in prior years.[21]

The most important bacterial cause of sore throat is the Group A streptococcus, also known

TABLE 2. Non-sexually Transmitted Infectious Diseases that May Involve the Nasal Mucosa

Viral	Bacterial	Fungal	Parasitic
Adenovirus[3]	*Klebsiella ozaenae* (Ozaena)	*Aspergillus* species	*Leishmania*
Coronavirus[4]	*Klebsiella rhinoscleromatis*	Mucormycosis	species
Enteroviruses	(Rhinoscleroma)	*Rhinosporidium seeberi*	
Influenza viruses[9]	*Mycobacterium leprae*		
Parainfluenza viruses[10]	*Mycobacterium tuberculosis*		
Respiratory syncytial	*Streptococcus pyogenes*[21]		
virus[11]	*Staphylococcus aureus*		
Rhinoviruses[12,13]	(Furunculosis)		
Rubella			
Rubeola			
Varicella-zoster			

as *Streptococcus pyogenes*. Other strains of beta-hemolytic streptococci, such as Groups C and G, occasionally produce an identical clinical picture but without the risk of such serious sequelae as rheumatic fever or glomerulonephritis. Other bacterial pathogens that may on occasion mimic streptococcal pharyngitis, such as *Corynebacterium diphtheriae*,[15] *C. hemolyticum*,[16] *C. ulcerans*,[17] *Franciscella tularensis*,[18] *Hemophilus influenzae*,[19] *Brucella* species,[25] *Listeria monocytogenes*,[26] *Coxiella burnetii*,[27] and *Yersinia enterocolitica*,[23] are much less common and usually occur in special epidemiologic settings; they are rarely important considerations in the usual patient with sore throat. The same can be said of pharyngeal involvement with such sexually transmitted pathogens as *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.[30]

Group A streptococci cause only 15–30% of all sore throats and about half of those with tonsillar exudates. Somewhat higher figures are

reported during epidemic periods, and somewhat lower percentages are found in young infants with pharyngitis.

Streptococcal sore throat occurs most often in patients between the ages of 5 and 15 years, and in temperate climates the highest incidence of illness occurs in the colder months. Transmission of disease is usually by person-to-person spread of respiratory droplets, although epidemics of streptococcal pharyngitis (both Groups A and G) have been traced to contaminated food or water.[22]

The usual incubation period is 2–5 days with a range of 1–10 days. Illness typically begins abruptly, with fever, chills, headache, and sore throat. Clinical manifestations, however, may vary greatly in severity from patient to patient. The most severe forms of tonsillopharyngitis are seen in epidemics occurring in closed institutional settings (eg, military barracks).

Abdominal pain, nausea, vomiting, and coryzal symptoms are more often present in

TABLE 3. Non-sexually Transmitted Infectious Diseases of the Vagina

Viral	Bacterial	Fungal	Parasitic
Herpes simplex I	*Actinomycetes*	*Candida* species	*Enterobius ver-*
(Autoinoculation from	? *Hemophilus influenzae*		*micularis*
oral lesion in children)	*Gardnerella vaginalis* ("Bac-		(Pinworm)
	terial vaginosis"; "Nonspec-		*Schistosoma*
	ific vaginitis")		species
	Mycobacterium tuberculosis		
	Shigella species		
	Salmonella species		
	Streptococcus pyogenes		
	Staphylococcus aureus		

children than adults. Cough or hoarseness is not typically seen in streptococcal pharyngitis and suggests a viral etiology.

About 15-20% of asymptomatic school children carry Group A streptococci in their throats in winter months, as do 20-60% of asymptomatic family contacts of index cases. Thus, the majority of individuals who harbor this organism have no complaints whatsoever. Many of these individuals appear to be carriers; that is, this streptococal species behaves as a commensal, does not elicit an antibody response, and at least for a time blends into the "normal flora."[31]

Although many patients with streptococcal pharyngitis appear moderately ill, with tachycardia and fever of 101F or greater, others look well and may be afebrile. Erythema, edema, and lymphoid hyperplasia of the posterior pharynx will be present, and the uvula may be edematous. The tonsils are typically enlarged and may be covered with exudate. Petechial stippling is sometimes seen on the soft palate. Tender, anterior cervical node enlargement is common. Infants tend to have less localization of their disease to the lymphoid tissue of the faucial and posterior pharyngeal areas. Indeed, exudative pharyngitis in children less than 3 years of age is rarely due to streptococci.

The complications of streptococcal pharyngitis may be placed in two categories, suppurative and nonsuppurative. The suppurative ones include peritonsillar abscess, sinusitis, otitis media, retropharyngeal abscess, and, very rarely, brain abscess, meningitis, or septicemia. The nonsuppurative complications are acute rheumatic fever and glomerulonephritis.

Whether or not the use of antibiotics hastens clinical recovery, once a highly controversial issue, has now been resolved on the basis of several new studies as well as re-analysis of an older one. Use of appropriate antibiotics shortens the duration of illness by 24-48 hours if begun early.[32-37] In fact, it is so unlikely for fever to persist beyond the first 24 hours of treatment that another diagnosis or a suppurative complication should be considered when this occurs. Antibiotic therapy also prevents rheumatic fever, provided that the streptococcal organism can be eradicated from the pharynx. It is doubtful, however, that antibiotics prevent or attenuate acute glomerulonephritis, a complication that occurs more frequently after cutaneous streptococcal infection.

Studies in the past with intramuscular penicillin (benzathine penicillin G) had shown nearly uniform success in clearing S. pyogenes from the oral mucosa. Slightly lower cure rates were reported for oral penicillin preparations, probably because of poor compliance with the full 10-day course of therapy. Even a 7-day treatment course with oral penicillin has been shown to be significantly less effective than the 10-day regimen.[38]

Of concern, therefore, is the unfavorable bacteriologic response to penicillin therapy found in almost all recent studies. Regardless of the penicillin preparation, 20-40% of symptomatic patients have had positive post-treatment cultures.[38-41] Furthermore, retreatment was unsuccessful in 30-62% of patients. Resistance of the organism did not appear to explain this outcome, since the streptococcal organisms were extremely sensitive to the inhibitory effects of penicillin. On occasion, apparent failures are actually reinfections from close personal contacts or possibly even from pets who may harbor the organism.[42] However, this explanation was evaluated but considered unlikely in at least one study that involved a semiclosed population.[40]

A bacteriologic cure rate with penicillin of 80% or less is low in absolute terms. This figure is even more striking, however, when it is compared with the 71% spontaneous cure rate of streptococcal pharyngitis, observed in a study published in 1961, of symptomatic children in Chicago who were not treated with an antimicrobial.[43]

Role of the Normal Flora in Streptococcal Treatment Failures

Itzhak Brook has made an increasingly persuasive argument that the growing number of penicillin failures is due to the recent emergence of penicillin-resistant β-lactamase-producing microorganisms (ie, penicillin-destroying) in the "normal" mouth flora.[41] According

to this theory, β-lactamase-producing orga-
nisms, by inactivating penicillin, protect Group
A streptococci from the antibiotic. In addition
to *Staphylococcus aureus*, the oropharyngeal
cavity may normally harbor a number of other
aerobic and anaerobic organisms that have the
potential to produce β-lactamase. These orga-
nisms include various *Bacteroides* and *Hemo-
philus* species and *Branhamella catarrhalis*. In
studies of children with recurrent tonsillitis
who underwent tonsillectomy, Brook and Yo-
cum were able to correlate the presence of β-
lactamase activity measured directly in tonsil-
lar tissue with recovery of β-lactamase-produc-
ing flora from culture of the tonsils.[44] In a
subsequent clinical trial, 100 children with
acute Group A streptococcal tonsillitis were
treated with a 10-day course of an oral penicil-
lin.[41] Sixty-three of the children were bacterio-
logically cured, and 37 were considered treat-
ment failures. Prior to therapy, β-lactamase-
producing organisms were recovered from oral
cultures of 25% of the 63 children who were
cured compared with 68% of the 37 children for
whom treatment failed. Also β-lactamase pro-
ducing organisms were present in significantly
larger numbers in the nonresponders than in
the responders. Other data suggest that peni-
cillin treatment itself promotes the emergence
of a penicillin-destroying flora[45,46] and that
these resistant strains may be transferred to
household contacts.[46] Further evidence to sup-
port the role of β-lactamase-producing bacte-
ria in streptococcal treatment failures comes
from an experimental model in which a mixed
subcutaneous abscess containing both a penicil-
lin-susceptible Group A streptococcus and a
β-lactamase-positive strain of *Bacteroides* spe-
cies is produced in mice. In these studies, mice
treated with either clindamycin (active *in vitro*
against both isolates and not susceptible to β-
lactamase) or penicillin in combination with a
β-lactamase inhibitor (clavulanic acid) had a
greater reduction in abscess size and in total
number of streptococci recoverable on culture
than did untreated control animals or those
receiving penicillin alone.[47] Thus, it is reason-
able to suggest that greater cure rates in
patients with streptococcal pharyngitis might
be achieved by one of several therapeutic strate-

gies:

1. Use of an antimicrobial (with or without
   penicillin) which is not susceptible to β-
   lactamase.
2. Use of combined therapy with penicillin
   and a second drug that either inhibits β-
   lactamase directly, such as clavulanic
   acid, or which inhibits the bacteria that
   are responsible for β-lactamase produc-
   tion.

Consistent with this hypothesis, in compara-
tive studies using regimens similar to these
such as clindamycin alone,[48,49] an oral cepha-
losporin alone,[50,51] dicloxacillin alone,[52] or peni-
cillin plus rifampin,[53,54] cure rates were superior
to those with penicillin alone.

It is quite fortunate that despite documenta-
tion of increasing difficulties in eradicating
streptococci, and little convincing evidence for
a decrease in the frequency of streptococcal
pharyngitis, that the incidence of rheumatic
fever has not increased. On the contrary, rheu-
matic fever has all but vanished from suburban
America. One county in California reported
430,000 cases of streptococcal illness over an
11-year interval but only three cases of rheu-
matic fever.[55] Similarly, the incidence of acute
rheumatic fever among whites in suburban
and rural parts of Shelby County (Tennessee)
was only one case per 200,000 school children
annually over the 5-year period from 1977
through 1981.[56] Rheumatic fever rates are
somewhat higher in inner city areas of major
United States metropolitan centers and higher
yet among large segments of the developing
world in Asia, Africa, or South America.

It is difficult to define precisely the contribu-
tion of penicillin to the downward trend in
rheumatic fever incidence. Considerable evi-
dence exists, however, that antibiotic use may
not be the primary factor and that the principal
reason for the decline is actually a change in the
"rheumatogenicity" of prevalent streptococcal
strains.[57] In fact, the decrease in incidence of
rheumatic fever antedated the discovery of
penicillin and began even before the causative
relationship to Group A streptococci was known.
Older studies, done when rheumatic fever was
more common, indicate that about one third of
patients with rheumatic fever do not recall a

preceding respiratory tract infection and thus would not have received treatment for a streptococcal infection. If penicillin therapy were the only reason for the decline in incidence of rheumatic fever, one might anticipate that among newly diagnosed cases, the proportion who had an asymptomatic streptococcal pharyngitis and consequently did not receive penicillin would be higher. Instead, Land and Bisno[56] recently reported that of 41 patients with rheumatic fever diagnosed between 1977 and 1982, 31.7% denied a preceding upper respiratory infection or sore throat—a figure nearly identical to the 34% figure cited in a study published 13 years earlier.[58]

How important then is the lessened efficacy of penicillin preparations for streptococcal pharyngitis noted in recent studies? Clearly, inadequate bacteriologic responses have not been associated with a resurgence in rheumatic fever cases in this country, nor apparently with a rise in suppurative complications or a poorer *clinical* response during acute infection. Vigilance for such changes, rather than abandonment of penicillin as first-line therapy, seems the appropriate course of action at present.

Another concern in the management of patients with possible streptococcal pharyngitis is when to begin antibiotic treatment. Endemic cases cannot be diagnosed reliably on clinical grounds alone unless the characteristic rash of scarlet fever is present. A properly performed throat culture has been the diagnostic method of choice.[59] In 90% of patients, a single negative throat culture will suffice to exclude the diagnosis. In 10% of cases, a second throat culture is necessary to detect the organism, which, under this circumstance, is usually present in low numbers and possibly not etiologic for the pharyngitis.[60] The clinical dilemma has been whether or not to give antibiotics during the usual 24–48 hour period it takes to process throat cultures. Withholding antibiotics may significantly delay clinical recovery in patients shown to have streptococcal sore throat, whereas routinely starting them will expose a great many patients with viral infections (that should not be treated) to potential drug toxicities, including an alteration in mouth flora.

Fortunately, recent technologic advances may help to adjudicate this dilemma.

Group A streptococcal antigen detection systems based on agglutination reactions with specific extracted Group A cell-wall antigens are now offered as kits for practitioners.[61,62] Results can be available in as short a time as 15 minutes. The specificity of these systems is excellent, often over 98%, whereas the sensitivity is somewhat lower, 80–95%, when compared with standard culture. Use of Rayon throat swabs appears to give better results than do cotton ones.[63] Therefore, a practical approach to management is to base the decision to give or withhold treatment on the result of such an immediate diagnostic test, and to confirm the negative reactions by culture.[64]

Other Causes of Pharyngitis

Members of the mouth flora, usually what appears to be a mixture of anaerobic bacteria and spirochetes, are an uncommon cause of acute pharyngitis (Vincent's angina), sometimes complicated by tonsillar abscess formation. With this infection, a purulent exudate and a foul odor to the breath may be present. The lesion typically begins unilaterally but may spread to the other side of the pharynx or to the larynx. Regional lymphadenopathy and leukocytosis are common. Septicemia, specifically with the penicillin-sensitive anaerobe *Fusobacterium necrophorum*, can be a disastrous complication of this condition (Lemierre's disease), which may be associated with jugular vein septic thrombophlebitis and metastatic infection of the lung, joints, and other sites.[14] Peritonsillar abscess formation also occurs unilaterally and is associated with severe pain and dysphagia.

In one retrospective review of 12 patients who presented with peritonsillar abscess or cellulitis, throat cultures were negative for Group A streptococci in 11 (92%) prior to any treatment.[65] Cultures of the tonsillar pus obtained by needle aspiration also failed to grow Group A streptococci in seven of eight patients, and the one patient with a positive culture had had a prior negative throat culture. Thus, this unusual group of patients is liable to go un-

treated initially because of a negative throat culture. One can only speculate as to the number of such patients who may have been benefited inadvertently by the liberal and perhaps excessive use of penicillin for patients with exudative pharyngitis. The existence of such cases certainly argues against overly dogmatic recommendations on the "necessity" of withholding antibiotics, at least early on, in sick patients without streptococcal disease. More information is still needed on diagnosis and pathogenesis of this infection.

A related infection known as acute necrotizing ulcerative gingivitis (Vincent's disease, Vincent's stomatitis, or trench mouth) is caused by the same or similar microorganisms indigenous to the oral cavity. The typical patient experiences the sudden onset of gingival pain and has tender, bleeding gums, fetid breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a gray exudate, which is removable with gentle pressure. Involvement of the gingivae is usually patchy but may be more extensive or spread to the posterior pharynx (Vincent's angina—see above). If the ulceration is extensive, fever, cervical lymphadenopathy, and leukocytosis occur. Most patients are young adults with poor oral hygiene. Treatment includes local debridement and lavage with oxidizing agents, which usually brings prompt relief. Antibiotic therapy with penicillin or metronidazole is highly effective.[66]

Mycoplasma pneumoniae is another treatable cause of pharyngitis that has been incriminated etiologically in varying frequencies up to approximately 10% of cases.[20] The illness is relatively mild, although an exudate is sometimes seen. In the absence of concomitant myringitis or pneumonitis, however, it would likely go undiagnosed since mycoplasmal cultures are generally unavailable and routine antibody testing would be impractical. Erythromycin or tetracycline, not penicillin, is the drug of choice.

Viruses cause the majority of cases of pharyngitis in which some pathogen is identified, and may well be responsible for most of the other approximately 40% of cases without a

known cause.[67] Usually, the sore throat is mild and merely part of the overall symptom complex of the common cold. Rhinoviruses are the most frequently isolated viruses, but several other viruses can cause an identical clinical picture (Tables 1 and 2).[4,10-13] Sore throat is often a major complaint in patients with influenza but is rarely the only manifestation of the disease.[9] The clinical presentation of pharyngitis due to adenovirus may be quite severe with pharyngeal erythema and exudate, more closely mimicking streptococcal infections.[3] Distinguishing features of adenoviral infections include their occurrence in the summer and the presence of conjunctivitis, which occurs in one third to one half of patients. Conjunctivitis is unilateral in 75% of patients.

Pharyngitis associated with primary herpes simplex infection or that due to strains of coxsackievirus may be recognizable clinically. Both are characterized by the presence of vesicles and shallow ulcers. Primary herpes infection varies from asymptomatic to agonizingly severe. Vesicles and ulcers are often numerous and may occur anywhere in the mouth, sometimes with a concomitant gingivitis. Tender cervical adenopathy and fever are seen in the more ill patients.[8] Herpangina primarily affects children between the ages of 3 and 10 years, is usually caused by coxsackievirus A (types 1-10, 16, and 22) and less commonly by coxsackievirus B (types 1-5) or echoviruses (types 3, 6, 9, 16, 17, 25, and 30), and is characterized by two to six small vesicles typically confined to the posterior pharynx (soft palate, uvula, anterior tonsillar pillars).[5] In some cases, the presence of anorexia and abdominal pain mimic acute appendicitis. Gingivitis, prominent systemic toxicity, and cervical lymph node enlargement are not seen in herpangina. Hand-foot-and-mouth disease is also caused by coxsackievirus (usually type A-16 and less commonly A-5, A-7, A-9, A-10, B-2, and B-5). This illness occurs predominantly in children under 10 years of age and is associated with vesicles in the oral cavity. Unlike herpangina, however, in hand-foot-and-mouth disease, the oral lesions characteristically occur in the front of the mouth, especially on the inner aspects of the lip, the anterior buccal mucosa, and the tongue,

and in most cases, lesions are also found on the extremities. The skin lesions are tender and consist of papules and clear vesicles with a surrounding zone of erythema.[6,7]

Pharyngitis with tonsillar exudate persisting for 4 or more days with a negative throat culture for group A streptococci, or occurring in association with diffuse lymphadenopathy, splenomegaly or with many atypical lymphocytes on blood smear suggests the possibility of infectious mononucleosis (IM) (Epstein-Barr virus). Pharyngeal involvement occurs in over 80% of patients with IM, and tonsillar exudate and a palatal enanthem are each found in approximately one quarter of patients.[24] In most cases, the severity of the pharyngitis increases over several days, peaks around 5 days, and then slowly improves.[24,68] Inflammation of the pharynx may be severe and may pose one of the infrequent life-threatening complications of the disease. Both pharyngeal and laryngeal edema can occur along with massive tonsillar enlargement (anginose mononucleosis, see Fig. 1). Inspiratory stridor with significant airway obstruction secondary to lymphoid tissue hypertrophy is a medical emergency.

In the past, concurrent streptococcal pharyngitis was reported to occur in 30% of patients with IM.[69] More recent studies, however, have failed to confirm this association.[70-72] Prior studies also emphasized that the use of ampicillin is associated with the development of a macular-papular skin rash in up to 95% of patients with IM.[73,74] The pathogenesis of this phenomenon is unknown, but evidence exists that discounts an allergic basis.[75] Interestingly, patients appear to tolerate penicillin normally. In a more recent study from three community hospitals of 80 patients with IM who received ampicillin, only 10 (28%) developed a rash.[76] The reason for the discrepancy between this and prior studies is unknown.

Diagnosis of IM is established either by documentation of the presence of heterophile antibody, which is present in 90% of patients, or by demonstration of the characteristic antibody responses to specific Epstein-Barr viral antigens.

Management of patients with anginose mononucleosis is controversial. Various therapies have
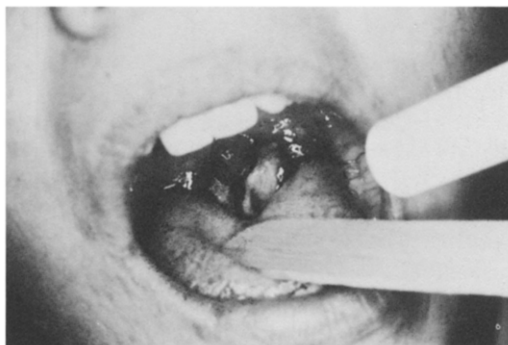

FIG. 1. "Kissing tonsils" seen in a patient with anginose infectious mononucleosis.

been promoted only to be later discarded. These include neoarsphenamine, gamma globulins, bismuth, chloroquine, and metronidazole. Differing opinions exist concerning the role of therapeutic or symptomatic intervention with corticosteroids. Seven prospective controlled studies with a total of 349 patients have been done to evaluate the effect of corticosteroids on the duration of sore throat and/or resolution of tonsillar enlargement.[77-82] Findings are conflicting. Further, anecdotal cases of patients with anginose IM have been reported for whom tracheostomy, placement of a temporary airway or emergency tonsillectomy was required despite the use of corticosteroid therapy. Therefore, the value of these medications in preventing airway obstruction in anginose IM has not been established by objective data in the published literature. Whether or not the immunosuppressive properties of corticosteroids may enhance the potential oncogenicity of the Epstein-Barr virus is unknown, but this consideration does warrant caution in their use.

Epstein-Barr virus has been shown to be susceptible *in vitro* to several antiviral agents including acyclovir,[83,84] adenine arabinoside,[85] leukocyte interferon,[86] and phosphonacetic acid,[87] and use of one or more of these drugs might seem a more logical and specific therapeutic approach. Andersson and colleagues[88] randomized 31 patients with IM who had symptoms for 7 or fewer days to treatment with intravenous acyclovir (30 mg/kg per day) or placebo for 7 days in a double-blind trial. Acyclovir significantly inhibited oropharyngeal viral shedding compared with placebo ($P < 0.001$);

however, there was no significant improvement in rate of recovery of sore throat or tonsillar swelling, and one patient in the acyclovir group required tracheotomy because of respiratory obstruction due to tonsillar enlargement. Therefore, to date, no therapy has been proved to be of clinical benefit to patients with anginose IM. Further studies are needed to determine if certain patients might benefit from the use of corticosteroids and/or specific antiviral drugs.

Recently, several investigators have reported a syndrome of prolonged atypical illness thought to be an Epstein-Barr-associated chronic mononucleosis syndrome.[89,91] Patients with this illness have had pharyngitis, chronic fatigue, low-grade fevers, lymphadenopathy, and other nonspecific symptoms in association with elevated antibody titers to certain Epstein-Barr viral antigens. The pathogenesis and treatment of this condition have not been elucidated.

Conclusion

Mucosal infections are common and extremely varied. As illustrated by the preceding discussion of non-sexually transmitted infections of the oral mucosa, it is clear that the pathogenesis of many of these infections is directly related to phenomena that affect the background ("normal") microbial flora. Depending on conditions, this flora may assume divergent roles for the host, ranging from protector, to commensal, to pathogen. Interactions between these organisms and those exogenous microbial species encountered by the host are undoubtedly complex but of immense interest to students of infectious diseases, and of potential practical importance in the day-to-day management of patients. Emerging evidence has also suggested that the normal flora may influence the success of antibiotic therapy for streptococcal pharyngitis, adding still another dimension to the complicated interrelationship between these organisms and mucosal disease.

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