Human Necrobacillosis, with Emphasis on Lemierre’s Syndrome

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Lemierre’s syndrome is the classical presentation of human necrobacillosis. It is characterized by a primary infection in the head in a young, previously healthy person who subsequently develops persistent high fever and disseminated metastatic abscesses, frequently including a septic thrombophlebitis of the internal jugular vein. The main pathogen is Fusobacterium necrophorum, an obligate anaerobic, pleomorphic, gram-negative rod. Clinical microbiologists have a key role in alerting clinicians and advising proper antibiotic treatment when the characteristic microscopic morphology of the pleomorphic F. necrophorum is seen in Gram stains from positive anaerobic cultures of blood and pus. Early diagnosis and prolonged appropriate antibiotic treatment with good anaerobic coverage are crucial to reduce morbidity and mortality. F. necrophorum also causes human necrobacillosis with foci caudal to the head, mainly in elderly patients with high mortality related to age and predisposing diseases, such as cancers of the primary focus.

History

Fusobacterium necrophorum has been known to cause necrotic infections in wild and domestic animals since the late nineteenth century [1]. In 1884, Loeffler [2] discovered that the bacterium caused calf diphtheria, and in 1891, Bang [3] isolated it from liver abscesses of cattle. Necrotic stomatitis of calves, lambs, and pigs, foot rot in cattle and sheep, gangrenous dermatitis in horses and mules, and multiple abscesses in lung and liver in cattle and pigs are all diseases caused by F. necrophorum, and all have severe economic impact for farmers [1, 4–7].

The English name for human F. necrophorum sepsis is necrobacillosis, which refers to the necrotic abscesses produced by the bacteria [4]. The first reported case of human necrobacillosis is probably from 1900, when Courmont and Cade [8] described a patient who died of an overwhelming plague-like sepsis shortly after an acute tonsillitis and from whom an obligate anaerobic bacillus was isolated from the blood. Several articles followed on the subject [9–22].

In 1936, Lemierre [23] described 20 French cases of “anaerobic septicaemias,” of which 18 patients died. These cases were mainly but not exclusively caused by Bacillus funduliformis, the contemporary synonym of F. necrophorum. Lemierre divided the patients into 6 groups on the basis of the primary infectious focus: inflammatory lesions of the nasopharynx, particularly tonsillar and peritonsillar abscesses; similar lesions of the mouth and jaws; otitis media or mastoiditis; purulent endometritis following parturition; appendicitis; and urinary tract infections.

He called the first group “anaerobic postanginal septicaemias.” These patients presented with the original “Lemierre’s syndrome,” characterized by an initial pharyngotonsillitis or peritonsillar abscess in young, previously healthy persons, often followed by swelling and tenderness along the sternocleidomastoid muscle, representing a septic thrombophlebitis of the ipsilateral internal jugular vein. Within a week the patients developed high fever and rigors and later metastatic embolic abscesses, usually in the lungs and bones. The patients often died within 7–15 days after onset. Lemierre claimed that “the syndrome is so characteristic that it permits a diagnosis before bacteriological examination, including blood culture, has provided conclusive proof” [23].

In 1955, Alston [4] reported 280 cases of necrobacillosis, including patients from Germany (94 cases), the United States (87), France (31), Hungary (24), Great Britain (21), Holland (15), French Indochina (6), and Scandinavia (2). He divided the cases into 4 groups: primary infection in the skin or subcutaneous tissues; infection starting in the throat, sometimes after a tonsillectomy, or following a sore throat or otitis media; primary infection in the female genital tract, following an abortion, or in the puerperium or primary foci in the alimentary tract (in either sex), sometimes after surgery, or in the urinary tract; and a first symptom of empyema, with or without lung abscess.

Alston’s second group is almost identical with Lemierre’s groups 1–3. Alston did not register the numbers in each group,
Microbiology and Pathogenesis

*F. necrophorum* has had many synonyms, including *Bacillus necrophorus, Sphaerophorus necrophorus, Schmorl's bacillus, Sphaerophorus funduliformis, Actinomyces necrophorus, Fusiformis necrophorus, Streptothrix necrophora, Bang's necrosis bacillus, Actinomyces necrophorus,* and *Bacillus funduliformis* [1, 3, 38–43].

*F. necrophorum* is a nonmotile, filamentous, nonfusiform pleomorphic, non-spore-forming, obligate anaerobic gram-negative bacterium, kanamycin and metronidazole sensitive [1, 7, 38, 44]. Today improved anaerobic diagnostic facilities and enriched media result in visible growth after 1–3 days inoculation from clinical specimens, whereas 2–5 days was needed in the past [1, 26, 30, 38].

*F. necrophorum* has a characteristic smell of butyric acid and a characteristic pleomorphic morphology with filaments, short rods, and cocccoid elements that are shown by Gram staining, characteristics that differ from those of other fusobacteria such as *Fusobacterium nucleatum* and *Fusobacterium mortiferum* [38, 44]. This characteristic morphology (figure 1) should be known to all clinical microbiologists and should immediately suggest the diagnosis of necrobacillosis and guide the treatment.

Identification depends on a few positive reactions, such as indole, lipase, DNase, and alkaline phosphatase [1, 38, 45]. *F. necrophorum* is the only *Fusobacterium* species that ferments lactate to propionate, a fact that is used to confirm the identification of *F. necrophorum* by gas-liquid chromatography [1, 38–45]. However, gas-liquid chromatography is not commonly available. When tested by commercial kits (e.g., API rapid ID 32A; BioMérieux, Marcy l’Etoile, France), the only positive tests are indole and alkaline phosphatase. It is our experience that the latter test is not consistently positive and, in cases of negativity, wrongly suggests *F. nucleatum*. Clinical laboratories may thus need to consult a local reference laboratory to confirm the identification of *F. necrophorum*.

In 1954, Beerens [46] suggested that *F. necrophorum* should be divided into 3 subspecies, biovars A, B, and C. Biovar C is now considered a separate species, named *Fusobacterium pseudonecrophorum*, which does not produce hemolysin, lipase, or hemagglutinin [1, 38, 47].

Animal strains of the 2 other subspecies differ in morphology, biochemistry, and biology. Biovar A, today named *F. necrophorum* subspecies *necrophorum*, forms filaments 2–100 μm long, produces hemolysin, lipase, and hemagglutinin, and agglutinates chicken, human, and pigeon erythrocytes [1, 7, 38, 47–49]. A possible role of hemolysin may be to aid in creating an anaerobic environment for growth of *F. necrophorum* by lysing the erythrocytes and thereby reduce oxygen transport to the site of infection [7]. It has been suggested that phospholipase A and lyso phospholipase are the components responsible for

Table 1. Primary focus in Lemierre’s syndrome, as reported in original reports.

<table>
<thead>
<tr>
<th>Author (years covered) [reference]</th>
<th>Total (no. of deaths, when reported)</th>
<th>Ear</th>
<th>Oropharynx</th>
<th>Tooth</th>
<th>Not documented, but probably head</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alston (1955) [4]</td>
<td>11 (6)</td>
<td>1 (1)</td>
<td>6 (3)</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Felner and Dowell (1963–1969) [24]</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Sinave et al. (1974–1986) [25]</td>
<td>38 (2)</td>
<td>0</td>
<td>37</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Henry et al. (1975–1980) [26]</td>
<td>12 (2)</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Eynyn (1980–1984) [27]</td>
<td>40 (2)</td>
<td>7 (1)</td>
<td>30 (1)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Moreno et al. (1980–1987) [28]</td>
<td>11 (2)</td>
<td>—</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Leugers and Clover (1950–1993) [29]</td>
<td>40 (3)</td>
<td>—</td>
<td>40</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hagelskjaer et al. (1990–1995) [30]</td>
<td>24 (0)</td>
<td>7</td>
<td>15</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>186</strong></td>
<td><strong>18</strong></td>
<td><strong>149</strong></td>
<td><strong>3</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>

*a* Defines Lemierre’s syndrome as case with a primary focus in the head.

*b* Defines Lemierre’s syndrome as case of “postanginal” sepsis.

Lemierre’s syndrome was sparsely reported during the 1960s and 1970s, presumably because of the widespread use of penicillin in cases of acute tonsillitis [29, 31]. Improved biochemistry, and biology. Biovar A, today named *F. necrophorum* subspecies *necrophorum*, forms filaments 2–100 μm long, produces hemolysin, lipase, and hemagglutinin, and agglutinates chicken, human, and pigeon erythrocytes [1, 7, 38, 47–49]. A possible role of hemolysin may be to aid in creating an anaerobic environment for growth of *F. necrophorum* by lysing the erythrocytes and thereby reduce oxygen transport to the site of infection [7]. It has been suggested that phospholipase A and lyso phospholipase are the components responsible for
the hemolytic activity of *F. necrophorum*, thus correlating hemolytic activity and lipase activity [7, 50].

Biovar B, now called *F. necrophorum* subsp. *funduliforme*, is pleomorphic curved rods 1–10 μm in length mixed with longer filaments; this organism produces hemolysin, but quantitatively the hemolytic activity is weaker than for *F. necrophorum* subsp. necrophorum [1, 7, 38, 48, 51]. Some describe *F. necrophorum* subsp. *funduliforme* as lipase-negative [1, 38, 44], whereas others describe it as weakly lipase-positive [7, 52]. *F. necrophorum* subsp. *funduliforme* is negative by the slide glass method of hemagglutination testing, which is a qualitative test [1, 38, 46, 49]. However, it is weakly positive by quantitative testing for hemagglutination, whereas *F. necrophorum* subsp. necrophorum is strongly positive [49]. Hemagglutination may aid in initiating *F. necrophorum* infection by promoting blood clotting [7, 45].

Furthermore, *F. necrophorum* subsp. necrophorum and *F. necrophorum* subsp. *funduliforme* probably can be distinguished by DNase testing, the former yielding positive results and the latter negative [7, 45, 48].

Only *F. necrophorum* subsp. necrophorum aggregates human platelets—without lysing them [53, 54]. The platelet aggregation is associated with hemagglutination activity [54]. The intravascular coagulation caused by platelet aggregation may contribute to the establishment of a favorable anaerobic environment for growth of *F. necrophorum*.

Besides hemolysin and lipase, *F. necrophorum* excretes leukocidin [7, 48, 55]. Again *F. necrophorum* subsp. necrophorum produces more leukocidin than does *F. necrophorum* subsp. *funduliforme*, but with considerable variation in the leukotoxicity of strains of *F. necrophorum* subsp. necrophorum [7, 45, 55]. The leukotoxin impairs leukocyte migration and protects other facultative pathogens from phagocytosis [7, 56].

Like other gram-negative bacteria, *F. necrophorum* releases lipopolysaccharide. The quantity of lipopolysaccharide is greater for *F. necrophorum* subsp. necrophorum than for *F. necrophorum* subsp. *funduliforme* [7].

The platelet aggregation and the production of hemagglutinin and lipase may be related to the higher virulence and pathogenicity in animals of *F. necrophorum* subsp. necrophorum than of *F. necrophorum* subsp. *funduliforme* [1, 6, 45, 53].

Generally, most clinical reports of human *F. necrophorum* infections have not specified the subspecies involved [25–34, 36, 37, 57–68]. In 1954, Beerens [46] found that mainly *F. necrophorum* subsp. *funduliforme* was isolated from humans with necrobacillosis. This is supported by later studies [6, 7, 69, 70]. Apparently human and veterinary necrobacillosis refer to diseases that differ in important respects, which has implications for the use of animal models in studies of pathogenicity in humans [69, 70]. Further studies are needed to elucidate these aspects.

*F. necrophorum* is reported to be part of the normal microbiota of the oropharynx, gastrointestinal tract, and genitourinary tract of animals and humans and does not normally invade intact mucosal surfaces [7, 29, 39, 71]. It is not known why *F. necrophorum* penetrates the mucosa in some patients. A reduced host defense in the pharyngeal mucosa by viral or bacterial pharyngitis may play a role [6, 7, 29]. A synergistic, pathogenic complex has been demonstrated between *Fusobacterium* species and other anaerobic or microaerophilic bacteria or viruses in the formation of abscesses in animal models, facilitating the growth of *F. necrophorum* by lowering the oxygen tension and creating an anaerobic environment [6, 7, 72]. A similar synergistic relation may play a role in the pathogenesis of Lemierre’s syndrome in humans. In a study of 122 patients with peritonsillar abscess, *F. necrophorum* was found in 38% of those with mixed aerobic-anaerobic infections and in 93% of those with pure anaerobic infection [73]. Previous tonsillar or peritonsillar infections were common (52%) in those infected with *F. necrophorum* [73].

Infectious mononucleosis is frequently suspected in these patients and may predispose to Lemierre’s syndrome [57, 58, 74, 75]. Epstein-Barr virus infection is thought to induce immu-
nosuppression, with a transient decrease in T cell–mediated immunity that may predispose to a bacterial superinfection.

One-third of patients with Lemierre’s syndrome have polymicrobial bacteremia [26, 30]. The concomitant bacteria are mostly oropharyngeal microbiota, such as peptostreptococci, nonhemolytic streptococci, microaerophilic streptococci, and β-hemolytic streptococci of groups A, B, and C [26, 30]. Often these bacteria grow more rapidly than does F. necrophorum, and it is therefore important to reexamine the anaerobic blood cultures 24 h after the first finding of growth in cases clinically suggestive of Lemierre’s syndrome.

Anaerobic oropharyngeal infections account for 1%–5% of all anaerobic bacteremias [26, 60, 71, 76, 77]. F. necrophorum is the most common anaerobe in sepsis originating from the oropharynx, so whenever an anaerobic bacterium is found in such a patient, F. necrophorum should immediately be suspected [24, 59, 60].

In Lemierre’s syndrome, spreading of the local thrombophlebitis, for example via the internal jugular vein to the paraopharyngeal space, is often the focus for a persistent bacteremia that causes multiple metastatic septic emboli [37, 78]. Serum antibodies to F. necrophorum have been demonstrated in both healthy and infected humans, perhaps induced by the normal presence of F. necrophorum in the oropharynx in the same way as with Neisseria meningitidis [7]. However, immunoprophylaxis is not possible, and the control of F. necrophorum infection depends mainly on early detection and appropriate treatment [7].

Epidemiology

Human necrobacillosis tends to fall into 2 groups [4, 23–31, 61, 79]. The first is Lemierre’s syndrome in previously healthy persons without underlying diseases, and with the following age distribution of manifestations: children with otitis media, young adults with tonsillitis or peritonsillar abscess, adults with tooth infections, all ages with other foci (e.g., mastoiditis, sinusitis). The other type of human necrobacillosis affects older adults with predisposing diseases and portals of entry distal from the head.

Lemierre’s syndrome is reported to account for 46%–82% of cases of human necrobacillosis, with a male predominance of up to 75% of the patients [24–31, 75].

Lemierre’s syndrome is rare. In a Danish retrospective study, an incidence of ~1 case per million per year was found [30]. No prospective studies has been done to establish the real incidence, which is certainly higher.

No seasonal variation nor accumulation within families has been reported.

Diagnosis and Paraclinical Findings

Besides the primary focus and age distribution, cases of Lemierre’s syndrome are characterized by the following symptoms and signs [4, 23–31, 57, 61, 63, 68, 75, 80]: postanginal sepsis with intense rigors and high fever within 1 week after the primary local infection; ipsilateral neck tenderness parallel to the sternocleidomastoid muscle, representing suppurative thrombophlebitis of the tonsillar and peritonsillar veins and eventually the internal jugular vein; metastatic abscesses, mainly to the lungs but also joints; leukocytosis, normally ranging from 13.0 to 20.0 × 10^9 cells/L, with an increased amount of band forms and raised C-reactive protein levels; subclinical hyperbilirubinemia, reported in up to 50% of cases, sometimes associated with hepatomegaly; and mild disseminated intravascular coagulation with thrombocytopenia, developing in up to 23% of cases.

Fever, oropharyngeal pain, neck swelling, pulmonary symptoms, and arthralgia are common complaints and represent the classical symptoms of Lemierre’s syndrome [4, 23–31, 61]. It is primarily a clinical diagnosis, which should be suspected whenever a patient with severe sepsis and pulmonary symptoms presents after an acute pharyngotonsillar infection. Moreno et al. [28] found septic thrombophlebitis in 36% of patients with Lemierre’s syndrome. The characteristic, unilateral suppurative thrombophlebitis of the internal jugular vein is often misdiagnosed as cervical lymphadenitis [29, 30]. The thrombosis of the internal jugular vein can be diagnosed noninvasively by ultrasonography, axial CT scan, or magnetic resonance angiography of the neck [25, 29, 31, 78, 81–84].

Lemierre’s syndrome may be preceded by infectious mononucleosis, but this diagnosis must be confirmed by specific tests for antibodies to Epstein-Barr virus, because false-positivity is seen with the rapid tests [25, 29, 30, 37, 75].

Metastatic abscess formations are characteristic in Lemierre’s syndrome [23, 25, 28–31, 35, 60, 75]. Pulmonary involvement is reported in up to 85%, presenting as multiple bilateral necrotic infiltrates, frequently associated with pleural effusion, empyema, and/or pulmonary abscesses [28–30]. Leugers and Clover [29] found sterile pleural effusion in 51% of 39 patients with postanginal sepsis and lung abscesses in 41%, of whom 25% later developed pleural empyema. In patients suspected of having pneumonia, clinicians should be aware that the polymerase chain reaction test for Mycoplasma species often shows a false-positive result for patients with sepsis due to F. necrophorum [85]. A descending necrotizing mediastinitis may develop, which is a severe complication with a high mortality [86–90]. CT and magnetic resonance imaging serve to aid in both diagnosis and management of this condition [86, 89, 90].

Joint involvement, mainly of the major joints, is reported in up to 26% of cases as sterile effusions and sometimes as a suppurrative arthritis [23, 27, 29].

Diffuse abdominal pain is probably frequent, although rarely mentioned in the literature [24, 29–31, 60]. It may be caused by abdominal microabscesses or thrombophlebitis of the abdominopelvic veins [24]. Jaundice in septicemic anaerobic in-
Infections is frequent, but the pathophysiological mechanisms are not understood. It is not related to the development of liver abscesses. It may be caused by toxic effects of *F. necrophorum* endotoxins [25, 31, 80]. Intra-abdominal abscesses and hepatic abscesses are rare complications, as well as osteomyelitis, endocarditis, and meningitis [25, 29–31, 35, 64, 75, 91].

Meningitis due to *Fusobacterium* species is, however, a feared complication [35, 64]. Jacobs et al. [35] reviewed 17 cases of *Fusobacterium* meningitis that occurred from 1943 through 1991, of which most were identified as being due to *F. necrophorum*. The majority occurred in previously healthy children with a median age of 5 years and with acute otitis media as primary focus in 75% [35].

**Treatment and Outcome**

The optimal antibiotic regimen is not known. From the retrospective studies of Lemierre’s syndrome, it is not possible to draw any conclusions about the efficacy of different antibiotic regimens. The syndrome is too rare to run any randomized, controlled clinical studies. We have most of our information about antibiotic therapy from a few in vitro studies with animal and human strains of *F. necrophorum* [92–99].

Normally, *F. necrophorum* is reported to be susceptible to penicillin, cephalosporins, metronidazole, clindamycin, tetracyclines, and chloramphenicol [92–99]. β-lactamase-producing strains of *F. necrophorum* have only very rarely been reported, and still no resistant strains have been found in Europe [98, 99]. However, other *Fusobacterium* species and concomitant bacteria may produce β-lactamase and make penicillin therapy insufficient. Therefore, some clinicians instead prefer clindamycin [93, 98–101]. *F. necrophorum* is resistant to aztreonam and trimethoprim-sulfamethoxazole and, like other anaerobic bacteria, nonsusceptible to aminoglycosides [77]. Metronidazole, which is bactericidal and has a low MIC, has good penetration into most tissues and also achieves a high concentration in cerebrospinal fluid [35, 75], but monotherapy with metronidazole is not recommended because of the severity of the infection and because concomitant metronidazole-nonsusceptible microaerophilic and aerobic streptococci are found in *F. necrophorum* infections relatively often [30, 77].

Most authors recommend a combined treatment with high-dose penicillin and metronidazole or monotherapy with clindamycin for 2–6 weeks [28, 30, 31, 58, 60, 74, 75, 100]. The initial treatment should be with intravenous penicillin, for example, penicillin G at 1.2–3.0 g 4 times daily (children, 24–60 mg/kg 4 times daily), and iv or rectal metronidazole, for example, 500 mg 3 times daily (children, 10–15 mg/kg 3 times daily). Alternative treatment is monotherapy with iv clindamycin at 0.6–0.9 g 3 times daily (children, 10 mg/kg 3 times daily).

Even after several days or weeks of iv therapy, viable *F. necrophorum* can be found in necrotic abscess formations. Despite appropriate therapy, the patient’s temperature often remains high for a prolonged period, which is probably explained by the endovascular nature of the infection and the frequent occurrence of metastatic necrotic abscesses [29, 30, 37, 62, 102]. Treatment of septic thrombophlebitis is often difficult and requires prolonged therapy, because the fibrin clots protect the *F. necrophorum* from aerobiosis and make it difficult for antibiotics to penetrate [102].

When the infection is clearly under control, and temperature and inflammatory parameters have normalized, oral treatment in equivalent high doses may be appropriate. During oral treatment, penicillin should be replaced by amoxicillin, for example, tablet amoxicillin at 500 mg 3 times daily (children, 10–15 mg/kg 3 times daily), because it is more reliably absorbed [77].

Many physicians consider primary anaerobic lung infections unlikely, and therefore metronidazole is rarely prescribed from the start [30, 77]. Instead “atypical pneumonia,” such as Legionnaire’s disease, is often suspected and erythromycin therapy initiated [30]. However, this is problematic, because there are several reports that *Fusobacterium* sepsis progressed during erythromycin treatment [30, 32, 58]. Erythromycin as well as ciprofloxacin should be considered insufficient for treatment of *F. necrophorum* infections [44, 92, 103], although some studies found that strains were susceptible in vitro [71, 77, 94, 96, 97]. In patients with penicillin allergy, penicillin should be replaced by clindamycin, not erythromycin.

Surgical drainage of empyemas and abscesses and debridement of necrotic tissue is often indicated to accomplish appropriate antibiotic therapy [29, 31, 59, 103–105]. In cases of mediastinitis, extensive surgical intervention is absolutely essential, along with iv antibiotic, as described [77, 86–90]. The treatment response should be followed intensively by chest radiography and CT of the chest. The treating clinician must remain alert to the necessity of aggressive mediastinal exploration via repeated open thoracotomies and repeated removal of pus and necrotic tissue, before the infection is under control [77, 86, 89, 90]. In these cases, *F. necrophorum* can be cultured for several weeks during treatment with appropriate antibiotic therapy, because the bacteria grow under supreme anaerobic conditions in the necrotic abscesses.

Ligation of the internal jugular vein was common in the pre-antibiotic era but is today replaced by appropriate antibiotic therapy along with surgery, which has eliminated the problem of persistent sepsis and emboli [31].

Anticoagulation is normally not advised in Lemierre’s syndrome, because of the risk of extending the infection [29, 31, 58, 60]. Anticoagulation has been reserved for cases of thrombosis propagating retrograde to the cavernous sinus; it consists of iv heparin followed by up to 3 months of treatment with oral coumarin to reduce morbidity among survivors and to allow adequate collateral channels to develop [31, 74, 82, 106, 107]. The internal jugular vein does not usually recanalize after resolution of the infection [31]. Prospective studies on the use
of anticoagulation in patients with septic thrombophlebitis are warranted, because the reservation against anticoagulation can be questioned. For example, there is cumulative experience in the gynecologic literature for successful treatment of septic pelvic thrombophlebitis with heparin [74, 78, 108].

In the pre-antibiotic era, Lemierre’s syndrome was associated with a case-mortality rate of 32%–90%, with embolic events in 25%, and endocarditis in 12.5% [4, 23, 26, 27, 31]. It is still a potentially life-threatening disease with a reported mortality of up to 17% [25–30, 62, 75]. In patients with F. necrophorum meningitis, mortality reaches 30% despite appropriate antibiotic therapy, and half of the survivors suffer permanent sequelae [35].

Necrobacillosis with Primary Foci Caudal to the Head

These patients are mainly elderly adults with predisposing diseases, who have a mortality of up to 25% [24, 26–27, 29, 30]. Fever is common, whereas oropharyngeal and pulmonary complaints are rare. Disseminated intravascular coagulation in these patients is reported by some authors to be associated with increased mortality [26, 29]. A combined antibiotic course with a β-lactam and metronidazole for 2 weeks is normally sufficient to resolve the infection, which is rarely complicated by metastatic abscesses. The main problem in these patients is their age and the frequent relation of infection to cancers, which occurs in up to 69% of patients with F. necrophorum infection from the gastrointestinal and urogenital tracts [23, 24, 26, 30, 109]. Whenever F. necrophorum bacteremia is diagnosed in this age group, thorough examination for cancer is obligatory, if it has not already been diagnosed.

In the past, appendicitis in young patients was a common gastrointestinal focus [24, 26]. Also frequent were infection of the female genital tract and postpartum Fusobacterium bacteremia, often with a rather benign course [26, 27, 110]. Today this is an uncommon primary focus, maybe because poorly performed illegal abortions and postpartum infections are today rare in the developed world. However, some of these infections may remain undiagnosed if blood cultures are not done, because the infections generally have a benign course. Anaerobes, especially F. nucleatum and F. necrophorum, may play a previously unrecognized role in the pathogenesis of occult amnionitis and premature labor and in relation to intruterine device-associated infections [110, 111]. In 23 cases of occult amnionitis, Easterling and Garite [110] found that Fusobacterium species accounted for 50% of the febrile cases and 30.4% of the total cases.

Conclusion

Once observed, Lemierre’s syndrome is unlikely to be forgotten by the spectator, but for the collective memory it is “the forgotten disease” because of its rarity [36, 37, 62, 65]. The reported retrospective incidence of 1 per 1 million persons per year in Denmark is most likely an underestimation of the accurate incidence [30].

Lemierre’s syndrome is primarily a clinical diagnosis, and it should always be suspected whenever a young, previously healthy person is seen by the general practitioner with an oropharyngeal infection that has an unexpected course or when such a patient is admitted to hospital with sepsis and with pulmonary symptoms after an acute pharyngotonsillar infection. However, in patients with sepsis and pulmonary infiltrations, cardiopulmonary infections, such as Legionnaire’s disease or endocarditis, are often primarily suspected [30]. In patients with abnormal liver function, clinicians may suspect hepatobiliary disease or leptomeningitis [80]. When anaerobic bacteremia is reported, but not the characteristic microscopy and the suspicion of a Fusobacterium species, clinicians are often misled to seek an intra-abdominal focus [30]. In addition, the slow clinical response in patients with Lemierre’s syndrome often results in changing antibiotic regimes and extensive, and retrospectively unnecessary, examinations in the search for such underlying causes as malignant diseases [28–31].

Early admission to hospital of septic young patients with tonsillitis or neck infections is essential. The classical clinical features of Lemierre’s syndrome and a careful examination of the neck are important diagnostic tools, which can lead the clinician to suspect Lemierre’s syndrome. Initiation of appropriate iv antibiotic therapy should be begun immediately on clinical suspicion [28–31].

Blood taken for culture before antibiotic treatment is initiated is essential to confirm the diagnosis and to arouse suspicion in cases in which clinicians are not familiar with the syndrome and fail to recognize it. Whenever an anaerobic blood culture yields positive results, the clinical microbiologist is the key person to recognize the very characteristic microscopic morphology of F. necrophorum and should immediately report the suspicion of Lemierre’s syndrome to the clinicians and guide the treatment, without waiting for further culture results. Alertness to the possibility of Lemierre’s syndrome, suspicion of the diagnosis by the clinicians and microbiologists, and prolonged appropriate iv antibiotic therapy is important to reduce morbidity and mortality [28–31, 75].

References