ORIGINAL CONTRIBUTION

Fusobacterial Infections

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Anaerobic, Gram-negative bacilli of the genus *Fusobacterium* have been implicated in the etiology, pathophysiology, and complications of several diseases, including periodontal diseases, Lemierre's syndrome, tropical skin ulcers, and intraamniotic infections (IAI). As part of the normal flora of the oral cavity, female genital tract, and gastrointestinal tract, fusobacteria have a number of natural entry points to cause disease. *F. nucleatum* plays a critical role in the development of periodontal diseases by acting as a microbial bridge between early and late (pathogenic) colonizers of the oral tissues. *F. necrophorum* is the causative agent of Lemierre's syndrome, a rare infection that can have devastating effects on the joints, lungs, and central nervous system. A variety of fusobacteria have been implicated in the development of tropical skin ulcers, which continue to cause significant debility in regions of the tropics. Fusobacteria have been associated with a significant proportion of preterm low birth weight infants due to IAI. Morbidity and mortality may result from IAI, and the incidence of IAI has not decreased in recent years. Typically, antimicrobial drugs provide effective treatment of fusobacterial infections, which can affect people of all age groups.

INTRODUCTION

Fusobacteria, which form part of the family *Bacteroidaceae*, are asaccharolytic obligately anaerobic, non-spore forming, Gram-negative bacilli (1,2). Historically, the production of butyric acid, rather than isobutyric or isovaleric acids, has been used to differentiate fusobacteria from other members of the family *Bacteroidaceae*. More recently, fusobacteria have been subdivided into species and subspecies by the comparative analysis of cellular fatty acid patterns and small-subunit rRNA gene sequences (1,3,4).

Fusobacteria, either alone or in combination with other anaerobes and aerobes, have been isolated from a wide variety of clinically significant anaerobic infections. However, positive identifications cannot always be made because these bacteria require specific growth conditions, appear with varying cell morphologies, and give primarily negative responses in routine biochemical tests (5). On the other hand, the occurrence of fusobacteria as part of the normal flora of the oral cavity, female genital tract, and gastrointestinal tract (5-7) provides many opportunities for these bacteria to initiate infections.

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PERIODONTAL DISEASES

Severe destructive periodontal diseases affect 5-20% of the population, at considerable social and economic costs (8,9). These diseases are characterized by local tissue inflammation, tissue destruction, and bone loss (8). Periodontal diseases, which eventually result in the loss of teeth, can also have a variety of systemic effects (8,10). It is well known that transient bacteremias can occur as a result of normal oral hygiene practices, such as the brushing of teeth (10,11). Such transient bacteremias can cause complications in susceptible patients. For example, patients with damaged heart valves or prosthetic devices are susceptible to infective endocarditis or infection of the prosthesis (10,12,13), and precautions are taken to avoid complications due to transient bacteremias arising from professional dental care (12). Infection by *Chlamydia pneumoniae* and other microbial factors have been implicated as risk factors for atherogenesis (14-16), and many epidemiologic studies have indicated that patients suffering from periodontitis are also at an increased risk of developing coronary ar-

tery disease (CAD) (17-19). A cross-sectional study by Mattila *et al.* (18) has suggested that dental infections, particularly gingivitis and periodontal diseases, are as important as the classical risk factors (age, smoking, diabetes, hypertension, and elevated serum triglycerides) in the pathogenesis of CAD. DeStefano *et al.* carried out a prospective cohort study (9760 subjects followed for a median of 14 years) in which it was determined that men under 50 with periodontitis had a stronger risk for CAD, but overall, they found that periodontal disease was associated with a small increased risk (19). Diabetic patients may have a reduced need for insulin following treatment for periodontitis (10,20,21), and it has been noted that potential respiratory pathogens may become established in the oral flora of patients with periodontal disease (10). A number of studies which examined the relationship between oral health and the sense of well-being, especially in the elderly, have concluded that eating difficulties lead to social withdrawal, especially in the elderly (10,22,23).

Infectious periodontal diseases, including gingivitis and periodontitis, are complex, multifactorial diseases, primarily due to the interaction between organisms and the immune system (1). Many reviews have described the pathogenesis in detail (1,2,24-29); a simplified summary follows. The initial event in periodontal diseases is the growth of predominantly aerobic, saccharolytic bacteria along a clean gingival margin (30,31). These early colonizers are primarily Gram-positive streptococci and Gram-positive rods which are capable of adhering to human tissues, such as tooth enamel and gingiva. The anaerobic, asaccharolytic bacteria (1,2) responsible for periodontal diseases do not adhere directly to human tissue, and buildup of these species occurs by coaggregation with other bacteria, a phenomenon particularly associated with oral bacteria (1,30). The interactions among the various genera and species colonizing the oral mucosa (1,30,32-38) are cell specific; the late colonizers found in periodontal diseases do not coaggregate with the early colonizers. The ability of *Fusobacterium nucleatum* to coaggregate with most early and late colonizers (1,30) suggests that it acts as a microbial bridge between the early and late stages of infection (1,30,36,38). Because of this role, relatively large quantities of *F. nucleatum* are often found in subgingival pockets affected by periodontal disease (1,39-41). While *F. nucleatum* coaggregates with the three microorganisms that are normally implicated in the etiology of periodontal diseases (1,30) - *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Bacteroides forsythus* - the relationship between *F. nucleatum* and *P. gingivalis* appears particularly strong (1,35,36).

F. nucleatum, being part of the normal oral flora, can be isolated from the healthy gingiva of most adults (6,42). This is not to say, however, that the organism is benign; the many virulence factors that enable it to be pathogenic in periodontal diseases are likely to be quite important in systemic diseases as well. The lipopolysaccharide (LPS) in the cell wall of *F. nucleatum* is structurally related to the LPS of other Gram-negative bacteria, and has a biological activity similar to that of *Escherichia coli* (1,43-45). In addition to its toxic properties, the LPS of *F. nucleatum* activates complement, provoking an inflammatory response, resulting in further tissue destruction (1,2,46). The production of butyric acid by fusobacteria inhibits the proliferation of gingival fibroblasts which normally compromises the rapid healing of wounds (1,47,48).

The outer membrane proteins (OMPs) of *F. nucleatum* have a role in bacterial nutrition (1) and may play a role in the pathogenesis of adult periodontitis (49). OMPs in *F. nucleatum* display bioactivities similar to those of LPS, but are present in greater quantities (49). In other Gram-negative bacteria, OMPs provide a route for the uptake of antibiotics, and the OMPs in *F. nucleatum* may display similar activities (1,50). Evidence for the production of extracellular proteolytic enzymes by fusobacteria is weak (51,52), although its occurrence cannot be discounted (53).

LEMIERRE'S SYNDROME

Lemierre's syndrome (synonyms: postanginal sepsis, necrobacillosis) classically presents with a severe sore throat, followed by fever, rigors, and painful cervical lymphadenopathy in a previously healthy child or young adult (6,54-58). Jaundice may also be present (57). Both exudative and non-exudative tonsillar and peritonsillar abscesses, and/or lesions in the mouth and jaw may be present (56). Lemierre reported that the syndrome, which he referred to as "postanginal septicemia", may result following otitis media, mastoiditis, appendicitis, urinary tract infection, or "purulent" endometritis following parturition (56). Of these alternative presentations, otitis media is most frequently encountered, but overall, Lemierre's syndrome has not been very common in the antibiotic era (6,57-59). Recently, there has been some disagreement as to whether Epstein-Barr virus (EBV) may predispose patients to this condition (6,55).

Infections of *Fusobacterium necrophorum* are responsible for Lemierre's syndrome. Following oropharyngeal infection, the jugular vein becomes palpable as bacteria begin to colonize it (as well as other local veins) (6,54,60). The suppurative internal jugular vein may be mistaken for lymphadenopathy (6,54). Septic emboli from the jugular vein allow distant metastatic spread of *F. necrophorum* to the lungs, as well as to the joints and central nervous system (CNS) (6, 57,58). As infection spreads to the lungs, multiple infiltrates quickly cavitate and can result in pleural effusion, empyema, and/or pneumothorax (54,57). Septic arthritis usually affects one or more large joints, such as the hip or knee (6). *F. necrophorum* meningitis can follow pharyngeal infection and may also be otogenic (59). Cranial palsies and brain abscesses leading to infarction are possible CNS sequelae (6,61).

Lemierre's syndrome is relatively easy to diagnose clinically and timely antibiotic therapy can prevent complications or death (54). However, rates of morbidity and mortality (mortality: 4-18%) remain high, partly because unfamiliarity with the disease leads to delays in diagnosis, underdiagnosis, and delays in the choice of a proper antimicrobial agent. Unfortunately, identification of the pathogen by culture is often the first indication of the disease (6), but

growth on solid media in a laboratory takes at least 48 hours. This emphasizes the need for a prompt clinical diagnosis (6,55,58,62). Computed tomography (CT) or ultrasound of the neck may be used to confirm involvement of the internal jugular vein (6). X-rays may be used to localize some cranial and pulmonary lesions, and to follow the progress of treatment. The fairly recent reviews by Eyken and Sinave *et al.* should be helpful in correctly diagnosing this syndrome (57,58). It is ironic that Lemierre himself stated: "The appearance and repetition several days after the onset of a sore-throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible"(56).

TROPICAL SKIN ULCERS

Tropical skin ulcers (synonyms: Naga sore, tropical septic ulcer, ulcus tropicum, tropical phagedenic ulcer, tropical sloughing phagedena) (63) are common among children and young adults in the tropics, but are not confined to these areas (64,65). Patients are predominantly between 5 and 15 years old, with those over 35 years of age being rarely affected (63). Although tropical skin ulcers are relatively common and are the leading cause of morbidity in parts of the tropics (65), they remain understudied. This is mainly because they usually occur in rural areas, away from large research centers (66). Much of what is known about the etiology and pathogenesis of tropical skin ulcers is due to epidemiologic studies by Adriaans, and an experimental study by McAdam, who induced these ulcers in 20 volunteers by bathing intact skin with ulcer pus for 6-10 days (63,67,68).

The major etiological factors of tropical skin ulcers have been identified as trauma and secondary infection. The trauma may be extremely minor, such as leg contact with previously infected shrubbery and plants (68). For this reason, the lesions usually occur on exposed skin (68,69). A small localized inflammatory reaction develops into a pustule about 1 cm in diameter after 5 or 6 days (68). Once the pustule ruptures, a foul-smelling blood-stained pus is discharged, and the round ulcer is raised above the surrounding edematous skin (68). The ulcer, which is usually solitary, involves the skin and subcutaneous tissues, but if the deep fascia is penetrated, the ulcer can destroy tendons, muscles, joints and bone (68,70). During its acute stage, the ulcer is extremely painful, leading to difficulties in sleeping and ambulating. An ulcer can bleed as much as 90 mL in 15 minutes (68). The margins of the ulcers often have what is described as pseudoepitheliomatous hyperplasia (67); squamous carcinoma, perhaps due to the hyperplasia, occurs in about 2-15% of ulcers of more than 3 years duration (63). The nutritional status of the patient does not appear to be particularly relevant to the development of ulcers, as was once thought (63). Moisture is apparently necessary to induce infection and subsequent ulceration, as there is an increased incidence in the wet season (63,68). Patients often do not develop immunity to the infectious agents; it has been observed that recurrence of the ulcers is possible if patients are re-exposed to the causative organisms (63).

Fusobacteria are the most frequently isolated bacteria from early tropical ulcers, having been implicated in about 35% of all cases (67). *F. nucleatum*, *F. necrophorum*, and *F. ulcerans* are the species usually associated with this disease, and the rapid tissue destruction involved has led to the inference of bacterial toxin production (5,64,65).

INTRAAMNIOTIC INFECTION

Premature infants with low birth weights (<2500 g) are a major social and economic public health problem. A more intensive hospital-based management of low birth weight infants, and not a decline in incidence, has resulted in the most recent reductions of infant mortality in more developed nations (71-73). Although the exact pathogenesis of intraamniotic infection (IAI) (synonyms: clinical chorioamnionitis, amnionitis, amniotic fluid infection, intrapartum infection) is unknown, infection has been established as a major etiological factor in premature rupture of chorioamniotic membranes and as a cause of prematurity (74-79). The incidence of IAI has been reported to be 1-4% by Gibbs and Duff, although incidence rates up to 10.5% have also been described (74,75,80).

The hallmark of IAI is maternal fever, although uterine tenderness, foul-smelling amniotic fluid, maternal tachycardia, and fetal tachycardia have also been noted (74-76). Common maternal complications associated with IAI have been dysfunctional labor and postpartum infections (74,79,81). Neonatal complications are usually related to premature birth; the newborn may also be born with an infection or sepsis (78).

The bacteria most related to prematurity have been reported to be fusobacteria and group B streptococci (82). According to Altshuler and Hyde, fusobacterial infections have been associated with 18% of IAI cases that result in prematurity, but figures as high as 30% have been reported (77,83-88). Although the mechanism by which bacteria precipitate labor is unclear, translocation of endotoxins and maternally-produced prostaglandins in response to bacterial phospholipase A_2 have been implicated (71,77,89).

OTHER INFECTIONS

Case reports have documented the involvement of fusobacteria in osteomyelitis (90,91), urinary tract infections (92), pulmonary nodules (93), infective endocarditis (94), pericarditis (95), septic arthritis of the sternoclavicular joint (96), liver and splenic abscesses (97-100), fatal pneumonia (101), and disseminated intravascular coagulation (102), among others. In most of these infections, the most probable route of entry for fusobacteria is the oropharynx. Fusobacterial sternoclavicular infections are now exceedingly rare, but in the preantibiotic era, *F. necrophorum* was the most important anaerobe in these infections (96). However, splenic abscesses

may be more common in specific subgroups within the population, particularly intravenous drug users who have the habit of licking needles before injection to ease passage of the needle, to check the potency of the drug, and to ensure that the bevel is sharp (99,100).

Although *F. nucleatum* and *F. necrophorum* are considered the most pathogenic in this genus, other fusobacteria do occasionally cause infection. *F. russi* has been associated with animal bite infections, and *F. varium* with conjunctivitis and intra-ocular infections (5). *F. mortiferum* sepsis has been documented as well (103).

THE ROLE OF ANTIMICROBIAL THERAPY IN FUSOBACTERIAL INFECTIONS

In general, fusobacteria display variable resistance to vancomycin, erythromycin, amoxicillin, ampicillin, and aminoglycosides (*e.g.* neomycin) (1,101,104-109). There are no general guidelines for choosing an antimicrobial agent, but antibiotic susceptibility testing is advised if the case is not urgent. Otherwise, empiric use of broad spectrum antibiotics with activity against anaerobes will suffice (110). Some commonly used antibiotics for anaerobic coverage include metronidazole, imipenem, and penicillins (110).

In periodontal diseases, antibiotic therapy is usually directed against *P. gingivalis*, *B. forsythus,* and *A. actinomycetemcomitans*, and typically involves a combination of a common tetracycline or penicillin antibiotic with metronidazole or ciprofloxacin (29). Antibiotics can be administered systemically or locally in the periodontal pocket. *F. nucleatum* often displays resistance to tetracyclines, and beta-lactamase producing strains are becoming more common (1,106,108,111). It has been estimated that 40-60% of clinically isolated fusobacteria strains are beta-lactamase producing, but the clinical significance of this finding is not yet clear (110). Treatment of periodontal diseases is not usually directed toward elimination of *F. nucleatum*, although certainly many antibiotic therapies may act against this organism (29).

Despite *in vitro* susceptibility to a number of antibiotics, numerous case reports have documented the ineffectiveness of many antibiotics in treating *F. necrophorum* infections (Lemierre's syndrome). As a result, the drug of choice is a combination of metronidazole usually with a penicillin for aerobic coverage, although certainly other drugs may also be effective (1,6,24,53-55,59,60,62,90,101,102,112,113). Surgical interventions may be necessary in some cases (54). If treatment is delivered effectively, full recovery without sequelae is the rule unless there is cerebral involvement or osteomyelitis. Antibiotic treatment should be at least 6 weeks in duration for Lemierre's syndrome (58).

Antibiotics are effective in the early stages of tropical skin ulcers (64,68), but they should be administered systemically, as local application often causes sensitization (63,114). The epithelium usually begins healing around the margin of the ulcer within 24 hours of administration (68). For more severe ulcers, skin grafts may be necessary (68).

There is no broad agreement on the selection of antibiotics for IAI, but there is accordance that both antibiotic therapy and delivery are essential to cure this condition (75). Gibbs and Duff report that many retrospective and prospective studies have evaluated the use of a penicillin with an aminoglycoside (75).

CONCLUSION

Fusobacteria are capable of producing infections that result in significant morbidity and mortality. The presence of *F. nucleatum* in the mouth is critical to the development of periodontal diseases, which affect a significant proportion of elderly patients. *F. necrophorum* causes Lemierre's syndrome, an entity which is less common in the antibiotic era, but which can have potentially devastating consequences if unrecognized. Lemierre's syndrome usually affects young adults, and often begins as a pharyngeal infection. Tropical skin ulcers have been attributed to a number of different species of fusobacteria; although the incidence of these ulcers seems to be declining with better living standards, they remain a significant cause of morbidity in parts of the tropics. Fusobacteria, although not the most common cause of IAI, have been associated with a significant proportion of premature births. The incidence of prematurity does not appear to have declined. Fusobacterial infections can affect a wide range of age groups throughout the world. The presence of fusobacteria as part of the normal flora of the oropharynx, female genital tract, and gastrointestinal system appears to be critical to the pathogenesis of a number of these infections.

ACKNOWLEDGMENTS

We thank the Pharmaceutical Manufacturer's Association and the Faculty of Medicine at Dalhousie University for a scholarship to SS and Dr. S.F. Lee for helpful discussions.

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