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Viral Pharyngitis

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Review articles on the topic of pharyngitis usually focus on the importance of not missing the diagnosis of group A beta-hemolytic streptococcal (GABHS) infections. This emphasis derives from the treatability of these infections, including the acute and subacute complications of initially untreated GABHS infections. In this context the viral pharyngytides are addressed only peripherally, to round out a differential diagnosis and to point out the classic presentations of pharyngitis caused by herpes simplex virus, Epstein-Barr virus, and enteroviruses so that an unnecessary course of antibiotics can be avoided. However, the viral pharyngities have unique issues of transmission, pathogenesis, clinical presentation, morbidity, and treatment that make them well worth discussing as an independent group.

With these issues in mind, this review will provide an overview of the viral etiologic agents of pharyngitis. Because several of the important viral agents of pharyngitis cause widespread oropharyngeal disease and often involve other organ systems, this review will incorporate a discussion of diseases involving any portion of the oral cavity in which there is objective tonsillar or pharyngeal involvement. Unique aspects of the organisms will be described, focusing on issues of pathogenesis, pathology, systemic versus localized disease, questions about treatment, and possible complications arising either from an agent itself or from the mistreatment or misdiagnosis of a more virulent pathogen.

Pharyngitis, Nasopharyngitis, and Pharygotonsillitis

The term pharyngitis as used in the United States incorporates any illness in which objective erythema and inflammation of the oropharynx occurs. These illnesses include: nasopharyngitis, in which the principle symptoms are coryza and erythema is the only pharyngeal finding; strict pharyngitis, manifested by subjective sore throat and objective erythema of the posterior pharyngeal wall; pharyngotonsillitis, involving enlargement and erythema of the tonsillar pillars, with or without exudates; infections involving the entire oral cavity with petechiae, vesicles, or ulcers; and systemic illnesses with varying degrees of oropharyngeal involvement. This review will consider the viral agents most often involved in all of these conditions, specifically, any agents that have as a component of their illness pharyngeal and tonsillar erythema and subjective sore throat. The specific clinical features that may allow differentiation of the organism will be discussed in the respective sections.

Viruses are the most common cause of pharyngitis in all age groups. However, this fact is of little comfort to the practitioner who is attempting to differentiate viral from specifically GABHS infection. There is no foolproof way to make that distinction because viral pharyngitides are so protean in their manifestations and may absolutely mimic GABHS disease. Thus, if there is any suspicion that GABHS may be involved, then GABHS must be ruled out. That said, the principal agents of viral-induced pharyngitis are adenoviruses, Epstein-Barr virus (EBV), Herpes Simplex virus (HSV 1 and 2), enteroviruses, rhinoviruses, respiratory syncytial virus, influenza, parainfluenza viruses, and coronaviruses.

Adenoviruses

The adenoviruses as a group are the most common viral agents of pharyngitis, accounting for up to 5% of total respiratory illnesses in children and up to 25% of viral respiratory illnesses.[1,2] The most common adenovirus types involved in pharyngitis are types 1, 2, 3, and 5, and, less commonly, types 6 and 7. Adenovirus infections are common in children younger than 5 years old, and notably in areas of close continuous contact such as day care settings or institutions. By 5 years of age, 70% to 80% of children will have neutralizing antibody to 1 or more adenovirus types.[3,4] This fact is reflected in data showing that only 1% to 2% of pharyngitis in college students is caused by adenovirus infections.[5]

Epidemiology

Adenoviral respiratory infection occurs in all age groups, but agents causing febrile pharyngitis have the highest incidence in children 6 months to 3 years old.[4,6] Most children (more than 90%) possess transplacentally acquired neutralizing antibodies to at least one adenovirus serotype, but this passive protection is largely lost by 6 months of age, when the percent of children with complement fixing antibodies declines to 14%.[7] Other studies have shown that more than 50% of children have demonstrable neutralizing antibodies against adenoviruses types 1, 2, and 5 by 5 years of age.[4,8] Overall, types 1, 2, 3, 5, 6, and 7 are most common as causes of respiratory infections. In a well-controlled longitudinal study, 81% of adenoviral isolates from children with febrile respiratory infections were type 1 or 2.[6] A similar study of transmission in a day care setting determined that types 1, 2, and 5 accounted for 92% of typed isolates.[8]

Adenovirus respiratory infections have been shown to be distinctly seasonal in most studies, with epidemic disease most common in the winter and spring.[9] However, unlike respiratory syncytial virus and influenza, adenovirus does not disappear

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completely for periods of time; sporadic adenoviral respiratory disease occurs throughout the year. Notably, pharyngoconjunctival fever is reported principally in the summer, probably because of its mode of transmission in swimming pools. Adenoviruses involved in respiratory infections are transmitted primarily by aerosolized droplets. The infectivity of aerosolized adenovirus may depend both on the virus serotype and on other conditions, like crowding.

Pathogenesis and Clinical Disease

When acting as agents of pharyngitis, adenoviruses are thought to be inoculated directly into the conjunctivae, nose, or oropharynx, where initial replication occurs. Local replication may be followed by extension to regional lymph nodes, may spread to the lower respiratory tract, or may result in viremia with spread to distal sites. In those infections in which replication is limited to the upper respiratory tract, the incubation period is 2 weeks or less, with virus first detectable a few days before the onset of clinical illness. Clinical illness is associated with the appearance of serum neutralizing antibodies specific for the adenovirus serotype involved. Virus may be detected in the oropharynx for up to 8 days after the onset of illness; but prolonged oropharyngeal shedding does not appear to be the rule.[6] In a longitudinal study of adenovirus transmission and disease, Fox et al[10] observed that detecting serum neutralizing antibodies was the most sensitive measure of adenovirus infection, that fecal excretion could be prolonged even with mild, nonenteric disease, and that the greatest predictor of illness was the presence of respiratory excretion of the virus.

The clinical manifestations of adenovirus infection are protean and usually not distinguishable from those caused by other viral or bacterial agents. The respiratory manifestations of adenovirus infection may range from coryza or otitis media to bronchiolitis and pneumonia. One feature that is fairly constant is the presence of fever. In a study by Edwards et al[6] of clinical manifestations of adenovirus in children with febrile respiratory infections, 14.5% of the children with fever and pharyngitis were positive for adenovirus, as were 9.5% of the children with fever and otitis media and 6.4% of the children with fever and coryza alone. Because fever was a selection critera for entry to the study, the investigators did not address the role of adenovirus in these conditions in the absence of fever. An earlier study by Moffet et al[11] found that 23% of young children hospitalized for febrile exudative pharyngitis were positive for adenovirus.

The manifestations of pharyngitis also may be variable. Exudative pharyngitis is common. The exudates of adenoviral pharyngotonsillitis have been described as follicular, spotty and thin, or thick and membranous. Follicular involvement of the posterior tongue and pharyngeal wall is most common, with thin yellow exudates. Indeed, this is the classic description of adenovirus pharyngitis and, when present with fever, cervical lymphadenitis, and conjunctivitis, is very specific for adenovirus infection.[12] However, thick, membranous exudates also can occur, making it more difficult to differentiate between GABHS, EBV, or in rare instances, *Corynebacterium diphtheriae.* This is especially true because the severe pharyngitis with exudates may be accompanied by high fever ($>39.0°C$), long duration of fever (more than 6 days), and elevated white blood cell count without a prominent lymphocytosis.[12] In general, the age at illness is most helpful in differentiating adenovirus from more serious bacterial infections: adenovirus infections occur mostly in children under 3 years old, whereas GABHS is most common in older children.

Diagnosis

Isolation and cultivation of the adenovirus on human embryo kidney cells is both sensitive and specific, but detecting it is dependent on the time and nature of sampling. Although respiratory shedding usually is present at the time of illness, the extent of shedding may vary.[10] Thus, the type of sample, specifically swab versus wash, may have some effect on the ability to isolate the virus.[6] Interestingly, fecal shedding was detectable during some respiratory illnesses when the virus could not be isolated from respiratory specimens.[10] It was suggested that concentration of the virus by swallowing and/or limited gastrointestinal replication of the virus was responsible for this phenomenon.

Antibody responses also are useful in diagnosing adenoviral infection and may be used for specific typing of virus. Serum Immunoglobulin M (IgM) may be detectable by enzyme-linked immunosorbent assay (ELISA) during acute infection, or seroconversion to adenovirus group antigen may be detectable by ELISA.[4] A majority of children with documented adenovirus, febrile, upper respiratory infections demonstrated a greater than fourfold neutralizing antibody response to the infecting virus, and such assays may be useful for virus typing.

In summary, febrile pharyngitis in a child between 6 months and 5 years old is caused most frequently by adenoviruses. An exudative, membranous, or follicular pharyngotonsillitis, especially if associated with coryza and/or conjunctivitis, is more likely to be adenovirus than GABHS in this age group.

Epstein-Barr Virus

The classic presentation of infectious mononucleosis (IM) caused by Epstein-Barr virus (EBV) is rarely missed or mistaken for another clinical entity; an older child, adolescent, or young adult presents with fever, malaise, anorexia, exudative pharyngotonsillitis, diffuse or local tender lymphadenopathy, splenomegaly, elevated white blood cell count with absolute lymphocytosis, and the presence of atypical lymphocytes on smear. The diagnosis is confirmed with slide tests such as the mono-spot agglutination test. Thus pharyngotonsillitis is only one of a number of components of a multi-organ illness; however, there are interesting aspects of EBV upper airway disease that make it important to consider and that may not be present as typical EBV IM.

Organism, Pathogenesis, and Typical Illness

EBV is a DNA virus and a member of the herpesvirus family. EBV contains a large, double-stranded DNA genome that encodes more than 70 proteins. It can replicate in a number of cell lines, but in humans it appears to be tropic primarily for cells of B lymphocyte lineage. EBV can cause transformation of B cells, resulting in its well-known association with Burkitt's lymphoma.[13]

EBV appears to be transmitted rather inefficiently, with transmission occurring primarily by intimate contact. The moniker of the "kissing disease" is a result of rather prolonged shedding of EBV in upper respiratory secretions after EBV infection and in asymptomatic adults, as well as the close contact required for effective transmission. EBV can be found in the blood and other body fluids, especially in immunocompromised patients, but blood-borne transmission is unusual under normal circumstances.[14]

The pathogenesis of EBV infection involving pharyngitis has not been well described. Since entry is via the mouth and oropharynx, it might be assumed that local replication in tonsillar B cells initiates infection, followed by spread to regional lymph nodes, viremia, B cell proliferation, and spread to distal sites. In fact, this appears to be the case. There is a persistent oropharyngeal infection with excretion for sometimes prolonged periods in more than 85% of patients with IM.[15] B lymphocytes infected in the oropharynx undergo polyclonal transformation and spread to distal sites, localizing primarily in the lymphoid organs. Early in the infection, a significant percentage of circulating B cells are infected (between 5% and 20%), but this rapidly declines during the second week of infection (to fewer than 2%) as infected cells are cleared.[13] Clinical mononucleosis is probably a manifestation of the immune response to the infected B cells. By the time clinical illness manifests, few circulating B cells are EBV-positive; the reactive lymphocytosis consists primarily of T cells, principally of the cytotoxic T cell category.[16]

Oropharyngeal Presentation of Infectious Mononucleosis

The incubation period of EBV IM is 30 to 50 days. There is a prodrome of malaise, headache, and anorexia lasting 3 to 5 days, followed by the onset of fever and sore throat in more than 80% of cases.[13,14,17] The pharyngitis of EBV mononucleosis may present as simple erythema of the tonsillar pillars; more often it presents with cryptic hyperplasia, palatal and uvular edema, and the presence of a yellow-gray exudate on the tonsils. Palatal petechiae occasionally can be observed at initial presentation. The oropharyngeal findings usually are not isolated, but are associated with fever as high as 39.5°C which may last for as long as 7 to 10 days after the onset of illness. In addition, the findings of tender adenopathy (primarily cervical but also frequently involving multiple other locations) and splenomegaly in 50% of IM patients are helpful diagnostic clues.[17-19]

The above presentation of EBV IM generally is not hard to recognize and diagnose. However, there are circumstances in which the differential may be somewhat broader. Specifically, the acute onset of exudative pharyngitis, cervical lymphadenopathy, and fever in an older child or adolescent is consistent with GABHS, which must be ruled out. Interestingly, 30% of EBV mono patients also will be positive for GABHS in their throats.[13] Sometimes the diagnosis of EBV is made when these patients are placed on ampicillin and develop a characteristic fine macular rash. Another circumstance in which a diagnosis may be more difficult is in the child less than 4 years old. It has been thought that EBV infection usually is asymptomatic in this age group, and that classic "adult type" infectious mononucleosis rarely occurs. But Sumaya and Ench[17] have demonstrated that illness consistent with clinical IM may not be as uncommon as previously thought.[17] The variation in clinical presentation with younger age and the decreased heterophile antibody response may have been responsible for this underestimation of EBV mono in young children. Children less than 4 years old may have a similar incidence of exudative tonsillopharyngitis but more rashes, neutropenia, and hepatosplenomegaly than do older children and adults. In relation to the oropharynx, recurrent tonsillopharyngitis may be associated with EBV infection in very young children. Airway obstruction and pneumonia may be more common in this age group as well. Thus, it may be important to make the diagnosis of EBV disease in these young children.

Diagnosis

EBV must be considered in patients at any age in whom exudative tonsillitis, adenopathy, and fever are found. The child less than 4 years old is less likely to have absolute lymphocytosis, with the likelihood decreasing as age decreases. The diagnosis had been more difficult in younger children because tests to identify heterophile antibodies are positive less often in children under age 6, but the advent of specific EBV serologies has enabled the diagnosis of EBV infection in any aged child. In a child over age 6, the diagnosis can be made with reasonable certainty with tests for heterophile antibodies, such as the Mono-Spot. This is a qualitative test based on the Paul-Bunell-Davidson quantitative heterophile tests. The "rapid slide tests" use horse erythrocytes, which are agglutinated in the presence of heterophile antibodies. In fact, these qualitative tests appear to be as good (approximately 80%) as quantitative heterophile tests with horse erythrocytes in detecting EBV in children as young as 4 years old.[18] At ages less than 4, the poor sensitivity of rapid slide tests probably results from lower levels of heterophile antibodies, because quantitative assays also detect fewer cases of confirmed EBV infection. Thus, in the case of suspected EBV in a child less than 4 years old, specific serologies are more likely to be useful. Specifically, the detection of IgM antibodies against the viral capsid antigen (VCA-IgM) is as useful in young children and infants as in older children and adults. It may be important to make sure that VCA-IgM can be quantitated at titers of less than 160, because they may be lower (<40) and more short lived (2 to 4 weeks) than in adults.[18]

Treatment, Complications and Other Considerations

EBV IM is predominantly a self-limited illness with no sequelae. However, infrequent complications related to the upper airway can be life threatening and, therefore, require recognition of the primary EBV infection and an awareness of the potential for the complication. During acute infection, the tonsils in Waldeyer's ring may become so enlarged that they may obstruct the upper airway. This is a rare complication but may be slightly more common in children less than 4 years old, with an incidence of 3% to 4%.[17] There have been no controlled studies of managing this complication, but both corticosteroids and emergency tonsillectomy have been used successfully to relieve airway obstruction.[17,20] Hydrocortisone, methylprednisolone, and prednisone have all been used in acute airway obstruction, with the

following caveats: (1) Because the long-term effects of steroids in this setting are not known, they should be used cautiously, if at all; (2) steroids should not be used for enlarged tonsils but only with evidence of worsening or impending airway compromise, such as stridor, nasal flaring, retractions, or sleep apnea; and (3) Steroids should be used only if the diagnosis of EBV IM is secure—ie, if clinical and laboratory findings leave no significant doubt about the etiology of tonsillar swelling or airway obstruction.

Another infrequent but important upper airway complication is peritonsillar abscess. It may arise either from GABHS or from oral anaerobes, and may contain mixed flora. One study indicates that 1% of patients with EBV IM requiring hospitalization may develop peritonsillar abscess and, conversely, that a larger proportion (up to 20%) of patients presenting with peritonsillar abscess may have a preceding recent history of infectious mononucleosis with exudative pharyngitis.[21,22] The pathogenesis of post-mono peritonsillar abscesses is not known. However, because several patients who presented with this complication had been treated previously with steroids for tonsillar enlargement, speculation has arisen that steroids may increase the incidence of this complication. It is just as plausible to argue that because patients who receive short-term steroid treatment are those who have more serious tonsillar, lymphatic, and oropharyngeal involvement, they are inherently more likely to experience complications such as peritonsillar or abscess. EBV is known to cause lymphatic stasis, impairment of migration of neutrophils, and impaired production of antibodies from B cells; it is possible that these factors may act together with steroids to favor formation of peritonsillar abscess.[21,22] Treatment of these abscesses involves aspiration and drainage, along with appropriate antibiotics.

A third rare but important complication of EBV infection is Lemierre's disease. This is a potentially catastrophic imitator of EBV mononucleosis but also has been reported as a complication of EBV infection. Lemierre's disease was first described in 1936 and consists of fever, dysphagia, severe exudative pharyngitis, and swelling over the sternocleidomastoid in an adolescent or young adult.[23] The symptoms and duration may mimic exactly the exudative pharyngitis, fetor oris, fever, and lymphadenopathy of EBV. Lemierre's disease, however, is caused by *Fusobacterium necrophorum,* a gram-negative anaerobe which is a frequent, normal inhabitant of the oral cavity. The severe pharyngitis of Lemierre's disease is a direct invasion by the organism, and the swelling over the sternocleidomastoid is septic thrombophlebitis of the internal jugular vein. It is important to quickly differentiate this syndrome from EBV IM because *F necrophorum* can rapidly and destructively disseminate to bones, central nervous system (CNS), lungs, liver, and kidneys, resulting in CNS and lung abscesses, multifocal osteomyelitis, and overwhelming sepsis.[24-26]

Thus, we return to the importance of the other fairly consistent features of EBV IM such as splenomegaly, lymphocytosis with atypical lymphocytes, and heterophile positivity. In the absence of these features, one should be suspicious of an EBV diagnosis. Even with confirmed EBV disease, the presence of severe continued exudative tonsillitis, or new findings such as shortness of breath or joint pain, should bring Lemierre's disease to mind. One reason why Lemierre's disease is infrequently seen is that *F necrophorum* does not produce B lactamase and is generally susceptible to penicillin.

This raises questions about the role of anaerobes in the oropharyngeal manifestations of EBV mononucleosis. The foul smelling, exudative tonsillitis and occurrence of peritonsillar abscess suggest a significant role. One prospective study addressed this issue by comparing the treatment of "anginose" infectious mononucleosis using metronidazole or clindamycin with no treatment at all. The number of patients in this study was small, and the study itself was not randomized or blinded; however, the treated group had a significantly shorter duration of fever and less severe tonsillitis than did the controls.[27]

In summary, EBV mononucleosis causes a typical illness of variable severity characterized by exudative tonsillitis, fever, lymphadenopathy, and lymphocytosis. EBV mononucleosis may be more common in younger children than previously recognized and should be considered in any compatible or suspicious condition. Although complications of EBV mono, such as peritonsillar abscess and acute airway obstruction, are rare, they can be life threatening. Other diseases may imitate EBV mono and need to be rapidly distinguished, as in the case of Lemierre's disease. Treatment of EBV with antivirals is not yet feasible, and treating complications of acute airway obstruction with steroids, although clinically demonstrated to be helpful, should be done cautiously and with knowledge of potential bacterial complications that could be masked or potentiated.

Enteroviruses

The enteroviruses are frequent causes of pharyngitis and tonsillitis. Enteroviruses such as coxsackie A, coxsackie B, and echoviruses are etiologic agents in upper respiratory infections and are associated frequently with a variety of oropharyngeal manifestations. In general, enterovirus infections are associated with a relatively short incubation period of 3 to 6 days, with an abrupt onset of fever (which may be significantly elevated) and with a myriad of exanthematous and enanthematous findings. Oropharyngeal characteristics of enterovirus infections may range from mild tonsillar injection, to exudative pharyngitis, to vesicular, pustular, and ulcerated lesions associated with hand-foot-and-mouth disease and herpangina.

Epidemiology, Transmission, and Pathogenesis

Enterovirus species are picornaviruses, members of a family of small RNA-containing viruses that possess a protein capsid. They generally are shed in the stool and spread by fecal-oral transmission. Interestingly, they are stable in stool and sewage, and appear to survive in brackish and salt water as well, but are thought to be sensitive to ultraviolet radiation, elevated temperatures, and dessication. Thus, they may have limited spread by the respiratory routes commonly associated with pharyngitis-causing agents.

The pathogenesis of enterovirus infection begins with intraoral inoculation. Not surprisingly, acquisition of enteroviruses is most common in young children who have more promiscuously bad hygiene than do adults and who transmit enteroviruses via feces, skin, and fingers-to-mouth. Initial replication occurs to relatively high levels in the oropharynx and proximal gastroin-

testinal tract within the first 1 to 3 days. This replication is followed by primary viremia with spread to other regions of the reticuloendothelial system and then by more replication over the next 3 days, with subsequent viremia and dissemination. Oropharyngeal manifestations of enterovirus infection appear to be a result of viremia spread back to the oropharynx, rather than of continued replication in situ with local responses. This conclusion is predicated on the lack of prodrome and the appearance of pharyngeal lesions at the same time as the onset of fever and other manifestations of enterovirus disease, such as rash or hepatitis. Enteroviral illnesses usually last from 3 to 6 days, with malaise and relatively high fever, which rapidly resolves, leaving no sequelae.

Hand-Foot-and-Mouth Disease

The oral lesions of hand-foot-and-mouth (HFM) disease are characteristic but require the presence of hand and foot lesions for unequivocal clinical diagnosis. Hand-foot-and-mouth disease results from infection with a variety of enteroviruses and typically occurs in summer and fall. The vast majority of hand-foot-and-mouth disease is caused by Coxsackie A16, although cases have been reported due to A5, 7, 9, and 10.[28,29] The disease has a typical incubation period of 3 to 6 days, followed by acute onset of moderate fever, malaise, and sore throat. Oral lesions appear 1 to 2 days later, followed by other skin lesions. Oral lesions are more common than hand and foot lesions, while hand lesions are more common than those on the feet. Oral lesions are present in 90% to 100% of young children with Coxsackie virus A16 infection; they present as small (4 to 8 mm) ulcerated lesions principally on the buccal mucosa and posterior tongue, although the palate, uvula, and anterior tonsillar pillars are involved about 40% of the time.[30-32]

Because the exanthem is not always present, and because exanthem becomes increasingly uncommon with older children and adults, the oropharyngeal lesions of HFM frequently are misdiagnosed as apthous ulcers or herpes simplex stomatitis. There is little practical consequence to this mistaken identity, however, because HFM is a self-limited illness which clears within 4 to 6 days. Specific diagnosis usually is not made because identifying Coxsackie viruses requires inoculation into the brain of suckling mice, and serologies usually are not performed.

Herpangina

Herpangina refers to small papular, papulovesicular, or ulcerated lesions of the oropharynx in association with other systemic symptoms such as fever, malaise, and anorexia. Herpangina is caused primarily by Coxsackie A and B viruses, and much less frequently by echo and other enteroviruses. In contrast to HFM, herpangina is caused by a wider variety of viruses. In a study of 538 Japanese patients, Coxsackie A 1-10, 16, 22 and Coxsackie B 1-5 comprised 75% and 12%, respectively, of the responsible agents.[33] Transmission is thought to be primarily by the fecal-oral route, although at least one prospective volunteer study[34] and one retrospective review of herpangina suggest that airborne transmission may be more common than previously thought.[33]

As with HFM, the illness is heralded by acute onset of fever, sore throat, and anorexia, although the acuity and severity of these symptoms is variable. The lesions of herpangina may appear anytime within the first 48 hours after the onset of nonspecific symptoms. These lesions are characterized as 1 or more discrete papular lesions that progress to vesicles, which subsequently become small (1 to 2 mm) ulcers that may enlarge to 3 to 4 mm. The lesions are surrounded by a zone of erythema and, in contrast to HFM, are more common on the tonsillar pillars, palate, uvula, and posterior pharyngeal wall but also may be present on the posterior tongue and buccal mucosa. The small size of the lesions and posterior location is characteristic of herpangina. As with HFM, herpangina usually resolves in 3 to 6 days without complications.[35]

No general laboratory tests are useful in diagnosing herpangina. Culture of the oropharynx or rectal swabs may yield an organism if it is caused by Coxsackie B viruses or echoviruses. But because the majority of cases of herpangina are caused by Coxsackie A viruses, suckling mouse inoculation would be required for their diagnosis. This inoculation might be warranted in the case of an epidemic or herpangina with significant other complications.[29]

Herpes Simplex Virus

The oral manifestations of primary HSV infection in young children consist of vesicular and ulcerated lesions potentially involving the entire oral cavity, including the buccal mucosae, gums, tongue, tonsils, uvula, and palate, as well as the lips and skin surrounding the mouth. The principal agent is herpes simplex virus type 1 (HSV-1), although herpes simplex virus type 2 (HSV-2) is increasingly common, especially in adolescents and young adults.[36]

Epidemiology, Transmission, and Pathogenesis

HSV is very infectious. Its most common manifestation in young children is herpetic gingivostomatitis. HSV is transmitted by virus in secretions, principally saliva, and has a strong predilection for infecting mucosal surfaces and other tissues of ectodermal origin. However, only a very small percentage of children seropositive for HSV-1 have any history consistent with oral infection, specifically gingivostomatitis. An exception is the high percentage (31%) of seropositive Navajo children reported to have a history of gingivostomatitis.[37] This suggests that other factors may be critical in the progression from infection to clinically apparent gingivostomatitis. Herpes gingivostomatitis is seen primarily in children between 10 months and 3 years old.[36,38]

Transmission of HSV may occur by direct contact, by transmission on fingers, or by transmission on other objects, although this is less common. Primary oropharyngeal infection appears to remain localized, with no viremia detected by culture during clinical disease in one study.[39] However, this study did not use hybridization or polymerase chain reaction, and it measured virus at only one time point, so it is still possible that low level viremia may occur at some point during infection. The incubation period of the virus is short (1 to 3 days), and illness begins with fever and irritability, followed by the appearance of vesicular lesions on the lips, buccal surfaces, tongue, and gingivae. The vesicular lesions may progress rapidly (over a few

hours) to pustules and ruptured vesicles, leaving shallow, erythematous, painful ulcers. The lesions may bleed on contact, and the gums may be swollen and tender. Lesions often are noted around the nares, cheeks, lips, and chin, and there may be associated significant tender cervical adenopathy. Beginning with the prodromal period, children with significant involvement may drool, appear in great distress, and refuse to eat or drink fluids. The latter complications are most often the reason for hospitalization of these children. The normal course is continued appearance and evolution of lesions for up to 5 days, followed by complete resolution over 1 to 2 weeks without scarring.

Differential Diagnosis and Treatment

HSV gingivostomatitis in young children is most likely to be confused with either herpangina or HFM disease. As described in the previous section, herpangina and HFM both involve more posterior structures, whereas HSV gingivostomatitis, although capable of involving the tonsils, is primarily an anterior oral cavity disease. Also, herpangina and HFM generally are of more acute onset and shorter duration than HSV disease. Other ulcerative diseases include Steven-Johnson's syndrome and apthous stomatitis. HSV oral infection in adolescents may present as a primary exudative tonsillitis sometimes without obvious ulcers. In one study of pharyngitis in university students of upper socioeconomic background, 11% of the cases was caused by HSV.[40] These cases of pharyngitis were clinically difficult to distinguish from pharyngitis of GABHS, EBV, and other pathogens. In a more recent, similar study of college students with pharyngitis, 5.7% of the cases resulted from HSV, and more than 80% presented with erythematous or exudative pharyngitis alone.[41] Thus, in the presence of isolated exudative tonsillitis with fever and adenopathy, it may be impossible on clinical exam to differentiate HSV from the exudative tonsillitis of EBV or GABHS.

Treatment of primary HSV gingivostomatitis in children has not been well studied. By analogy to studies of primary HSV genital infections in adults, it is thought that acyclovir might shorten the duration and severity of primary infection. One small study with 10 patients each in acyclovir and control groups concluded that acyclovir reduced the pain and salivation in the treatment group but did not affect the number or severity of lesions.[42,43] In practice, intravenous acyclovir has been used in children hospitalized with severe gingivostomatitis associated with dehydration and toxicity. The impact of early treatment on recurrences is not known.

Other Agents of Pharyngitis

There are many other viral infections that have pharyngitis as part of their clinical presentations. These include viruses caused by common pediatric pathogens such as the parainfluenza viruses 1-3, influenza virus, respiratory syncytial virus, measles, rubella, rhinoviruses, coronaviruses, and reoviruses.[44,45] The pharyngitis of the rhinoviruses and coronaviruses usually is limited to erythema and subjective sore throat, with coryza a more prominent feature. Influenza virus infection during epidemics also may result frequently in erythema of the tonsils and pharynx, with significant pain. Respiratory syncytral viruses and parainfluenza viruses may cause erythematous pharyngitis, but this is usually mild and is overshadowed by the other respiratory components of these illnesses. Interestingly, reoviruses may have erythematous pharyngitis as part of their clinical presentation, which is primarily gastroenteritis. The enanthem of measles has no characteristic pharyngeal lesions, but again is primarily erythema; the Koplik's spots on the buccal mucosae are the distinguishing characteristic of the oral pathology. Thus, these agents present primarily as erythematous pharyngitis and their diagnosis is dependent on recognizing other aspects of the illness and on laboratory tests.

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