California Association for Medical Laboratory Technology

Distance Learning Program

The Many Diseases Caused by *Fusobacterium necrophorum*

Course # DL-012

by

James I. Mangels, MA, CLS, MT(ASCP)
Consultant
Microbiology Services
Santa Rosa, CA

Approved for 3.0 CE
CAMLT is approved by the California Department of Public Health as a CA CLS Accrediting Agency (#21)

Level of Difficulty: Intermediate

39656 Mission Blvd. Phone: 510-792-4441
Fremont, CA 94539 FAX: 510-792-3045

Notification of Distance Learning Deadline
DON’T PUT YOUR LICENSE IN JEOPARDY!

This is a reminder that all the continuing education units required to renew your license/certificate must be earned no later than the expiration date printed on your license/certificate. If some of your units are made up of Distance Learning courses, please allow yourself enough time to retake the test in the event you do not pass on the first attempt. CAMLT urges you to earn your CE units early!
DISTANCE LEARNING ANSWER SHEET
Please circle the one best answer for each question.

COURSE NAME THE MANY DISEASES CAUSED BY FUSOBACTERIUM NECROPHORUM  COURSE # DL-012

NAME__________________________________________________ LIC. # _________________ DATE_________

SIGNATURE (REQUIRED) _______________________________________________________________________

EMAIL______________________________________________________________________________________

ADDRESS ____________________________________________________________________________________

3.0 CE – FEE: $36.00 (MEMBER) | $66.00 (NON-MEMBER)

PAYMENT METHOD: [ ] CHECK OR [ ] CREDIT CARD # ____________________________ TYPE – VISA or MC

EXP. DATE ________  |  SECURITY CODE: ___  -  ___  - ___

1. a b c d  11. a b c d  21. a b c d
2. a b c d  12. a b c d  22. a b c d
3. a b c d  13. a b c d  23. a b c d
4. a b c d  14. a b c d  24. a b c d
5. a b c d  15. a b c d  25. a b c d
6. a b c d  16. a b c d  26. a b c d
7. a b c d  17. a b c d  27. a b c d
8. a b c d  18. a b c d  28. a b c d
9. a b c d  19. a b c d  29. a b c d
10. a b c d  20. a b c d  30. a b c d

DISTANCE LEARNING EVALUATION FORM

According to state regulations, this form must be completed and returned in order to receive CE hours. Your comments help us to provide you with better continuing education materials in the distance learning format. Please circle the number that agrees with your assessment with, with 5 meaning you strongly agree and 1 meaning you strongly disagree.

1. Overall, I was satisfied with the quality of this Distance Learning course. 5 4 3 2 1
2. The objectives of this Distance Learning course were met. 5 4 3 2 1
3. The difficulty of this Distance Learning course was consistent with the number of CE hours. 5 4 3 2 1
4. I will use what I learned from this Distance Learning course. 5 4 3 2 1
5. The time to complete this Distance Learning course was: ________ hours
6. Please comment on this Distance Learning course on the back of this sheet. What did you like or dislike?
THE MANY DISEASES CAUSED BY
FUSOBACTERIUM NECROPHORUM

Course #DL-012
3.0 CE
Level of Difficulty: Intermediate

James I. Mangels, MA, CLS, MT(ASCP)
Consultant
Microbiology Services
Santa Rosa, CA

OUTLINE
A. Introduction
B. History of Fusobacterium necrophorum infection
C. Transmission
D. Illness/Symptoms
E. Microbiology of F. necrophorum
F. Pathogenic Mechanisms
G. Diagnosis and Identification of F. necrophorum infection
H. Treatment
I. Prevention
J. Conclusion
K. References

COURSE OBJECTIVES
After completing this course the participant will be able to:

1. outline the history of Fusobacterium necrophorum infection
2. discuss the various types of infections caused by Fusobacterium necrophorum
3. explain the pathogenicity factors of F. necrophorum
4. outline the clinical features of Lemierre's disease caused by F. necrophorum
5. explain how Fusobacterium necrophorum is identified
6. state methods to recover Fusobacterium necrophorum
7. outline methods of treatment of Fusobacterium necrophorum infection

A. INTRODUCTION
Fusobacterium necrophorum is a Gram-negative, non-spore-forming, nonmotile, obligately anaerobic (requires strict anaerobic conditions for growth), pleomorphic (varies in size and shape) bacterium. The current genus name, Fusobacterium, comes from the Latin word “fusus,” meaning spindle, and was given to describe the most common species, Fusobacterium nucleatum, which is spindle shaped. However, the other species of Fusobacterium, including Fusobacterium necrophorum, are not spindle shaped. The species name “necrophorum” is derived from the organism’s frequent association with necrotic lesions in humans and animals (4). F. necrophorum is part of the normal flora of the oral cavity, gastrointestinal tract, and
genitourinary tract of animals and humans (4,8). The organism is also a normal inhabitant of the rumen of cattle and sheep.

*F. necrophorum* is a more frequent pathogen in animals than in humans, although as will be described in this paper, infection in humans, although rare, can be severe, life threatening, and often overlooked. Clinicians and laboratory personnel should be aware of *F. necrophorum* infection because it is more prevalent than previously thought and because it can cause extreme illness or death, especially in teens and young adults. Also, the current decrease in usage of antibiotic therapy to treat pharyngitis has caused a recurrence of *F. necrophorum* infection.

The organism is generally associated with abscesses and various necrotic infections, particularly oral, paraoral and lower respiratory tract infections in animals and in humans. It is recovered in animals as a major pathogen causing infections such as foot rot, calf diphtheria, and liver abscesses in cattle, horses, goats, pigs, and sheep. When *F. necrophorum* is involved in disease it can cause necrotic lesions that are generally referred to as “necrobacillosis” (death of tissue due to the pathogenic factors of the organism). See Section F. Pathogenic Mechanisms.

In humans, *F. necrophorum* infection is most commonly associated with various oral and tonsillar abscesses, persistent or chronic sore throat, and other abscesses throughout the body. A very severe complication of tonsillar abscess or oral infections due to *F. necrophorum* is Lemierre’s syndrome, also called Lemierre’s disease or post-anginal sepsis, which can be a life threatening complication. Lemierre’s syndrome occurs predominately in older children or young adults (15-24 years of age. Note: The definition of the word post-anginal is any extreme pain that feels suffocating (not just heart pain). In Lemierre’s disease, the first symptom is an extremely painful sore throat (pharyngitis) that subsides but is followed by thrombophlebitis (a blood clot) of the jugular vein and septicemia (organisms in the blood stream) that travel to and cause distal abscesses (infections in other parts of the body), particularly in the lungs, pleural space, liver and large joints in the body. Other complications from *F. necrophorum* infection include meningitis, thrombosis of the cerebral veins, and infection of the urogenital and the gastrointestinal tract.

The classic symptom of Lemierre’s syndrome is a sudden acute jugular vein thrombophlebitis, followed by fever and sepsis (inflammatory response including shock and drop in blood pressure). The ability of *F. necrophorum* to stimulate clot formation with subsequent systemic spread is a fundamental feature of the pathogenesis of *F. necrophorum*. See Section F. Pathogenesis Mechanisms. This syndrome is the most important life-threatening manifestation of *F. necrophorum* infection in man. Lemierre’s syndrome will be described in greater detail in Section D. Illness/Symptoms.

Recently, *F. necrophorum* has been associated with recurrent or chronic sore throat in humans. Some studies have found that *F. necrophorum* is present in 10-15% of the time in patients aged 15-24 with chronic pharyngitis, and may be an agent of pharyngitis as often as beta *Streptococcus* Group A, (*Streptococcus pyogenes*) in some studies (1,3,9,10) See Section D. Illness/Symptoms. Consequently, some medical centers and clinics have started to use specific selective media for the isolation of *F. necrophorum* for the workup of chronic sore throat in specific age groups. See Section G. Diagnosis and Identification of *F. necrophorum* infection.

There are two subspecies of *F. necrophorum*. Human infection is usually caused by *F. necrophorum* subsp. *funduliforme*. In animals, the common pathogen is *F. necrophorum* subsp. *necrophorum*. There are some minor differences in the pathogenicity, immunology, and biochemical activity between the two organisms. However, in this course, the two subspecies will be considered the same.
Among all the cases of human infection with Gram-negative anaerobes, *Fusobacterium necrophorum* constitutes only a tiny proportion, perhaps less than 1%, of all anaerobic isolates in various infections (4,5). However, *F. necrophorum* is unique among the Gram-negative anaerobes for its pathogenicity and for its association with very unusual infections in humans and in animals.

This Distance Learning Course will describe the many diseases caused by *F. necrophorum*. Some of the unusual and often life-threatening types of infection caused by this organism will be outlined. In addition, this course will describe the history, transmission, pathogenesis, diagnosis, identification of the organism, and clinical features of these infections in animals and in humans.

B. HISTORY OF *FUSOBACTERIUM NECROPHORUM* INFECTION

Since *Fusobacterium necrophorum* is a more common pathogen in animals than in humans, it is not surprising, therefore, that the first reports of infection were from animals. Probably the earliest report of *Fusobacterium necrophorum* infection in animals was in 1876 by G. Dammann (a veterinarian in Germany) when he described diphtheritic (necrotic laryngitis) infections in calves (2). The symptoms and clinical features Dammann observed are typical of *F. necrophorum* infection we see today. Dammann, however, believed he was observing infection due to the organism called, at the time, *Bacillus diphtheria*. In 1884, F. Loeffler (a German microbiologist) demonstrated that calf diphtheria was actually due to a Gram-negative organism called, at the time, *Actinomyces necrophorus*. He identified and described a thin Gram-negative rod with filamentous forms in stained sections from necrotic tissue of diphtheritic material. When Loeffler injected this necrotic material into mice, they developed an infection that generated foul-smelling purulent lesions containing bacilli similar in morphology to the original necrotic material. Loeffler was able to grow the organism in calf serum broth, but was not able to subculture the organism and perform further testing. Other reports in 1886 called the same organism *Bacillus necrophorus*, isolated from infections in hogs.

Probably the first reported human *F. necrophorum* infection was in 1891, when C.G. Schmorl (a German pathologist) reported hand abscesses in himself and his assistant after they handled rabbits they had experimentally infected with *F. necrophorum* to study necrobacillosis (2). Stained smears of the pus from their hand abscesses showed the same characteristic filamentous Gram-negative bacilli as from the rabbits. Schmorl named the organism *Sphaerophorus funduliformis*. Schmorl also noted in his report the ability of *Sphaerophorus funduliformis* (*F. necrophorum*) to produce a zoonotic infection (an infection passed from animals to humans).

The first isolation and a detailed description of *F. necrophorum* from humans was made by Jean Hallé in 1898 as part of a Ph.D. thesis on the bacteriology of the female genital tract. He called the organism *Bacillus funduliformis*, a descriptive term of the Gram stain morphology, from the Latin fundula (little pockets), because he felt that some of the bacilli resembled irregular shaped sausages (9). His line drawings of the microscopic appearance of the organism under different conditions are still accurate today. See Fig. 1. Line Drawings of *Bacillus funduliformis*.

Two French physicians in 1900 reported the first description of an infection in a patient who had symptoms similar to what we now call Lemierre’s syndrome, i.e., a post-anginal septicemic infection (pharyngitis preceding fever, rigors, internal jugular thrombophlebitis, and distal abscesses). The patient initially appeared to be improving after his severe sore throat and
Fig. 1. Line drawings of *Bacillus funduliformis*

*Line drawings from J. Halle, 1898. Adapted from reference number 8.*

Comments from a thesis by J. Halle: “Top left, common short, slightly curved rods seen in pus and tissues; top right, rare giant forms; bottom left, poorly staining vesicular forms sometimes seen in culture; bottom right, bizarre pleomorphic forms commonly seen in culture.”
acute tonsillitis, but suddenly after 4 or 5 days, the patient had an onset of rigors and progressed
to an overwhelming sepsis (inflammatory response leading to shock and decreased blood
pressure) and died (9). See Section D. Illness/Symptoms. The two French physicians were able
to isolate anaerobic pleomorphic Gram-negative bacilli from the abscess material and from the
patient’s blood culture. They may have called the organism Bacterium necrophorum. However,
their description of the colonies and the Gram stain morphology of the organism are consistent
with F. necrophorum.

An understanding of the disease and symptoms of post-anginal infection was more
clearly characterized by Lemierre in 1936. Andrè Lemierre (1875 to 1956) was a physician and
professor of microbiology and infectious diseases at a hospital in Paris. He became aware of
serious human infections due to F. necrophorum, although the organism at that time was called
Bacillus funduliformis. Lemierre described a human system-wide septic thrombophlebitis
infection with F. necrophorum. The sentinel case he reported was a young child with chronic
purulent otitis presenting with septic arthritis of the knee, cerebral abscess, and signs of
overwhelming systemic infection (9). Smears of the abscess material showed organisms
consistent with current descriptions of F. necrophorum. Other investigators during this period
were calling this organism Bacillus symbiophiles or by other synonyms.

Lemierre believed that post-anginal septicemia and systemic septic thrombophlebitis
infection were a feature of the anaerobe F. necrophorum, and the recovery of the same organism
from other body sites of a patient was significant. Lemierre highlighted the confusion of
nomenclature for the identical organism, whereby German authors were referring to the
organism as Bacillus symbiophiles and French workers as Bacillus funduliformis. Lemierre
suggested that these might be a single organism on the basis of the properties of the organisms
and the clinical descriptions of the associated cases.

Lemierre’s main contribution to the understanding of this syndrome was the clarity of his
clinical description of post-anginal septicemia associated with the organism we now know as F.
 necrophorum. His comment on the ease of clinical diagnosis of the condition defines his
understanding of the disease. “To anyone instructed as to the nature of these septicemias it
becomes relatively easy to make a diagnosis on the simple clinical findings. The appearance and
repetition several days after the onset of a sore throat (and particularly of a tonsillar abscess) of
severe pyrexial (fever response) 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” (2,9).

Since the early reports of F. necrophorum infection in animals and in humans, this
organism has been classified under a variety of genera and species. The confused taxonomy for
many years has led to a misunderstanding of its significance in infection, and has caused
problems in the actual identification of the organism and lack of understanding of its pathogenic
mechanisms (2). The various synonyms of F. necrophorum are listed in Table 1, Previous
Synonyms of Fusobacterium necrophorum. Much of the confusion in taxonomy probably has
been due to inadequate anaerobic culture methods. Better anaerobic culture methods allowed the
isolation and identification of F. necrophorum and a clearer understanding of the role of the
organism in various infections (4).

By the start of the antibiotic era in the 1940’s, the features of Lemierre’s syndrome had
been established and the incidence of disease began to decline because of appropriate therapy.
However, with the decline in the incidence of Lemierre’s syndrome, the knowledge, experience,
and recognition of the severe disease in humans due to Fusobacterium necrophorum was often
forgotten and the disease not immediately diagnosed. The “forgotten” disease of Lemierre’s syndrome still exists and perhaps is undergoing a resurgence in Europe (2,9). Because of the resurgence of *F. necrophorum* infection, including Lemierre’s syndrome in Europe, there has been as increased awareness and screening in the U.S. (10). It is speculated that the resurgence of Lemierre’s syndrome observed in Europe may be due to their policies restricting antibiotic use in patents with pharyngitis, or the shift in prescribed antibiotics, such as penicillin, to macrolides and cephalosporins which lack activity against *F. necrophorum*. With the role of *F. necrophorum* in persistent or chronic sore throat, an understanding of the organism is extremely important. See Section D. Illness/Symptoms.

Table 1. Previous Synonyms of *Fusobacterium necrophorum*

<table>
<thead>
<tr>
<th>Synonym</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Actinomyces necrophorus</em></td>
</tr>
<tr>
<td><em>Actinomyces cuniculi</em></td>
</tr>
<tr>
<td><em>Bacillus filiformis</em></td>
</tr>
<tr>
<td><em>Bacillus funduliformis</em></td>
</tr>
<tr>
<td><em>Bacillus diphtheria</em></td>
</tr>
<tr>
<td><em>Bacillus necrophorus</em></td>
</tr>
<tr>
<td><em>Bacillus pyogenes anaerobius</em></td>
</tr>
<tr>
<td><em>Bacillus symbiophiles</em></td>
</tr>
<tr>
<td><em>Bacterium necrophorum</em></td>
</tr>
<tr>
<td><em>Bacterium necrophorus</em></td>
</tr>
<tr>
<td><em>Bacteroides funduliformis</em></td>
</tr>
<tr>
<td><em>Bacteroides necrophorus</em></td>
</tr>
<tr>
<td><em>Fusiformis necrophorus</em></td>
</tr>
<tr>
<td><em>Necrobacterium funduliforme</em></td>
</tr>
<tr>
<td><em>Streptothrix cuniculi</em></td>
</tr>
<tr>
<td><em>Sphaerophorus necrophorus</em></td>
</tr>
<tr>
<td><em>Sphaerophorus funduliformis</em></td>
</tr>
<tr>
<td><em>Streptothrix necrophora</em></td>
</tr>
</tbody>
</table>

*adapted from reference number 4.

**C. TRANSMISSION**

*F. necrophorum* is part of the normal bacterial flora of the gastrointestinal tract, the oral cavity, and the rumen in cattle, goats, and sheep. Therefore, transmission in animals commonly occurs as a result of direct contact with soil contaminated with animal feces, especially in wet, muddy, or unsanitary conditions. *F. necrophorum* is known to survive in the soil of pastures for up to 18 weeks (2), which is unusual from a microbiological standpoint since *F. necrophorum* is a non-spore-forming anaerobe. It is believed that contaminated soil leads to foot disease or foot rot in horses, sheep, and cattle, and it is believed that cattle or sheep diphtheria is likely contracted from contaminated food or food containers such as buckets, stalls, etc., containing *F. necrophorum*. Direct animal to animal contact is also a common transmission method in animals through open sores or from animal bites.

Since *F. necrophorum* is part of the normal bacterial flora of the oral cavity, genitourinary tract, and the gastrointestinal tract in humans, it has been assumed that primary transmission of the organism occurs from direct contact with body fluids or mucous membranes.
Another suggestion has been that transmission occurs due to contamination from one’s own normal bacterial flora, and *F. necrophorum* causes infection after either an injury or some type of break or change in immunity (9). Yet another suggestion has been that transmission may occur after surgical procedures, accidental trauma, from animal bites, or infected open sores of animals contaminated with *F. necrophorum*.

However, recent investigations using molecular techniques may show that in some cases severe *F. necrophorum* tonsillitis and its rare consequences, such as Lemierre’s, may be due to acquiring *F. necrophorum* from an exogenous source, perhaps from an animal, or by human to human transmission (9). Other interesting investigations show that severe *F. necrophorum* infection may be the result of another entirely different concurrent infection, such as infection with Epstein-Barr virus (EBV) which causes infectious mononucleosis, or another possible viral infection, which may alter the individual’s normal oral flora or lower one’s resistance so that *F. necrophorum* can begin to initiate disease acquired from another source (9). Approximately 10% of published cases of severe *F. necrophorum* infection are associated with infectious mononucleosis (9). Some investigators believe that alterations or changes in the pharyngeal mucosa during cases of infectious mononucleosis might allow invasion and penetration of *F. necrophorum* into the tonsillary epithelium, leading to potential infection.

Other studies in Finland suggest that dramatic changes of an individual’s normal oral flora, after pneumococcal vaccination for example, may cause a person to be more susceptible to *F. necrophorum* infection either from an exogenous source or from one’s own flora (2,9). The nasopharynx is colonized by multiple microorganisms, and disruption of the microbiota (microbe population at a body site) with its various synergistic and interfering interactions can either
facilitate or block respiratory tract infections. Pneumococcal vaccination has been shown to alter the carriage of other common pathogens such as Hemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. Finland has seen an increase in severe F. necrophorum infection since initiating a very comprehensive vaccination program, including the pneumococcal vaccine, since early 2000 (2,9). Therefore, it is speculated that the pneumococcal vaccine may be one reason for the increase in serious F. necrophorum infection.

So it is not clear at this time whether severe F. necrophorum infection in humans (such as recurrent sore throat, severe throat infection and tonsillitis leading to Lemierre’s syndrome) is caused by a person’s own normal flora, or is acquired from another source, or is caused by alteration of one’s normal flora.

D. ILLNESS/SYMPTOMS

This section will describe some unique illnesses (“The Many Diseases of F. necrophorum”) and symptoms of F. necrophorum infection in animals and humans. Although there are many illnesses due to F. necrophorum, primarily foot rot and calf diphtheria in animals, and acute tonsillitis leading to Lemierre’s syndrome, Vincent’s angina, and recurrent sore throat in humans will be described.

The animal diseases are described in this course to give an appreciation for how widespread, virulent and economically destructive F. necrophorum infection can be. While there are many types of F. necrophorum infections in animals, two major infections are foot rot in cattle, horses, and sheep, and calf diphtheria (necrotic laryngitis). For a description of other F. necrophorum infections in animals, such as pneumonia, bovine liver abscesses, pericarditis (infection of membrane surrounding the heart), subcutaneous abscesses (abscesses under the skin), chronic fibronecrotic rhinitis (inflammation of nasal membranes which can restrict air intake), and laryngeal chondritis (an upper respiratory tract disease which causes swelling and occlusion of the larynx), see reference 7.

Foot rot

Foot rot is probably one of the major infections in animals due to F. necrophorum. It causes foot destruction, leading to lameness in dairy and beef cattle, goats, and sheep. The disease can have a major financial impact on the cattle industry due to weight loss of the animal and reduction in milk production. The clinical signs of foot rot are usually a sudden onset of swelling, erythema (redness and inflammation), tissue destruction, extreme foul odor, and significant pain to the animal. This is often noted in animals when the animal shifts its weight constantly. If the infection becomes chronic, there may be atrophy in the affected limb and further infection of joints, bone, or tendons. Animals with foot rot typically have a terrible smell coming from their feet due to F. necrophorum producing butyric acid. Foot rot infection is usually treated with antibiotics and other methods. See Section H. Treatment. It is said that symptoms and clinical features of foot rot are so characteristic, that the presence of F. necrophorum may be predicted (7,8).

Calf diphtheria

Calf diphtheria (necrotic laryngitis), is probably the second most important infection in animals due to F. necrophorum. Calf diphtheria can be an acute or chronic infection of the laryngeal mucosa and cartilage of young cattle, characterized by fever, cough, and difficulty in breathing. The disease initially starts with swollen cheeks or ulcerations inside the mouth. It can progress to ulcers of the tongue and palate, and then to pneumonia. The ulcerations are very painful so the infected animal generally is unable to eat, causing extreme weight loss. The
Infection occurs primarily in feedlot cattle 3–18 mo of age. Cases of calf diphtheria are seen worldwide, are more prevalent in the fall and winter, and can have a major financial impact on the cattle industry (7,8).

**Acute tonsillitis and Lemierre’s syndrome**

In man, infection due to *F. necrophorum* is most commonly oral, tonsillar, or the severe post-tonsillar infection called Lemierre’s syndrome. If *F. necrophorum* gets into the bloodstream (bacteremia), generally as a consequence of Lemierre’s syndrome, the organism may then initiate secondary infections in the bone, lung, liver, or other body sites. Although Lemierre’s syndrome has been well documented for over a century, it is quite a rare condition and modern-day clinicians are frequently unaware of *Fusobacterium necrophorum* and the severity of symptoms it can cause. Acute tonsillitis can be caused by a variety of bacteria and viruses. In many instances, anaerobes—in particular, *Fusobacterium necrophorum*—have a role in an acute inflammatory process in tonsillitis (9). The inflammatory process can progress to more serious infection of nearby tissues and structures, leading to further infection.

Lemierre’s syndrome occurs when a *Fusobacterium necrophorum* throat infection progresses to the formation of a peritonsillar abscess, and this infection spreads to nearby tissues and into the jugular vein (a major blood vessel that drains blood from the brain, face, throat and neck and transports it to the heart). (2,9). Infection of the jugular vein may lead to systemic clot formation, or spread of bacteria through the bloodstream (septic thrombophlebitis). *F. necrophorum* has a strong tendency to form clots because of its pathogenic factors. See Table 2. Summary of Pathogenic Mechanisms of *Fusobacterium necrophorum*. Pieces of the infected clot break off and travel to the lungs as emboli, blocking branches of the pulmonary artery, or to other sites.

Lemierre’s syndrome generally develops in previously healthy young people (typical age group is 15-24). The pharyngitis of the patient is typically severe and exudative (fluid filled and generally containing pus), followed by a high fever (101-103°F) and rigors (sudden feeling of cold, shivering and sweating) beginning on the fourth or fifth day after the initial sore throat symptoms and overall weakness (2,9). This is usually accompanied by a one-sided thrombophlebitis of the internal jugular vein due to the spread of the infection from the throat. There is swelling at the angle of the jaw and tenderness and pain along the overlying muscles. Metastatic abscesses are usually present and are most often in the lungs. Other sites of distant abscess frequently include the long bones and skeletal joints, which are often very painful. The patient’s condition often declines to extreme prostration or coma, and an untreated infection commonly ends in death within 7-15 days. Although severe tonsillar abscess and Lemierre’s syndrome are rare the mortality is extremely high. Therefore, the diagnosis of Lemierre’s syndrome should be considered in a young septicemic patient with *Fusobacterium necrophorum*, and in cases of isolated *F. necrophorum* infection occurring at unusual sites throughout the body.

Lemierre's syndrome was relatively common in the pre-antibiotic era with a high mortality rate of up to 90% (2,7). The syndrome seemed to disappear with widespread use of antibiotics for upper respiratory tract infection, including pharyngitis. However, in the last 15 years there has been a rise in incidence, possibly related to restriction of antibiotic use for sore throat. Lemierre’s is often referred to as a “forgotten” disease”, although it is probably best described as a “repeatedly discovered” disease, as it may not always be included in medical curricula, and often is not mentioned in some major medical textbooks, so many physicians are not familiar with the disease. There is some evidence that Lemierre’s syndrome may be on the increase, particularly in the United Kingdom, Finland, and France (2).
For a syndrome that is so characteristic, a diagnosis of Lemierre’s is often missed until an anaerobic Gram-negative rod is isolated from a blood culture or from another body site. Many clinicians and even laboratory personnel have never seen a case and are unaware of the condition (I have seen only one case in 30 years as a microbiologist). In many cases the original sore throat has resolved by the time a patient presents with septicemia. The various clinical manifestations of Lemierre’s syndrome can be difficult for physicians to single out; therefore, there can often be a diagnostic delay until more laboratory results are available.

Table 2. Summary of Pathogenic Mechanisms of *Fusobacterium necrophorum*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism of Pathogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesion</td>
<td>Cell surface molecules which permit attachment to host cells. This is key first step in pathogenesis.</td>
</tr>
<tr>
<td>Fimbriae</td>
<td>Hair-like structures on surface of <em>F. necrophorum</em> that permit attachment to host cell.</td>
</tr>
<tr>
<td>Leucocidin</td>
<td>Probably most significant exotoxin. It destroys leukocytes by causing pores in the leukocyte cell membrane so that cellular material leaks out.</td>
</tr>
<tr>
<td>Leukotoxin</td>
<td>This exotoxin contributes to the characteristic necrotic abscesses in <em>F. necrophorum</em> infection. Produces degeneration and lysis of the leukocyte cellular membrane causing death to the cell.</td>
</tr>
<tr>
<td>Lipopolysaccharide (LPS)</td>
<td>Important endotoxin within the cell wall of <em>F. necrophorum</em>. It produces abscesses, hemolysis, and tissue destruction. It also elicits a strong immune response which may include fever, shock, and decreased blood pressure characteristic of Lemierre’s syndrome.</td>
</tr>
<tr>
<td>Proteolytic enzymes</td>
<td>Various exotoxins that break down proteins in body tissue and lead to destruction, which permits invasion of organism into other tissues.</td>
</tr>
<tr>
<td>Plasminogen, platelet aggregation factor, hemolysin, and hemagglutinin</td>
<td>Important exotoxins that cause abnormal coagulation and the formation of clots characteristic of Lemierre’s syndrome.</td>
</tr>
</tbody>
</table>

*Adapted from references number 7 and 8.*
Vincent’s angina

Another unusual human infection due to *Fusobacterium necrophorum* is called Vincent’s angina (also known as trench mouth). Angina means intense local pain. Vincent’s angina is often seen in children, in patients who have poor dental hygiene, or in patients who have a compromised immunity. Vincent’s angina infections were initially reported from soldiers during WW I, and are very painful, with ulceration and tissue necrosis, and bleeding and swelling and sloughing off of dead tissue from the mouth and throat due to *F. necrophorum* and an oral spirochete (*Borrelia vincentii*). A foul discharge with consequent foul odor to the breath is a common symptom in Vincent’s angina. Some studies show that a severe case of Vincent’s angina can lead to Lemierre’s syndrome (2,8,9). There may be other secondary infections due to *F. necrophorum* in patients with Vincent’s angina, such as otitis (ear infections) or sinus infections.

Recurrent or persistent sore throat

Lastly, *F. necrophorum* in humans has been recently identified as a significant cause of persistent sore throat syndrome. This disease is characterized by a chronic, persistent sore throat that clinically resembles *Streptococcal* pharyngitis, but is negative for beta hemolytic *Streptococcus*. The sore throat typically has persisted for longer than 5 days with no improvement. Sometimes the patient’s sore throat symptoms can become increasingly worse during the episode. Studies in the United Kingdom and in other parts of Europe have investigated the cause of persistent sore throat (1,2,3,10). A recent surge in complicated cases of pharyngitis, particularly in adolescents, prompted more elaborate microbiological testing (1,3). DNA studies revealed that *Fusobacterium necrophorum* is as common as Group A *Streptococci* in the 15-24 year old age group. In several studies, the investigators cultured for beta-hemolytic *Streptococcus* groups A, C and G, and *F. necrophorum* (1,3,10). Among a total of 248 samples, 27 were positive for beta-hemolytic *Streptococcus* Group A, two were positive for beta-hemolytic *Streptococcus* group C, five for beta hemolytic *Streptoccus* G, and 24 were positive for *F. necrophorum*. In this same study, *F. necrophorum* was recovered in 10% of patients with acute sore throat, 21% of recurrent sore throats and 23% of peritonsillar abscesses. Group A *Streptococci* were recovered in 10% of patients 15-24 years of age. The study points out that the consequences of acute rheumatic fever from streptococi are very rare, while the consequences of severe tonsillitis due to *Fusobacterium necrophorum* causing Lemierre’s are 1 in 400 cases (1,2,3). In other words, *F. necrophorum* can cause Lemierre’s syndrome at an incidence higher than that at which Group A *Streptococcus* can cause acute rheumatic fever. The consequences of severe *F. necrophorum* infection have a greater morbidity and mortality than Group A *Streptococcus* infection. Therefore, the authors suggest that the diagnostic workup for adolescent pharyngitis should be expanded to consider *F. necrophorum* (1,2,3).

Typically, physicians have considered Group A *Streptococcus* as the only important cause of sore throat because it can lead to acute rheumatic fever. Physicians typically ignore other organisms because those organisms cause either self-limited symptoms without serious
sequelae (consequences of disease), or in the case of viruses there is no treatment available. The guidelines for treating Group A *Streptococcus* have evolved into algorithms for sore throat management that encourage many offices, urgent care centers, and emergency departments to use a rapid strep test for patients with sore throat symptoms. Often the rapid strep test is ordered routinely for patients with sore throat, in lieu of basing the decision to test on a targeted history and physical examination that takes into account the patient’s age. This strategy results in patients being diagnosed only as having or not having strep throat, resulting in a decision that antibiotics are not needed if the patient does not have strep throat (1,3).

But when the patient's symptoms persist or worsen, and if the patient is in a certain age group, these criteria no longer apply and more careful workup is needed. When an adolescent or young adult (ages 15-24 years) patient has a sore throat, the physician needs to pay special attention to the following red flags: rigors, shaking chills, high fever (greater than 102°F), night sweats, and unilateral neck swelling (1,3). These red flags should indicate that the patient may have a more serious illness. *Fusobacterium necrophorum* pharyngitis and chronic sore throat occurs predominately in the same age group as patients who have Lemierre’s syndrome. Though much remains unknown about *F. necrophorum*, it appears to cause sore throats just as commonly as strep does in adolescents and young adults, and Lemierre’s syndrome in this age group appears to be more common than acute rheumatic fever. Dealing with adolescent and young adult pharyngitis is more complicated than many practitioners realize.

Fig 2. Gram stain of *Fusobacterium necrophorum*
*Adapted from archival photos from Centers for Disease Control and Prevention, 2014.

Fig. 3. Photograph of Positive Lipase Reaction of *Fusobacterium necrophorum* *

*adapted from Anaerobe Systems and Hardy Diagnostics. Photo on left is looking at whole plate; photo on right is close up of positive lipase reaction observing oily sheen and iridescence.
E. MICROBIOLOGY

The colony size of *Fusobacterium necrophorum* on brucella blood agar is 2-3 mm in diameter in 24 to 48 hours (*E. coli*, by comparison, is 3-4 mm in diameter) if the medium used is enriched with vitamin K₁ and hemin, and if the medium is pre-reduced (a process in which the medium is never exposed to oxygen). The morphology of the colony is circular, convex to umbonate (a conical or surface elevation like half an egg and raised), and the surface often can be bumpy and uneven, with a margin of scalloped to erose (irregular notched margin) (5,8). Colonies are cream-yellow in color, smooth and round, and they often produce an odor of cabbage due to the production of butyric acid. There can be some alpha-hemolysis (greening around colonies on blood agar plates) following exposure to oxygen. *F. necrophorum* may not grow on media that is not enriched or has not been manufactured pre-reduced, since the organism is an obligate anaerobe (6).

The cellular morphology of *F. necrophorum* is a Gram-negative, nonsporeforming, pleomorphic bacillus that ranges in size from 0.5 to 0.7 µm in diameter, with swelling round bodies to 1.75 µm in diameter, and with some of the cell filaments longer than 10 µm in length (5,8). See Fig 2. Gram-stain of *Fusobacterium necrophorum*. The bacterial cells are usually extremely pleomorphic (vary in size from small, almost coccoid bodies to long filaments with parallel sides and blunt ends). The morphology will be affected by the type of media used and the age of the culture. Filamentous forms are usually seen more frequently in young cultures and from a broth medium, while bacilli forms are more common in older cultures and when grown on agar. With standard stains, e.g., safranin or carbol fuchsin, irregular staining or beading may be seen. Older cultures appear to stain more irregularly; some attribute the loss of staining ability to aging and degeneration. Some speculate that the irregular staining characteristics and extreme pleomorphic nature of *F. necrophorum* may be due to exposure to oxygen, and that when the organism is stained under an anaerobic atmosphere, the cells may be more regular. The highly pleomorphic Gram stain morphology of *F. necrophorum* allows differentiation from *F.*
Fusobacterium nucleatum, which is seen as long, thin, spindle shaped rods. See Table 3. Features and Biochemical Characteristics of Most Common Fusobacterium species.

Biochemically, F. necrophorum is indole positive, nitrate reduction test negative, esculin hydrolysis negative, and produces lipase on egg yolk agar (5,8). See Fig 3. Photograph of Positive Lipase Reaction of Fusobacterium necrophorum. All species of Fusobacterium produce butyric acid in high amounts from a broth medium containing glucose, and ferment lactate to propionate, detected by gas liquid chromatography. Use of special potency antibiotic disks as a means to initially group anaerobes show all species of Fusobacterium resistant to vancomycin 5 µg, but susceptible to kanamycin 1000 µg and colistin 10 µg (5). See Table 4 for Special Potency Disk Reactions. Under a long-wave UV Woods Lamp, Fusobacterium species colonies fluoresce with a vivid greenish-yellow color (chartreuse) (5). The most direct means of identification of F. necrophorum is with Gram stain, indole production, and lipase reaction. See Table 3. Features and Biochemical Characteristics of Most Common Fusobacterium species. Other biochemical tests show that some strains grow in 20% bile and are catalase negative. F. necrophorum does not generally ferment carbohydrates or can be variable and often weak in its fermentation reactions. The organism’s major energy substrate is lactic acid, which is converted mainly to acetate, butyrate, and small amounts of propionate (8,9).

Some rapid commercial identification kits for anaerobic bacteria incorrectly identify Fusobacterium necrophorum. Often this is because too small a number of F. necrophorum isolates is included in the data base of the commercial anaerobic identification system to permit adequate differentiation and separation from other anaerobes, and because F. necrophorum often does not utilize many of the substrates employed in the commercial system. So, take this into account if you only use a commercial anaerobic identification system to identify this organism.
Table 3. Features and Biochemical Characteristics of Most Common Fusobacterium species*

<table>
<thead>
<tr>
<th>Species name</th>
<th>Cellular morphology</th>
<th>Indole</th>
<th>Growth in 20% bile</th>
<th>Lipase</th>
<th>Esculin hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>F. mortiferum</em></td>
<td>bizarre, round bodies</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><em>F. necrophorum</em></td>
<td>pleomorphic with swellings and long rods</td>
<td>+</td>
<td>-+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>F. nucleatum</em></td>
<td>slender pointed end rods</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>F. varium</em></td>
<td>bizarre, round bodies</td>
<td>V</td>
<td>+</td>
<td>V*</td>
<td>-</td>
</tr>
</tbody>
</table>

Key: - is negative, + is positive, V is variable, -+ most strains are negative a few stains are positive, + most strains are positive a few strains are negative, V* some strains may be positive after 5 days of incubation.

Indole: Some organisms are able to oxidize tryptophan into indole. A positive test of indole is indicated in this chart by a +.

Growth in 20% bile: Some anaerobic gram-negative rods can grow in the presence of high concentrations of bile. Growth is indicated by turbidity and is indicated in this chart by +.

Lipase: Some organisms produce the enzyme lipase that can break down triglycerides in media, producing an oily iridescent sheen on and surrounding colonies on a medium such as egg yolk agar.

Esculin hydrolysis: Some organisms are able to hydrolyze esculin to esculetin, which reacts with iron in the medium to produce a dark brown or black complex. A positive test is indicated in this chart by a +.

* adapted from references number 4 and 7
<table>
<thead>
<tr>
<th>Organism</th>
<th>Kanamycin 1,000 µg</th>
<th>Vancomycin 5 µg</th>
<th>Colistin 10 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive organisms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S&lt;sup&gt;b&lt;/sup&gt;</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Bacteroides fragilis group</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>Bacteroides ureolyticus group</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Fusobacterium sp.</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Porphyromonas sp.</td>
<td>R</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>R</td>
</tr>
<tr>
<td>Prevotella sp.</td>
<td>R</td>
<td>R</td>
<td>V</td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td>S</td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>

<sup>a</sup> R, resistant; S, susceptible; V, variable

<sup>b</sup> Exceptions: Rare strains of *Lactobacillus* sp. and *Clostridium* sp. may be vancomycin resistant

<sup>c</sup> *Porphyromonas* sp. is vancomycin sensitive, but fluoresces or is pigmented

*adapted from reference number 4.
F. PATHOGENIC MECHANISMS

*F. necrophorum* has a variety of unusual and complex pathogenic mechanisms to cause disease in man and in animals. See Table 2. Summary of Pathogenic Mechanisms of *Fusobacterium necrophorum*.

One of the major virulence factors of *F. necrophorum* is leukotoxin, a secreted protein active specifically against leukocytes. The leukotoxin of *F. necrophorum* is a unique protein that does not share DNA sequence similarity with any other leukotoxin (8,9). Leukotoxin produces degeneration and lysis of the leukocyte cellular membrane, releasing the cellular contents of the leukocyte and causing death of the cell. Leukotoxin contributes to the formation of necrotic abscesses characteristic of *F. necrophorum* infection. The production of necrosis helps *F. necrophorum* evade the host immune response and to proliferate.

Another major pathogenic factor of *F. necrophorum* is a cell wall lipopolysaccharide endotoxin (LPS) which is chemically similar to the LPS seen in aerobic gram-negative bacteria. An endotoxin is part of the outer membrane of the cell wall of Gram-negative bacteria. The biological potency of the lipopolysaccharide resembles that of *Salmonella* endotoxin in capacity to produce local and generalized reactions (2,9). The lipopolysaccharide of *F. necrophorum* produces abscesses, hemolysis, and tissue destruction. Lipopolysaccharide also produces fever, shock, and a decrease in blood pressure, which are clinical features commonly seen in patients with Lemierre’s syndrome.

Other pathogenic mechanisms in *F. necrophorum* include various exotoxins (secreted toxins that damage normal host cell metabolism) that destroy leukocytes and prevent migration of leukocytes into the infected area. Some of these exotoxins are hemolysin, leucocidin,
hemagglutinin, plasminogen, platelet aggregation factor, and several other extracellular enzymes, such as phosphatases, proteases, and deoxyribonucleases (2,9). All these pathogenic mechanisms contribute to entry, colonization, proliferation, and establishment of the organism, and to the development of lesions and abscesses. Leucocidin is likely one of the most significant exotoxins of *F. necrophorum* and is linked particularly to the destruction of polymorphonuclear leukocytes (PMNs). This exotoxin appears to function by causing the formation of pores (holes) in PMN’s so that the cellular contents leak out.

Activation of the other important exotoxins, such as plasminogen, platelet aggregation factor, and the production of hemagglutinin by *F. necrophorum*, cause abnormal coagulation and the formation of the clots and thrombotic complications that are common features seen in Lemierre’s syndrome. The exotoxins of *F. necrophorum* first initiate an inflammatory response that causes platelets to aggregate and blood vessels to dilate, and then finally produce clotting abnormalities. In addition, *F. necrophorum* produces various proteolytic enzymes that aid in the pathogenesis of the organism by breaking down proteins, leading to tissue destruction and permitting invasion and entry into other tissues.

Lastly, *F. necrophorum* has two clever ways of attaching itself to host cells so that the above pathogenic factors can cause disease. One is adhesions (cell-surface molecules that allow adherence to specific host cell sites) and another is fimbriae (hair like structures on the perimeter of the organism) for attachment to the host cell (2,9). Once attachment occurs, the pathogenic mechanisms of *F. necrophorum* can start to function on host cells.

However, one of the most striking and unanswered aspects of the pathogenesis of human *F. necrophorum* infection is the tightly clustered age distribution in late teens and early 20’s. This applies not only to Lemierre’s syndrome, but also to tonsillitis, peritonsillar abscess, and persistent sore throat. There are interesting questions that remain unanswered such as, is there a change in exposure to *F. necrophorum* at that age group, is there a change in the individual’s immunity at this age, is this young person likely exposed to a more virulent strain with different pathogenic factors, are there structural changes to the tonsil at this age that make infection more likely, and is there an increase in possible concomitant viral infections such as EBV that might lead to *F. necrophorum* infection. All are interesting questions that scientists cannot answer yet.

**G. DIAGNOSIS AND IDENTIFICATION OF *F. NECROPHORUM* INFECTION**

Some *F. necrophorum* infections in animals or in man can be initially suspected by observing specific symptoms and history. For example, clinical signs of foot rot in an animal plus physical examination of the foot will lead to a presumptive diagnosis of *F. necrophorum* infection. Similarly, in humans, a history of recent severe sore throat followed by sepsis and distal infections in a teenager or young adult will lead to a presumptive diagnosis of Lemierre’s syndrome. The symptoms of specific syndromes are so characteristic and unique that *Fusobacterium necrophorum* may be speculated before any diagnostic testing is performed.

However, in most cases the diagnosis of infection and identification of *F. necrophorum* must be obtained by laboratory diagnostic tests. The clinical laboratory plays an important role in obtaining a diagnosis in Lemierre’s syndrome by using blood cultures, joint aspirates or specimens from other sites to test for the causative agent of the infection. The recovery of an anaerobic pleomorphic Gram-negative rod with filaments and swellings from blood cultures and/or from other sites is helpful in the preliminary identification of the organism.

Since *F. necrophorum* is an obligate anaerobe and sensitive to oxygen, the clinical specimen should be transported in an anaerobic transport device (such as those manufactured by
Anaerobe Systems, BD Diagnostics, Hardy Diagnostics, Remel, and others) to maintain specimen quality. Further, a good quality specimen (obtained by needle and syringe) free of contamination is important in the identification of the organism involved in the infection.

Once in the laboratory, the specimen should be plated onto enriched, pre-reduced anaerobic media (Anaerobe Systems, Morgan Hill, CA) to ensure good growth. Media such as pre-reduced Brucella enriched with vitamin K₁ and hemin is a good choice. One study showed poor growth or no growth of *F. necrophorum* on media that was not pre-reduced (6). Some laboratories are not able to recover *F. necrophorum* from clinical specimens because good anaerobic media along with the use of good anaerobic technique (jars or chambers) are not used. Anaerobic bacteria vary considerably in their sensitivity to oxygen. *F. necrophorum* is strictly anaerobic and is not able to tolerate the oxygen concentration found in most media (6).

In some instances, the laboratory may choose to use special media specifically formulated to provide presumptive identification of *F. necrophorum*. One such medium is egg yolk with kanamycin and vancomycin (EYKV), a selective and differential medium that contains a suspension of egg yolk as well as vancomycin and kanamycin for the isolation and presumptive identification of *Fusobacterium necrophorum* (one source of this medium is Anaerobe Systems). The egg yolk suspension allows for the detection of lipase activity, which if positive hydrolyzes the fats within the egg yolk medium, resulting in an iridescent sheen on the surface or surrounding the colony. See Fig 3. Photograph of Positive Lipase Reaction of *Fusobacterium necrophorum*. EYKV also contains vancomycin to inhibit the growth of gram-positive microorganisms and kanamycin to inhibit the growth of gram-negative, facultatively-anaerobic bacilli. The medium will not provide complete identification of *F. necrophorum*; additional biochemical testing must be performed to confirm the identity of the organism.

Another medium that can be used is Fusobacterium Selective Agar (FSA), a selective medium for the isolation and presumptive identification of *Fusobacterium* species. FSA medium contains josamycin, neomycin and vancomycin at concentrations that inhibit most gram-positive and most gram-negative anaerobes (one source of this medium is Anaerobe Systems). FSA should be inoculated directly with clinical material and streaked to obtain isolated colonies. A non-selective medium such as Brucella blood agar should also be inoculated with the clinical specimen to permit growth of all organisms present.

Isolated colonies should be subcultured to aerobic media to ensure that the organism recovered is an anaerobe, since most aerobic organisms will grow under anaerobic conditions. Therefore, the step called “aerotolerance testing” is necessary to determine if the isolate is an anaerobe. See reference number 5 for technique on how to perform aerotolerance testing. Once it is determined that the isolated colony is an anaerobe, further testing using special potency disks, indole, lipase, and other biochemical testing should be utilized to identify the isolate. See Section E. Microbiology of *F. necrophorum*, and Tables 3 and 4. For other biochemical testing and other methods which might be used to identify *Fusobacterium necrophorum*, see reference numbers 5 and 8. Recently, some larger clinical laboratories are employing the use of PCR techniques and confirmation of the organism with MALDI-TOF-MS (matrix assisted laser desorption ionization-time of flight-mass spectrometry) for rapid identification and confirmation of *F. necrophorum* (8,10). These techniques allow for more rapid identification of the organism since the organism is relatively slow growing and often is recovered from mixed polymicrobial samples. The usage of these techniques, however, must be assessed for their benefit, cost, size of the clinical laboratory and other factors versus the usage of selective media for the isolation of *F. necrophorum*. 
H. TREATMENT

To some extent, the choice of treatment of *F. necrophorum* infection depends upon the type and location of the infection, and upon the patient, but in general, treatment usually involves an antibiotic. *F. necrophorum* is susceptible to β-lactam antibiotics (pencillins and cephalosporins) and tetracyclines, clindamycin, and metronidazole. There have been some reports in the literature from Great Britain, Finland, and France that suggest that some isolates of *F. necrophorum* may produce β-lactamase (an enzyme that provides resistance to penicillin-like antibiotics) (2,9). In one study, about 2% of *F. necrophorum* isolates from blood cultures were resistant to pencillin (2). For the most part, resistance to penicillin-like antibiotics has not been observed in the United States. Studies in the United States consistently find that 100% of *F. necrophorum* strains are sensitive to metronidazole, ticarcillin-clavulanate, piperacillin/tazobactum, 3rd generation cephalosporins (ceftriaxone, ceftazidime, cefotaxime and others), clindamycin, cefoxitin, and imipenem, all of which can be used therapeutically to treat infections associated with *Fusobacterium necrophorum* (2,9). Often in patients with Lemierre’s syndrome or other systemic infections, penicillin or antibiotics that are combined with a beta-lactamase inhibitor such as clavulanic acid or tazobactum are used along with metronidazole or clindamycin. Lemierre’s syndrome is primarily treated with antibiotics given intravenously. In some instances, clindamycin can be given alone and can be used as the primary treatment in penicillin-allergic patients.

*F. necrophorum* is intrinsically resistant to gentamicin and quinolones (e.g., ciprofloxacin, levofloxacin), and tetracyclines show relatively poor activity against the organism. Unfortunately, *F. necrophorum* is not sensitive to erythromycin nor other macrolides that are often used for suspected Group A *Streptococcal* pharyngitis in penicillin-allergic patients, so these drugs would be ineffective in patients with a potential *F. necrophorum* infection. Penicillin or a cephalosporin remains the first treatment choice for adolescents and young adults with pharyngitis, and the addition of clindamycin is indicated for those with evidence of sepsis or neck swelling. Appropriate antibiotics should not be delayed, as mortality and morbidity are improved with the prompt administration of antibiotics (2,9). Generally, treatment for serious *F. necrophorum* infection, such as Lemierre’s syndrome, is treated for a total of 6 weeks, with about 2 to 3 weeks of intravenous antibiotic therapy because of the possibility of relapse (2,9).

Since septic thrombophlebitis is such a key part of Lemierre’s syndrome, the ability of antibiotics to penetrate and be active in fibrin clots is essential. Because clots are dense and not vascular they are hard for antibiotics to penetrate. It is also difficult for antibiotics to penetrate abscess and necrotic lesions. If antibiotic therapy does not improve the clinical picture, it may necessary to perform surgical drainage of any abscesses or focal infection, and/or perform ligation (surgical closure of a blood vessel) of the internal jugular vein where the antibiotic cannot penetrate.

Treatment in animals for foot rot, calf diphtheria, and other infections due to *F. necrophorum* is usually with antibiotics, such as penicillin, sulfadiazine/trimetroprim, and sulfadimethoxine (6). All should be given by injection for three days as topical therapy is not effective. Most cases of foot rot are usually treated with antibiotics plus foot baths using solutions of 1% sodium hypochlorite, 0.2% chlorhexidine, 70% ethanol, 2% glutaraldehyde, 3% hydrogen peroxide, iodophores, and others (7).

I. PREVENTION
There are some good prevention and control measures for *F. necrophorum* infection in animals. Vaccinations against *F. necrophorum*, for example, are available to help prevent foot rot and liver abscesses in animals and are very effective (7). Although controversial, the addition of antibiotics to animal feed to prevent foot rot and calf diphtheria helps reduce *F. necrophorum* infection (7). There are various preventive measures that can be taken around animals to prevent contact with *Fusobacterium necrophorum* contaminated soil and manure by improving the drainage around drinking and feeding areas. Also, the isolation of cows when infected, and the use of a protective boot during the early infectious stages of foot rot helps prevent other animals from obtaining the infection. The use of preventive foot baths using 5% copper sulphate or formalin, zinc methionine, and paraformaldehyde is also helpful (7). The antimicrobials most commonly used for animal prophylaxis are bacitracin, methylene disalicylate, chlortetracycline, oxytetracycline, and virginiamycin (7).

In humans, the most important preventive measure to reduce the impact of Lemierre’s syndrome is early recognition of symptoms of severe tonsillitis and tonsillar abscess in patients age 15-24. Once symptoms are recognized, it is important to start appropriate antibiotic therapy early since mortality and morbidity are reduced with rapid treatment. Although this infection is rare, researchers agree that this diagnosis should be considered in a septicemic patient with thrombosis from an unusual site, and in patients age 15-24. Prevention in humans is difficult, so physicians need to be on the alert for symptoms that predispose a patient to Lemierre’s disease. For example, in a 15-24 year old patient with persistent sore throat, a clinician should consider a possible infection *F. necrophorum* and culture for this organism (1,3).

**CASE STUDY**

A 16-year-old girl who had been in excellent health consulted her physician because she developed a five-day minor fever and very sore throat. He found that she had large, swollen tonsils with pus on the exterior surface. The physician considered that, based on her symptoms and history, she might have Group A *Streptococcus* pharyngitis. A rapid strep test performed in the office test was negative. In light of this finding the doctor thought she might have a viral pharyngitis, so he gave her no antibiotic, only medicine for her throat pain, fever, and nasal congestion.

Her symptoms and her sore throat abated temporarily; however, on the 8th day after her office visit, she suddenly developed a fever with chills, and pain on one side of her neck that progressed down toward her clavicle. She returned to her physician, who examined her again and felt she might have Group A *Streptococcal* pharyngitis even though her rapid strep test was negative. The physician was aware that the reported sensitivity of the rapid strep test is 85-90%. He started her on erythromycin since she was allergic to penicillin, and the patient went home.

The following day she was unable to get out of bed. She had a headache, a fever of 102°F, chills, painful joints, and a painful red area on the right side of her face with some neck stiffness. Her parents took her to the emergency department at the local hospital. The ER physician was concerned about her sepsis and fever, so he ordered two sets of blood cultures. He was able to aspirate fluid from the abscess in her neck. A stat Gram stain ordered on the neck abscess fluid showed many WBCs and some pleomorphic Gram-negative rods. Cultures were requested from the clinical material that had been obtained by needle and syringe and submitted to the laboratory in an anaerobic transport tube.

In the emergency room the examination of the patient showed there was marked neck stiffness and tenderness extending to the soft tissue of her shoulder. The patient had markedly
purulent and inflamed tonsils in addition to the abscess in her neck area. The patient also complained about pain in her legs and knees. Further examination revealed that she had low blood pressure and symptoms of shock. Stat laboratory tests were ordered, including a CBC, coagulation studies, erythrocyte sedimentation rate, liver function tests, and a C-reactive protein test. Radiological studies of the patient’s neck were requested. A computer tomography scan (CT) showed a thrombosis of the right internal jugular vein.

The laboratory test results showed a WBC count of 20,000/µl, thrombocytopenia, impaired renal function, increased erythrocyte sedimentation rate, elevated C-reactive protein and a normal coagulation profile. This teenage girl not only had an infection but was in shock. Based on clinical features of the patient and preliminary laboratory work, a diagnosis of Lemierre’s syndrome was made and antimicrobial therapy was initiated. She was treated with intravenous ceftriaxone and metronidazole and anticoagulant therapy and was transferred to a hospital room for further management.

The following day, laboratory data showed the blood cultures were positive with pleomorphic Gram-negative rods, which were subcultured to aerobic and anaerobic media. The neck abscess specimen showed growth of anaerobic pleomorphic Gram-negative rods. The laboratory was able to perform some spot tests on the isolate from the neck abscess, as well as subculture the isolate to a brucella sheep blood agar plate with special potency disks and to an egg yolk agar plate. Spot tests on the neck abscess material showed the isolate was indole positive and nitrate reduction test negative. The next day, growth from the anaerobic subculture plate that contained the special potency antibiotic disks showed the isolate was resistant to the vancomycin 5 µg disk, but susceptible to both kanamycin 1000 µg and colistin 10 µg disks. Growth on the egg yolk plate produced an oily iridescent sheen on top and adjacent to isolated colonies, indicative of a positive lipase test. Based upon these tests, the laboratory determined that the isolate was *Fusobacterium necrophorum*. The laboratory also performed a rapid 4 hr anaerobe identification kit on the isolate; however, the commercial test kit was not able to determine the name of the isolate.

Meanwhile, the patient began to slowly improve. Her fever came down to 100°F, and some of her symptoms of sepsis (shock, fever, and chills) were reduced, although her neck abscess still looked red and swollen. Her doctors were still concerned about the abscess in her neck and jugular vein. A surgeon performed a ligation of the vein and removed any clots. The young girl did well with her surgery and slowly became less febrile and more responsive.

Subsequent blood cultures were obtained, but were negative for any growth. Her doctor felt she was improving but needed to be on IV antibiotics for several weeks to prevent any chance of relapse. The patient was discharged with IV antibiotics for two weeks but needed to see her doctor after one week to make sure that the IV given on an outpatient basis was satisfactory.

**Case Study Review**

This case illustrates the problem of diagnosing *Fusobacterium* infection. Her physician was not aware of the possibility of pharyngitis in her age group being due to anything other than Group A *Streptococcus*, or a viral infection. Therefore, the patient was not worked up further.

When the symptoms of this patient became worse, she was taken to a hospital emergency department, where the ER physician was able to perform some tests to determine her diagnosis. The ER physician performed the correct steps to make a diagnosis and began appropriate antibiotics. Her symptoms of shock, her age, her one-sided neck pain and her history of having had a severe case of pharyngitis that abated temporarily provided clues to the ER physician. In
addition, laboratory results from the stat Gram stain led the doctor in the right direction, suggesting what additional tests to perform and which antibiotics to prescribe. The aspirate of the neck abscess showed pleomorphic Gram-negative rods, information the ER physician used to select antibiotics that covered most aerobic and anaerobic Gram-negative organisms.

The laboratory used the correct anaerobic transport system, enriched media, and environmental conditions to recover *Fusobacterium necrophorum*, an obligate anaerobe. It is likely that less optimal transport conditions, media, and environmental systems would not have allowed isolation of the organism.

Lemierre’s syndrome historically had a high mortality rate, up to 90% before the advent of antibiotics. Because the syndrome is seldom seen now it is called a “forgotten disease.” Further diagnostic delay could have been devastating to this patient. However, the patient did recover with surgical treatment of the jugular vein and the use of appropriate antibiotics for a prolonged time.

J. CONCLUSION

Human *F. necrophorum* infection, once less prevalent, is on the rise. It is important that clinicians and laboratory personnel become aware of the symptoms, course of disease, diagnosis and treatment of *F. necrophorum* infection because when it is missed, this organism can cause severe illness or death. *F. necrophorum* is now recognized as a causative agent in many cases of recurrent sore throat syndrome and tonsillitis. One of the aims of this course is to provide information about *F. necrophorum* and Lemierre’s disease.

As devastating as the disease can be in humans, the prevalence of *F. necrophorum* is far greater in animal populations and causes symptoms and diseases in cattle, sheep, and horses. Many of these infections have a significant economic impact.

*F. necrophorum* is unique among non-spore-forming anaerobes for its virulence, and for its ability to form necrotic tissue due to its many pathogenic factors. *Fusobacterium necrophorum* are part of the normal flora of the oropharyngeal, gastrointestinal and genital tracts of animals and humans.

Transmission of *F. necrophorum* in animals is due primarily to contaminated soil or food with manure. *F. necrophorum* can survive many weeks in the soil, even though it does not produce spores. Transmission of *F. necrophorum* in humans was believed to be due to acquiring the organism from one’s own normal flora. Recent studies have shown that this is not always the case. Other factors such as concurrent infection with a virus like EBV, or from an exogenous source may be factors.

*F. necrophorum* in humans causes a variety of infections that are often overlooked. The most recent finding is that *F. necrophorum* can be a cause in persistent sore throat. In one study, it was found that *F. necrophorum* is responsible for acute sore throats with the same incidence as caused by Group A *Streptococci* in specific age groups.

For the most part, the diagnosis of *F. necrophorum* infection depends upon the laboratory to isolate and identify the organism. It is important to use a good transport system to maintain viability of the organism, and once in the laboratory, to plate the specimen on good enriched media using good anaerobic techniques. Since *F. necrophorum* is a strict anaerobe many laboratories are not able to recover the organism unless good anaerobic techniques are used.

In humans early diagnosis and recognition of symptoms in patients in specific age groups is important to prevent Lemierre’s and further disease. The use of antibiotics early helps to prevent symptoms. Unfortunately, in many cases, the diagnosis of Lemierre’s syndrome is made
after a positive blood culture or after the recovery of *F. necrophorum* from other body sites. Awareness of the potential complications of Lemierre syndrome and prompt management are crucial in preventing disease. Lemierre’s syndrome carries a significant rate of morbidity and mortality. The high rate of morbidity and mortality is due not only the virulence of the organism, but also because of lack of awareness of the symptoms by a physician, its uncommon presentation, and because of the use of inadequate anaerobic culture methods.
K. REFERENCES
REVIEW QUESTIONS
Course #DL-012
Choose the one best answer

1. Which one of the following statements about *Fusobacterium necrophorum* infections is correct?
   a. causes abortion in cattle
   b. causes necrotic lesions
   c. more common infection in humans than animals
   d. causes infections that are difficult to treat

2. Which set of symptoms is most typical of foot rot in cattle due to *F. necrophorum*:
   a. fever, chills, swelling
   b. swollen cheeks, fever, pneumonia
   c. erythema, tissue destruction, foul odor
   d. pain, lameness, chronic arthritis

3. Which is not a pathogenic factor of *Fusobacterium necrophorum*:
   a. lipopolysaccharide
   b. leukotoxin
   c. hemagglutinin
   d. fibronectin

4. Which set of symptoms is most typical of Lemierre’s syndrome?
   a. peritonsillar abscess, fever, septic thrombophlebitis
   b. pharyngitis, flu-like symptoms, chronic arthritis
   c. sudden fever, chills, pneumonia
   d. peritonsillar abscess, fever, meningitis

5. Which set of biochemical test results best fits the profile of *Fusobacterium necrophorum*:
   a. indole positive, nitrate reduction test positive, lipase negative
   b. indole positive, nitrate reduction test negative, lipase positive
   c. indole negative, nitrate reduction test negative, lipase negative
   d. indole positive, nitrate reduction test positive, lipase positive

6. In what age group is recurrent sore throat due to *F. necrophorum* most prevalent:
   a. individuals >65 years old
   b. children 8-12 years of age
   c. 15-24 years of age
   d. 24-30 years of age

7. One pathogenic function of lipopolysaccharide from *F. necrophorum* is;
   a. attachment
   b. production of exotoxins
   c. chemotaxis of macrophages
   d. tissue destruction
8. One characteristic of *F. necrophorum* is the ability to fluoresce:
   a. black
   b. red
   c. chartreuse
   d. depending upon the medium used

9. Which set of features best describes the appearance of *F. necrophorum* on brucella blood agar:
   a. colonies are umbonate, scalloped margin, cream color
   b. colonies are circular, smooth edge, white color, smell of lemon
   c. colonies are rough, gray to translucent, with a narrow zone of beta hemolysis
   d. colonies are oval, smooth margin, yellow color

10. Which are the correct Gram stain morphological features of *Fusobacterium necrophorum*:
    a. Gram negative rod, sometimes in pairs, sometimes very small
    b. Gram negative coccobacillus, sometimes with large swellings
    c. Gram negative pleomorphic rod, sometimes with long cells, sometimes with swellings
    d. Gram negative rod, long, thin, spindle-shaped large cells

11. Attachment of *F. necrophorum* to host cells is initiated by:
    a. D-galactose residues
    b. Fimbriae
    c. the protein internalin
    d. leucocidin

12. What is a recommended antibiotic therapy for *Fusobacterium necrophorum*?
    a. penicillin plus metronidazole
    b. penicillin plus gentamicin
    c. cephalosporin plus ciprofloxacin
    d. penicillin plus macrolide

13. The function of leucocidin in the pathogenesis of *F. necrophorum* is that it:
    a. causes fever and shock
    b. promotes attachment to host cells
    c. causes destruction of polymorphonuclear leukocytes
    d. produces phagosome enzymes

14. The most common manifestations of Vincent’s angina include:
    a. high fever, bleeding and swelling of tissues from mouth, blood clot in lungs
    b. high fever, shock, one-sided thrombophlebitis of jugular vein
    c. painful ulcerations, swelling and sloughing off of dead tissue
    d. painful ulcerations, high fever, spread of infection throughout the body
15. The typical clinical history for a patient with Lemierre’s syndrome is:
   a. prior pharyngitis, high fever, one-sided thrombophlebitis
   b. prior pharyngitis, flu-like symptoms, meningitis
   c. flu-like symptoms, fatigue, bacteremia, pneumonia
   d. flu-like symptoms, high fever, one-sided thrombophlebitis

16. The most optimal preventive measures to reduce the impact of Lemierre’s syndrome are:
   a. early recognition of symptoms and start appropriate antibiotic
   b. treat patient after obtaining rapid strep testing result
   c. obtain X-ray and sonogram of jugular vein
   d. obtain blood cultures

17. One measure to prevent *F. necrophorum* infection in animals is not:
   a. to reduce the animal’s contact with manure
   b. to treat animals with macrolides
   c. to improve drainage
   d. to add antibiotics to food

18. The isolation and identification of *F. necrophorum* in the laboratory does not depend upon:
   a. a good specimen transported in an anaerobic transport device
   b. use of good enriched anaerobic media
   c. use of correct anaerobic environment
   d. use of commercial anaerobic identification system

19. The formation of clots and abnormal coagulation characteristics of *F. necrophorum* are due to:
   a. the activation of leukotoxin
   b. the activation of adhesion molecules and fimbriae
   c. the activation of plasminogen, platelet aggregation factor, and hemagglutinin
   d. the activation of leucocidin

20. The special potency antibiotic disk reactions of *Fusobacterium necrophorum* are:
   a. resistant to vancomycin 5 µg, and susceptible to kanamycin 1000 µg and colistin 10 µg
   b. susceptible to vancomycin 5 µg, and resistant to kanamycin 1000 µg and colistin 10 µg
   c. susceptible to vancomycin 5 µg, and kanamycin 1000 µg, but resistant to colistin 10 µg
   d. resistant to vancomycin 5 µg, kanamycin 1000 µg, and colistin 10 µg

21. Typically *F. necrophorum* produces:
   a. isobutyric acid from glucose broth
   b. formate from glucose broth
   c. acetone from glucose broth
   d. butyric acid from glucose broth
22. Lemierre’s syndrome usually occurs when:
   a. a peritonsillar abscess spreads to nearby tissues and to the jugular vein
   b. a peritonsillar abscess spreads to the lungs
   c. Vincent’s angina spreads to the oral cavity
   d. recurrent sore throat persists past 5 days and causes meningitis

23. One reason the diagnosis of Lemierre’s syndrome is often overlooked is because:
   a. symptoms are vague and mimic bacterial pneumonia
   b. the syndrome is rare and many clinicians have never seen a case
   c. the patient has flu-like symptoms
   d. the patient is thought to have Group B Streptococcus infection

24. Which statement is not correct to best describe recurrent or persistent sore throat:
   a. a sore throat that has persisted for longer than 5 days and is negative for Streptococcus Group A
   b. a pharyngitis particularly in patients 15-24 years of age
   c. 10% of cases in certain age groups may be due to F. necrophorum
   d. always caused by viruses

25. Which statement is not correct to describe the transmission of Fusobacterium necrophorum in animals:
   a. obtained from contaminated soil
   b. organism can survive in soil of pastures for up to 18 weeks
   c. direct animal to animal contact through open sores or bites
   d. obtained from contaminated water source

26. Professor Lemierre’s most important contribution to our understanding of F. necrophorum infection was:
   a. the clarity of his clinical description of post-anginal septicemia
   b. his clarity in determining the cause of foot rot infection in animals
   c. his clarity in his clinical description of bacterial pneumonia
   d. his understanding of the clinical impact of bleeding abnormalities in infection

27. Which statement is not correct to describe the transmission of Fusobacterium necrophorum in humans:
   a. obtained from our own normal flora
   b. obtained after a break or change in immunity
   c. obtained from contaminated food
   d. obtained during a concurrent infection with a virus
28. The term zoonotic infection means:
   a. an infection that occurs in animals from a zoo
   b. an infection that occurs in animals that can be transmitted to humans
   c. an infection that is transmitted to animals from man
   d. an infection caused by an organism in animals that can cause disease in other species of animals

29. Which statement is most likely the reason a clinical laboratory was not able to isolate \( F. \) necrophorum from a specimen after observing from a direct Gram stain:
   a. not using media enriched with sheep blood
   b. not using media enriched with vitamin K, hemin and was pre-reduced
   c. not using media that contains egg products
   d. not incubating media under 5% carbon dioxide

30. The production of a positive lipase reaction depends upon:
   a. the ability of organism to break down triglycerides in media
   b. the ability of organism to split tryptophan in egg yolk agar
   c. the ability of organism to break down lecithin in egg yolk agar
   d. the ability of organism to hemolyze fats in egg yolk agar