

# Expand the Pharyngitis Paradigm for Adolescents and Young Adults

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Current guidelines and review articles emphasize that clinicians should consider group A  $\beta$ -hemolytic streptococcus in the diagnosis and management of patients with acute pharyngitis. Recent data suggest that in adolescents and young adults (persons aged 15 to 24 years), *Fusobacterium necrophorum* causes endemic pharyngitis at a rate similar to that of group A  $\beta$ -hemolytic streptococcus. On the basis of published epidemiologic data, *F. necrophorum* is estimated to cause the Lemierre syndrome—a life-threatening suppurative complication—at a higher incidence than that at which group A streptococcus causes acute rheumatic fever. Moreover, these estimates suggest greater morbidity and mortality from the Lemierre syndrome. The diagnostic paradigm for adolescent pharyngitis should therefore be expanded to consider *F. necrophorum* in addition to group A streptococcus. Expanding the pharyngitis paradigm will have several important implications. Further epidemiologic

research is needed on both *F. necrophorum* pharyngitis (especially clinical presentation) and the Lemierre syndrome. Clinicians need reliable diagnostic techniques for *F. necrophorum* pharyngitis. In the meantime, adolescents and young adults who develop bacteremic symptoms should be aggressively treated with antibiotics for *F. necrophorum* infection. Physicians should avoid macrolides if they choose to treat streptococcus-negative pharyngitis empirically. Finally, pediatricians, internists, family physicians, and emergency department physicians should know the red flags for adolescent and young adult pharyngitis: worsening symptoms or neck swelling (especially unilateral neck swelling). Adolescent and young adult pharyngitis is more complicated than previously considered.

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Current pharyngitis guidelines and review articles (1, 2) focus on the diagnosis and treatment of group A  $\beta$ -hemolytic streptococcal infection. Recent evidence (3, 4) suggests that *Fusobacterium necrophorum* pharyngitis occurs as often as streptococcal pharyngitis in patients aged 15 to 30 years. Because *F. necrophorum* can cause a severe complication, the Lemierre syndrome, we should revise our diagnostic paradigm for pharyngitis in adolescents and young adults (persons aged 15 to 24 years) to include both group A streptococcus and *F. necrophorum*.

Our current paradigm started in the 1950s with the explicit goal of decreasing the incidence of acute rheumatic fever. Rheumatic fever has become rare in the United States, with an incidence of fewer than 10 cases per 100 000 patients with group A  $\beta$ -hemolytic streptococcal pharyngitis. Only 10% of patients with acute rheumatic fever have complicated disease, and only 1% of those die (5).

*Fusobacterium necrophorum* pharyngitis is a newly recognized cause of endemic pharyngitis in adolescents and young adults. Recent studies suggest that *F. necrophorum* may cause as much as 10% of cases of pharyngitis in this age group. This gram-negative anaerobe also causes suppurative complications, especially the Lemierre syndrome.

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## THE LEMIERRE SYNDROME

In 1936, Lemierre (6) described a clinical syndrome in adolescents whose illnesses started with tonsillitis or peritonsillar abscess. Although they initially had clinical improvement, the adolescents developed clinical signs of bacteremia, including rigors, after approximately 4 days. They then developed suppurative thrombophlebitis of the internal jugular vein, bacteremia, and metastatic infections (most commonly, pulmonary abscesses). Lemierre identified the causative organism as *Bacillus funduliformis*, later renamed *F. necrophorum*. He reported a 90% mortality rate among the 20 patients he observed. In their 2002 review, Chirinos and colleagues (7) noted that culture data confirm *F. necrophorum* as the etiologic agent in 81% of published cases.

The Lemierre syndrome remains life-threatening. Four recent case series (8–11) provide mortality data; the studies had a total of 303 patients and reported 13 deaths, for a mortality rate of 4.6% (95% CI, 2.6% to 7.3%). The most recent published case series (11) also included morbidity data. Of 37 patients whose disease started with pharyngitis, 11 required intensive care (with 7 requiring intubation) and 16 required surgical drainage of an abscess. One patient died, and 3 had permanent sequelae. Thus, permanent sequelae occurred in 10.2% (CI, 2.1% to 22%) of patients. Many of those who recovered had a long convalescence.

Most patients present with pharyngitis several days before the Lemierre syndrome develops; thus, it seems that *F. necrophorum* causes pharyngitis and that physicians could prevent the Lemierre syndrome by treating *F. necrophorum* pharyngitis with effective antibiotics. Recent European laboratory studies (3, 4, 12, 13) suggest that *F. necrophorum* causes endemic pharyngitis in adolescents and young adults, but clinical descriptions of affected patients are not

provided. Although no direct evidence shows that early treatment can prevent the Lemierre syndrome, evidence does show that early treatment leads to better outcomes (9).

### CAUSE OF *F. NECROPHORUM* PHARYNGITIS

Using a polymerase chain reaction assay for *F. necrophorum* DNA, Aliyu and colleagues (12) tested throat swabs from 100 patients with pharyngitis and 100 patients without upper respiratory tract symptoms in the United Kingdom. Ten percent of the patients with pharyngitis had positive results for *F. necrophorum*, but none of the control participants did. In another United Kingdom study (4), pharyngeal cultures from 248 patients with pharyngitis yielded group A streptococci in 27 patients (11%), group C streptococci in 2 patients (1%), group G streptococci in 5 patients (2%), and *F. necrophorum* in 24 patients (10%).

Amess and colleagues (3) in the United Kingdom performed cultures on all throat swabs sent to their laboratory. Among 1157 swabs, they found group A streptococci in 156 (13%), group C streptococci in 47 (4%), group G streptococci in 9 (1%), and *F. necrophorum* in 57 (5%). In an analysis of the 351 patients aged 16 to 30 years, 33 cultures were positive for *F. necrophorum* (10%) and 34 cultures were positive for group A streptococci (10%).

In a Danish study, Jensen and colleagues (13) developed a real-time quantitative polymerase chain reaction assay for *F. necrophorum* DNA and applied it to 61 adults with pharyngitis and negative group A streptococcus culture and 92 healthy control participants. They found that 48% of the patients with pharyngitis and 21% of the healthy control participants tested positive for *F. necrophorum* DNA. Quantitative DNA concentrations were higher in the patients with tonsillitis. After this exploratory study, the authors performed anaerobic cultures on all throat swabs from patients aged 18 to 32 years with tonsillitis. More than 15% of those throat swabs grew *F. necrophorum*.

These studies suggest that *F. necrophorum* causes approximately 10% of cases of acute pharyngitis in adolescents and young adults. If this estimate is correct, or at least close, how might this knowledge affect pharyngitis decision making?

### COMPARING STREPTOCOCCUS PHARYNGITIS WITH *F. NECROPHORUM* PHARYNGITIS

We should compare the reasons for treating group A streptococcus pharyngitis with the reasons (and thus potential benefits) for treating *F. necrophorum* pharyngitis. To do this, we must estimate the probability that *F. necrophorum* pharyngitis will progress to the Lemierre syndrome.

We have strong data on suppurative complications. A recent study (14) of the microbiology of acute ear, nose, and throat infections requiring hospitalization found that

#### Key Summary Points

*Fusobacterium necrophorum* causes endemic pharyngitis in adolescents and young adults, with an approximate incidence of 10%.

Use a penicillin or a cephalosporin (not a macrolide) for empirical treatment of rapid streptococcus-negative pharyngitis in adolescents and young adults.

Pharyngitis normally resolves in 3 to 5 days.

The 2 major red flags in adolescent and young adult pharyngitis are worsening symptoms or neck swelling.

If the patient has bacteremic symptoms, treat either with a combination of penicillin and metronidazole or with clindamycin alone.

group A streptococcus and *F. necrophorum* both cause approximately 14% of infections requiring hospitalization.

We have no data on the clinical presentation of *F. necrophorum* pharyngitis. Whether antibiotic therapy affects the duration and severity of pharyngitis symptoms or contagion is unknown, so these considerations cannot be included as a rationale for diagnosis and treatment.

### ESTIMATING RISK FOR THE LEMIERRE SYNDROME DUE TO *F. NECROPHORUM* PHARYNGITIS

The 2005 National Ambulatory Medical Care Survey (15) found that 6% of adolescents see a physician each year for sore throat. If 10% of them have *F. necrophorum* pharyngitis, that would be 6000 cases per 1 million adolescents. The only prospective study on the incidence of the Lemierre syndrome (11) found a rate of 14.4 cases per 1 million adolescents per year (persons aged 15 to 24 years). From these estimates, we calculate that approximately 1 in 400 cases of *F. necrophorum* pharyngitis will result in the Lemierre syndrome.

Although these probabilities are not exact, they suggest that the risk for the Lemierre syndrome after *F. necrophorum* pharyngitis greatly exceeds that for acute rheumatic fever after group A  $\beta$ -hemolytic streptococcal pharyngitis (Table). Of all potential serious complications of adolescent pharyngitis, the Lemierre syndrome trumps acute rheumatic fever as the most dangerous and probable complication of pharyngitis in adolescents and young adults.

### IMPLICATIONS OF EXPANDING THE PARADIGM

These new data on *F. necrophorum* pharyngitis support expanding the diagnostic paradigm of pharyngitis in adolescents and young adults to include both group A  $\beta$ -hemolytic streptococcal pharyngitis and *F. necrophorum*

**Table. Hypothetical Cohort of 1 Million Patients Aged 15 to 24 Years With Pharyngitis**

Outcomes, by Type of Pharyngitis	Events per 1 000 000 Patients, <i>n</i>
<b>Group A streptococcus</b>	100 000
Acute rheumatic fever	50*
Complex acute rheumatic fever	5
Death	1
<b><i>Fusobacterium necrophorum</i></b>	100 000
The Lemierre syndrome	250†
Long-term disability (11)	20‡
Death	11§

\* All rheumatic fever estimates are from reference 5.

† This estimate comes from a series of assumptions about *F. necrophorum* pharyngitis and the incidence of the Lemierre syndrome in adolescents.

‡ This number comes from 3 severe sequelae in 37 patients with the Lemierre syndrome. Given the 95% CI, the value could vary from 5 to 55.

§ This number results from combining mortality data found in 4 published case series (8–11). The number could vary from 6 to 18, given the 95% CI.

pharyngitis. In changing the paradigm, we complicate pharyngitis decision making, because we have much less information on *F. necrophorum* pharyngitis than we do on streptococcal pharyngitis. The current paradigm supports teaching students and residents to look for streptococcus and otherwise avoid antibiotics.

We should consider several steps. These recommendations apply only to adolescents and young adults. Pharyngitis in preadolescents does not need a new paradigm, because *F. necrophorum* pharyngitis rarely occurs before adolescence. Given the decreased incidence of the Lemierre syndrome in older adults, the paradigm for that group does not need to be changed.

Debate over the treatment or testing of pharyngitis scores of 3 or 4 is ongoing. The American College of Physicians guidelines (1) recommend empirical treatment, whereas the Infectious Diseases Society of America guidelines (2) recommend treating only patients with positive test results for rapid streptococcus. Until we have better clinical data, I would favor treating the 30% of adolescents and young adults who present with at least 3 of the following: fever history, tonsillar exudates, swollen tender anterior cervical adenopathy, or lack of cough (16).

When physicians do treat empirically, they should use penicillins or cephalosporins. Physicians should avoid macrolides for empirical therapy in pharyngitis in adolescents and young adults because macrolides are not effective against *F. necrophorum*. Penicillins and cephalosporins are already first-line recommendations for streptococcal infection, but physicians prescribe macrolides too often.

Currently, we have no simple option for identifying *F. necrophorum* pharyngitis and no commercial polymerase chain reaction tests are available. A clinical microbiology laboratory in Denmark (17) routinely cultures rapid streptococcus-negative swabs on special media to grow *F. necrophorum*. They plate all swabs from patients aged 10 to

40 years onto anaerobic plates containing vancomycin (2.5 mg/L) and nalidixic acid (5 mg/L). Cultures are positive in up to 20% of patients aged 15 to 20 years.

If physicians do not empirically treat patients, they should always prescribe antibiotics for patients with clinical indicators of bacteremia (such as night sweats or rigors). In those patients, physicians should obtain blood cultures and include clindamycin or penicillin–metronidazole in the antibiotic regimen.

Students and residents must learn the natural history of routine pharyngitis: resolution in 3 to 5 days. When disease does not resolve quickly, symptoms worsen, or unilateral neck swelling develops, physicians should consider an expanded differential diagnosis, including suppurative complications (peritonsillar abscess and the Lemierre syndrome); group A, C, or G streptococcal pharyngitis; infectious mononucleosis; and acute HIV infection (18).

This expanded paradigm will affect our research agenda. We need more epidemiologic data on *F. necrophorum* pharyngitis; studies should include clinical information to inform physicians on the clinical presentation. We need further incidence data on the Lemierre syndrome. We may need improved techniques for diagnosing *F. necrophorum* pharyngitis.

Expanding the diagnostic paradigm of pharyngitis also has important implications for education and patient care. Although the data are not yet definitive, they strongly suggest that we should think expansively about pharyngitis in adolescents and young adults. Complications after pharyngitis are unusual, but the potential devastation of the Lemierre syndrome deserves our consideration.

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