

Mini-review

Human infections with *Fusobacterium necrophorum*

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Received 10 November 2005; accepted 17 November 2005

Available online 22 December 2005

Abstract

Fusobacterium necrophorum is a Gram-negative anaerobic bacillus that can be a primary pathogen causing either localised abscesses and throat infections or systemic life-threatening disease. Systemic infections due to *F. necrophorum* are referred to as either Lemierre's disease/syndrome, post-anginal sepsis or necrobacillosis, but in the context of this mini-review, all are included under the umbrella term of 'invasive *F. necrophorum* disease' (IFND). Although IFND has been well documented for over a century, it is quite a rare condition and modern-day clinicians of various medical disciplines are frequently unaware of this organism and the severity of symptoms that it can cause. IFND classically occurs in previously healthy young people although the factors that trigger the invasive process are not fully understood. There are countless descriptive case histories and small series of cases of IFND disease in the literature and although commonly referred to as a 'forgotten' disease, in truth, it is probably best described as a repeatedly 'discovered' disease, as it may not always be included in medical curricula, and neither is it mentioned in some major medical textbooks. There is some evidence that IFND may be on the increase, particularly in the UK. The potential reasons for this are considered in this review along with an historical overview, and updates on disease incidence, patient demography, pathogenesis and laboratory diagnosis.

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1. Historical review of *F. necrophorum* infections

Historical accounts of infections in animals and man with symptoms that were typical of the condition primarily known as necrobacillosis, and descriptions of isolates that may well have been *Fusobacterium necrophorum* may be found in the literature as early as the late 19th and early 20th century. According to a review by Cunningham [1], Dammann, in 1876 probably made the first veterinary observation of infection with *F. necrophorum* when he described diphtheretic infections in calves. However, he believed he was observing infections due to *Bacillus diphtheriae*, and it was 8 years later in 1884 that Loeffler [2] demonstrated that calf diphtheria was due to a Gram-negative organism referred to at the time as *Actinomyces necrophorus*. In 1881, Koch may have also unwittingly seen *F. necrophorum* infection in sheep when he described an organism with very similar features in the sweat glands of sheep suffering from sheepox. In 1890, the German worker Bang coined the term 'nekrosebazillus' when referring to

an isolate from his studies of hog cholera [3]. Schmorl, in 1891 [4] alluded to a potential zoonotic association of *F. necrophorum* infection when he described hand lesions in himself and a colleague who handled rabbits that had been experimentally infected with *F. necrophorum*. He was also, it is believed, the first to actually grow the organism in vitro. In 1898, the French worker Halle mentioned an isolate with characteristics typical of *F. necrophorum* in his thesis on the bacteriology of the female genital tract [5]. He also documented Gram-negative bacilli from cases of otitis media and in the blood of 18 cases of patients suffering from suppurative conditions complicated by jaundice, all of whom died. Courmont and Cade [6] described a fatal case probably due to *F. necrophorum* of a patient who died shortly after acute tonsillitis and from whom an anaerobic bacillus was isolated from blood culture.

It was not until the 1930s however, when the French physician Anton Lemierre raised awareness of serious human infections with an organism that was referred to at the time as *Bacillus funduliformis*, in a lecture at the Middlesex Hospital Medical School in London on 3 March 1936 [7]. Although Lemierre gained the eponymous credit, and the condition eventually bore his name, there were

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several reports by earlier workers who noted infections typical of what is now known as Lemierre's disease. For example, in 1905 Ellerman [8] described a fatal infection in a 9 month-old girl dying of pseudo-diphtheria, laryngitis and pneumonia. Gram stained material from this patient showed long threadlike Gram-negative bacilli. In 1930, Cunningham [1] described two fatal cases, one in a 19-year old girl with a history of a sore throat and the other in a man of 64 years also with classical symptoms. Prophetically, he stressed the need for anaerobic blood cultures for proper diagnosis of this condition; it is salient therefore to remind those modern-day practitioners who sometimes question the value of anaerobic blood cultures of the lessons that were learnt over 75 years ago. There are other anecdotal reports of what were possibly zoonotic infections of the skin due to *F. necrophorum*, such as that of Shaw [9], who described its isolation from hand lesions of a meat inspector who had scratched his hand whilst investigating an ulceration on the lip of a sheep. Van Wering [10] also described a case from a forearm of a man who had been bitten by a cow. Curiously, there has been little evidence in more recent literature of the zoonotic potential of *F. necrophorum* however.

2. Taxonomy

Over many decades, this taxon has been classified under a variety of genera and species before eventually finding a home in the genus *Fusobacterium* in the 1970s. In 1956, a review of cases of bacteroides [*sic*] septicaemia by Gunn [11], reflected the confused taxonomy of the period when he described two main groups of bacteroides [*sic*] infections. His first group was *Bacteroides funduliformis*, which clearly fitted the description of *F. necrophorum*, and his second group was *Bacteroides fragilis*. He noted that the former was associated with high morbidity and mortality and the latter with localised infections and rarely septicaemia. This is an excellent example of how developments in taxonomy eventually match with clinical criteria thus enabling a better understanding of the epidemiology of infectious diseases. The various pseudonyms of *F. necrophorum* found in the early literature are listed in Table 1 and the description of the two sub-species *F. necrophorum ss. funduliforme* and *F. necrophorum ss. necrophorum* is considered in the section on pathogenesis.

3. Pathogenesis

It is often stated in textbooks that *F. necrophorum* is a commensal in the human oro-pharynx but the actual hard evidence for this in the literature is conspicuously absent. Although it may be isolated from cases of inflammation of the tonsillar region it is by no means a common resident in healthy oro-pharyngeal flora. As IFND is uncommon, it is likely that a number of factors are important in its development. As a sore throat or pharyngitis is often the primary symptom of severe disease, it is a reasonable

Table 1
Synonyms of *Fusobacterium necrophorum*

<i>Actinomyces necrophorus</i> ,
<i>Actinomyces cuniculi</i> ,
<i>Bacillus filiformis</i> ,
<i>Bacillus funduliformis</i> ,
<i>Bacillus pyogenes anaerobius</i> ,
<i>Bacillus symbiophiles</i> ,
<i>Bacterium necrophorum</i> ,
<i>Bacterium necrophorus</i> ,
<i>Bacteroides funduliformis</i> ,
<i>Bacteroides necrophorus</i> ,
<i>Bang's necrosis bacillus</i> ,
<i>Fusiformis necrophorus</i> ,
<i>Necrobacterium funduliforme</i> ,
<i>Schmorl's bacillus</i> ,
<i>Streptothrix cuniculi</i> ,
<i>Sphaerophorus necrophorus</i> ,
<i>Sphaerophorus funduliformis</i> ,
<i>Streptothrix necrophora</i> .

assumption that this may be due to an initial viral or bacterial insult. Alterations in the pharyngeal mucosa might then allow invasion by *F. necrophorum* with the resulting inflammation of local lymph nodes and spread to distant sites via the haematogenous route. Stenfors et al. [12] reported an increase in the penetration of bacteria into the tonsillar epithelium during cases of infectious mononucleosis and associations of IFND with Epstein Barr virus and the primary sore throat are due to reports of the Monospot or Paul-Bunnell tests for heterophile antibody being positive. Dagan and Powell [13] described three cases of postanginal sepsis following infectious mononucleosis diagnosed by monospot and confirmed by horse kidney and beef cell adsorption tests. Epstein-Barr virus infection is also thought to induce a degree of immuno-suppression with a transient decrease in T-cell mediated immunity that may predispose to a bacterial superinfection. There is certainly an overlap in the peak age range for both infections, but according to Burden [14], false-positive Monospot tests can occur in cases of IFND, and given the fact that EBV infection is so common while IFND is so rare, much more research needs to be done to confirm a link between EBV and IFND. Another possibility in the development of IFND is the acquisition of a particularly virulent strain of *F. necrophorum*. However, a molecular typing method recently applied to strains involved in invasive and non-invasive isolates from persistent sore throats showed no apparent differences [15]. Several virulence mechanisms of *F. necrophorum* have been described and probably the best understood of these is the endotoxic lipopolysaccharide (LPS) in the cell wall. This has been reviewed by Garcia et al. [16] who found that LPS constituted 4% of the cell wall components. It was lethal to mice, chick embryos and rabbits. They reported that the LPS of *F. necrophorum* produced both localised and generalised Schwartzman reactions in rabbits and resembled the physicochemical and biological behaviour of

classical endotoxin thus contributing significantly to the pathogenicity of *F. necrophorum*. They also postulated that endotoxic damage in bovine hepatic abscesses due to *F. necrophorum* might depend on several factors such as the rate of multiplication of the organism, the ability of fibrous connective tissue to encapsulate the focus of infection, and the effective clearance of endotoxin by the liver reticuloendothelial system.

Since settling in the genus *Fusobacterium* the species *F. necrophorum* has been divided into two sub-species; *F. necrophorum* (ss. *funduliforme*) and *F. necrophorum* (ss. *necrophorum*). These are also referred to as biovar B and biovar A, respectively. Biovar A are considered to be mainly of animal origin causing severe or life threatening infections in cattle, sheep and wallabies. Biovar B is the main human pathogen [17,18]. The biovars can be distinguished by chick erythrocyte agglutination and virulence testing in the mouse model. These tests are both positive for biovar B and negative for biovar A. The difference in virulence between biovar A and B in mice was investigated by Smith and Thornton [19]. Biovar A strains were generally more virulent giving rise to rapidly fatal infection with severe lesions in the liver and other organs compared to biovar B strains. Hall et al. [20] compared human and animal strains by SDS-PAGE, conventional biochemical tests and pyrolysis mass spectrometry. They conclude that *F. necrophorum* is a heterogeneous species forming at least two distinct sub groups that had differing morphology, biochemistry, whole cell and protein composition and host range specificity. Although they supported the sub-speciation as suggested by Shinjo et al. [21], they cautioned the total synonymy of the ‘human group’ with biovar B and the ‘animal group’ with biovar A pointing out anomalous strains that did not fit these groupings. They also agreed with the observations of Smith and Thornton [19] that the term necrobacillosis as used by medical and veterinary microbiologists refers to diseases that differ in several important aspects. The infectivity of *F. necrophorum* in a mouse model was investigated by Smith et al. [22]. They described how the presence of *Escherichia coli* or faecal material could reduce the minimum infective dose in a mouse thus explaining the occurrence of necrobacillosis in minor animal wounds contaminated with faecal material. The leukotoxin component of *F. necrophorum* is believed to be an important virulence factor particularly in animals. Narayanan et al. [23] showed *F. necrophorum* leukotoxin was toxic to bovine leukocytes although it remains to be proven that *F. necrophorum* sub-species *funduliforme* is equally toxic to human leukocytes. Other putative virulence factors are haemagglutinin, and haemolysin but little is known about their actual role in pathogenesis.

4. Clinical presentations of human infections due to *F. necrophorum*

The classical clinical picture of IFND as described by Lemierre is a young adult or adolescent with a history of a sore throat or pharyngitis, followed by high fever

(101–103°F) and rigors beginning on the fourth or fifth day after the sore throat symptom. This is usually accompanied by cervical lymphadenopathy, and commonly a one-sided thrombophlebitis of internal jugular vein. In his seminal paper [7], Lemierre commented that metastatic abscesses are always present and that these were most often in the lungs. These septic infarcts can cause intense thoracic pain with dyspnoea, blood stained sputum and pyo-pneumothorax. Other sites of distant abscesses frequently included the long bones and skeletal joints that are also often very painful. The patients’ condition often declines to extreme prostration or coma and untreated infection commonly ends in death within 7–15 days.

According to Lemierre, the disease follows such a distinctive course that (and his exact words used are often quoted) ‘it becomes relatively easy to make a diagnosis on the simple clinical findings’, and, that it ‘constitutes a syndrome so characteristic that mistake is almost impossible’ [7]. Unfortunately, probably because the condition is so rare, these wise words have gone unheeded by modern-day physicians and early mis-diagnosis of IFND is the norm. Certainly, in reviewing the descriptive case histories in the literature one is struck by the remarkably consistent clinical presentations that would probably be recognised were the disease to be more common.

In his original address, Lemierre listed the potential foci of infection as inflammatory lesions of the nasopharynx, particularly tonsillar and peritonsillar abscesses, similar lesions in the mouth and jaws, otitis media and mastoiditis, purulent endometritis and parturition, appendicitis and infections of the urinary passages. In 1955, Alston [24] described four classes of infections due to *F. necrophorum*. The first included skin or subcutaneous tissue, the second in the throat, the third in the female genital tract, and the fourth in the lungs. Lung abscesses often multiple in nature are a common sequelae to IFND and in nearly all cases there is pleuropulmonary involvement. Single or multiple nodular infiltrates with pleural effusions precede cavitating abscesses and account for presentations with chest pain and dyspnoea [25]. Of the 29 cases of classic Lemierre’s reviewed by Eykyn [26] 23 had chest pain, dyspnoea and haemoptysis. Of the 38 cases reviewed by Sinave et al. [27] 37 (97%) had the lungs as a site of metastatic infection. Other sites were septic arthritis of the hip, knee, ankle and shoulder in six patients. Soft tissue abscesses were present in four cases including a paravertebral abscess, two deep thigh abscesses and an orbital cellulitis.

Orbital cellulitis due to *F. necrophorum* occurs mainly in children and adolescents and a case was described by Escardo et al. [28] in a 16 year old girl with painful left proptosis preceded by a 2-week history of malaise, sore throat and rigors. Surgical drainage of the left ethmoid sinus yielded a large volume of pus that grew a pure culture of *F. necrophorum*. Despite surgery and 30 days of appropriate antibiotics she did not recover full use of her left eye. A similar case was described by Rathore et al. [29] in a 4-year old girl who had previously been treated for

acute sinusitis but developed an orbital abscess that required surgical drainage and the cultured pus grew *F. necrophorum*.

Cases often have disturbed hepatic functions and in Lemierre's case histories he stated that icterus was a common symptom. In the set of 38 patients listed by Sinave et al. [27] 15 had either frank jaundice or raised bilirubin levels.

Jaundice was also a relatively common feature in the series of cases reviewed by Leugers and Clover [30] with 49% of cases with this symptom and 15% having hepatomegaly independent of jaundice.

Another dramatic disease in which *F. necrophorum* is believed to play a causative role, albeit in concert with other members of the oral flora, is *cancrem oris* or noma. This disease is characterised by massive destruction of facial tissues resulting in terrible disfigurement and occurs in malnourished and immunocompromised children mainly in sub-Saharan Africa. According to Ewonwu [31] there are many similarities between noma and the lesions seen in cases of necrobacillosis in wallabies. *F. necrophorum* has been isolated from 87.5% of noma lesions examined by Falker et al. [32] and was more commonly present than other members of the oral flora.

5. Incidence of IFND

Estimates of the national incidences of serious infections with *F. necrophorum* classed as either necrobacillosis or Lemierre's are rare in the literature. Probably the most comprehensive recent national incidence data comes from Denmark. Hagelskjaer et al. [33] summarised the incidence and epidemiology of necrobacillosis and Lemierre's disease over the period 1990–1995 and reported a combined incidence of 2.3 cases per year per million persons with an increasing incidence over time. Twenty-four patients with Lemierre's disease were all young and previously healthy and none died. Twenty-five patients classified as suffering from necrobacillosis had a 24% mortality rate that correlated with age and other predisposing factors.

In the 1960s and 1970s post-anginal septicaemia was rarely reported and the generally held belief was that this was due to the widespread use of antibiotics for treatment of putative streptococcal throat infections in this era. Several indicators suggest the incidence is rising particularly in the UK and efforts to curb the spread of antimicrobial resistance, whilst well intended, may have inadvertently led to a resurgence in this severe disease. Jones et al. [34], in a review of cases in the South West of England noted an apparent increase over the period 1994–1999 with an accompanying drop in the number of cases that had received antibiotics prior to admission. Covering a total population of approximately 2 million, they reported an overall incidence of 0.9/m/year. However, double the number of cases were seen in 1999 that had occurred in 1997 and 1998 combined, and prior to that, only two cases were identified in the first 3 years of the

study. Between 1980 and 1995 Alvarez and Schrieber [35] reported only 12 cases in the English literature but over the next 3 years 11 cases were reported. Data from the Communicable Disease Surveillance Centre for England and Wales over the period 1990–2000 for positive blood cultures with *F. necrophorum* were analysed by Brazier et al. [36]. They reported 208 blood culture isolates with an average of 19 per annum, an incidence of approximately 0.6 cases per million per year. These data also show a rise in the number of cases in 1999 over previous years and this rise was mirrored by the rise in referrals of isolates of *F. necrophorum* to the UK Anaerobe Reference Laboratory (ARL) including other sources such as abscesses and joints [36]. Referral data to ARL is tabulated in Fig. 1 and shows a rise in the yearly average of infections confirmed as due to *F. necrophorum* since 1999.

For a disease that is so rare, its appearances in the literature are not that uncommon. Cases of IFND that are diagnosed are invariably written up as case presentations by many different medical specialities, purely because they are novel to non-microbiologists and cases tend to be dramatic and fit the classical description of the disease so well. A common title in descriptive case-histories is the 'forgotten disease' theme whereby clinicians from disciplines other than infectious diseases and clinical microbiology 'discover' the condition and publish their clinical findings using the term 'forgotten' when they were quite probably unaware of it in the first place. For example maxillofacial surgeons [37] emergency medicine physicians [38] and ear, nose and throat specialists [39] have all published along these lines.

Seasonal variation in the number of IFND cases has not generally been reported except for an approximate 25% increase in the incidence of *F. necrophorum* bacteraemias reported to CDSC in England and Wales during the winter months January–March, over the period 1990–2000 [36].

6. Demography and mortality rates of IFND

Despite Lemierre's original article finding no difference in the level of disease in males and females, several other

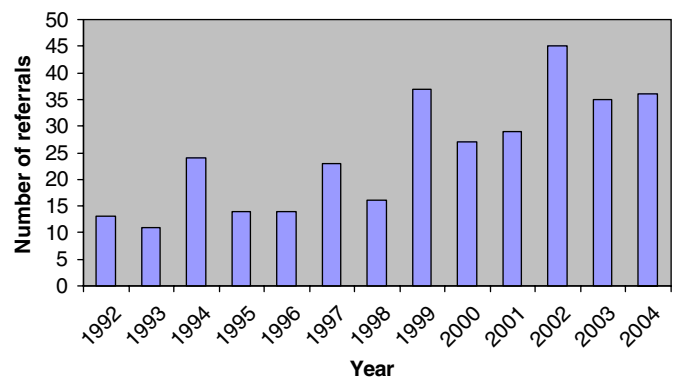


Fig. 1. Referrals of *F. necrophorum* to UK Anaerobe Reference Laboratory 1992–2004.

workers have noted a marked propensity for IFND in males. In the data analysed by Brazier et al. [36] there was a highly significant difference in the sex ratio of cases of bacteraemias due to *F. necrophorum* over the period 1990–2000 with a greater than 2:1 ratio of male to female ($P = <0.0001$). The review of cases over the period 1990–1995 in Denmark also showed a 2:1 male to female ratio, and in her review of 45 cases in 1989, Eykyn noted a similar 2:1 ratio of males to females [26]. In 39 cases reviewed by Leugers and Clover [30] 75% (3:1) were male, but a series of 38 cases reviewed in the literature between 1974–1988 by Sinave et al. [24] showed a less pronounced male to female ratio of 1.5:1. It is not known why males are more susceptible to invasive infections with *F. necrophorum*.

The age distribution of *F. necrophorum* bacteraemias in England and Wales was markedly in favour of young adults in the 16–23 years age band and many other studies have reported a similar peak incidence in teenagers and young adults. Of the 38 cases reviewed by Sinave et al. [27] the average age was 19.6 year (range 7–38 year). In the 29 cases summarised by Eykyn [26] the average age of cases in both sexes was 21.5, whilst the cases reported by Leugers and Clover [30] and Hagelskjaer et al. [33] found an average age of 18.9 and 17 year, respectively. It is not known why younger people are more likely to suffer from infections with *F. necrophorum*.

The mortality rates of IFND vary over the decades from those reported in the pre-antibiotic era of Lemierre where 18/20 (90%) cases died, [7] to those in the early days of antibiotic treatment such as Alston's report of a series of 21 cases with 13 (62%) fatalities [24]. Modern day data on mortality rates are lower, ranging from 4% to 18% [26,30,40–43]. However, Hagelskjaer et al. reported a group of 25 patients with a higher mortality rate of 24% that correlated with age and pre-existing malignancies [33].

7. Laboratory diagnosis of IFND

In a patient presenting with possible symptoms of Lemierre's disease, an array of laboratory investigations will undoubtedly be requested. Some of these will have no doubt been of a general investigative nature as the symptoms, although described as classic by Lemierre, will often go unrecognised and may be diagnosed as either a viral or unknown bacterial infection. Jones et al. [34] point out two simple investigations that could help differentiate early symptoms of IFND from a viral infection—a peripheral white cell count and a test for C-reactive protein. Both should be raised in a case of Lemierre's disease but not in a viral infection. However, Leugers and Clover described a case in a 20-year old male who had an initial examination including a full blood count who was discharged home with a diagnosis of a viral respiratory infection [30]. There may have also been an antibiotic intervention by a primary care physician that may add to the diagnostic confusion. Of the microbiological investiga-

tions it is usually the blood culture that first yields a positive result. Of course, this will only happen if an anaerobic blood culture bottle is incorporated as part of the blood culture set. Modern day advocates of discontinuing the anaerobic blood culture bottle as routine on the basis of saving costs, should bear this in mind and heed the advice of Cunningham given over 75 years ago. Several reports stress that inappropriate antibiotics at this stage could seriously compromise clinical outcome. [30,38]

Once a positive signal is detected in an anaerobic blood culture bottle, a Gram stained smear could provide a significant clue to infection with *F. necrophorum*. The classical cellular morphology of *F. necrophorum* is a short cocco-bacillus with occasional very long filamentous forms; a truly pleomorphic Gram-negative bacillus (Plate 1). However, it would take an experienced eye to recognise the characteristic morphology of *F. necrophorum*, and as infection is rare, it is very unlikely that it would be recognised by this characteristic alone. As *E. coli* and other coliform bacteria often grow in anaerobic blood culture bottles, a report of 'Gram-negative bacilli' at this stage could lead to an inappropriate antibiotic regimen that has little or no effect on anaerobic bacteria.

This apart, the only non-molecular rapid laboratory procedure that would confirm IFND at this stage in a blood culture would be analysis for the presence of volatile fatty acid end products by gas-liquid chromatography (GLC). A volatile fatty acid profile containing a single major peak of butyric acid (with minor peaks of acetic and propionic acid) is highly indicative of a member of the genus *Fusobacterium* [45]. This would not only enable prompt commencement of appropriate treatment, but would also provide laboratory diagnosis of a hitherto undiagnosed condition, and confirm any clinical suspicion of Lemierre's disease. Such a result is available after a 15 min assay and could guarantee appropriate therapy at an early stage. Unfortunately, it is rare for a routine diagnostic laboratory to have this capability these days.

Confirmation by conventional bacteriological methods requires sub-culture on to agar media that are nutritious enough to support the growth of *F. necrophorum* colonies. Basic blood agar medium is usually insufficient and requires additional supplementation with vitamin K, haemin and menadione. In the authors' experience, Fastidious Anaerobe Agar (FAA Lab M Ltd, Bury, UK) produces the best growth of all fusobacterial species. Once cultured on a suitable medium such as FAA, the colonial characteristics are also so typical as to make it easily recognisable by the experienced eye. The colonies are cream-yellow in colour, smooth or umbonate, round and entire with an odour redolent of over-cooked cabbage or rancid butter. Haemolysis may vary between strains, but most will have a narrow zone of complete (beta) haemolysis surrounding the colonies. Under long wave ultra-violet light colonies fluoresce a vivid greenish-yellow colour [46] although this property is medium dependent and best seen on FAA. It also produces indole, a

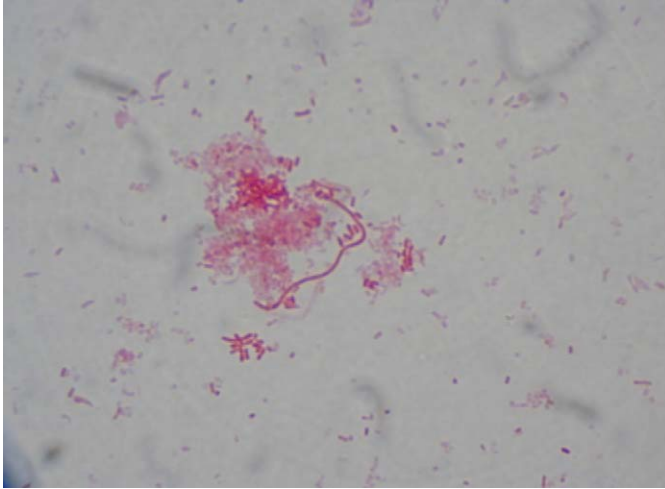


Plate. 1. Gram stain of *Fusobacterium necrophorum* pleomorphism in a blood culture.

metabolite that can be rapidly detected direct from colonies on an agar plate by using the spot indole reagent *p*-dimethylcinnamaldehyde. Another readily detectable feature of *F. necrophorum* is the production of lipase on an agar medium supplemented with egg yolk. A combination of these simple tests is enough to presumptively identify *F. necrophorum* with confidence and thus contribute to a diagnosis of Lemierre's or necrobacillosis. Definitive identification may possibly be obtained by use of a commercial anaerobe identification kit, or preferably by referral to a reference laboratory.

Although a sore throat is a primary symptom of IFND, if a throat swab is submitted for bacteriological investigation it is not common practice to include anaerobic cultures to look for *F. necrophorum*. Evidence is also emerging of the role of *F. necrophorum* in non-invasive throat infections as showed by a recent study of 248 throat swabs examined at the University College Hospital in London. This study found *F. necrophorum* in 10% of patients with sore throats, second only to the incidence of Group A streptococci [47]. A previous study by the same group found *F. necrophorum* in 21% of persistent or chronic sore throats and included one patient (one of the authors) with a history of persistent sore throats over many years from which a pure growth of *F. necrophorum* was obtained from a swab of the fauces and who made a good recovery after treatment with metronidazole [15].

The bacteriological examination of clinical material suspected of containing *F. necrophorum* should be performed to strict anaerobic protocols paying particular attention to minimise the exposure to air of recently inoculated agar plates. It is important not to expose microcolonies of *F. necrophorum* to air after overnight incubation; preferably they should have 48 h uninterrupted incubation. In mixed culture, colonies of *F. necrophorum* may easily be overlooked particularly by staff unfamiliar with their typical appearance. A selective agar for

Fusobacterium spp. was developed by Brazier et al. [48] based on a combination of josamycin, vancomycin and norfloxacin. Although very efficacious in isolating fusobacteria from mixed flora sites, it has not become commonly used in clinical microbiology laboratories most probably on grounds of cost. Similarly, a differential and selective agar for *F. necrophorum* was developed by Morgenstein et al. in 1981 [49]. Recently, real-time PCR technology has been applied to diagnose a case of Lemierre's disease. Aliyu et al. [50] demonstrated *F. necrophorum* specific DNA in brain and renal tissue after conventional methods had failed. Other branches of investigative medicine may play a role in the diagnosis of IFND. For example, radiologists Auber and Mancuso [44] investigating an adolescent girl suspected of having Lemierre's disease for septic metastatic emboli used magnetic resonance imaging (MRI) or computerised tomography to distinguish between inflammatory venous thromboses and abscesses. They stated that MRI was a key investigation in the diagnosis that led to surgery being avoided in this patient. Gudinchet et al. [51] described radiological investigations of two cases of Lemierre's disease with cervical colour Doppler ultrasonography (CDUS), cervicothoracic helical computerised tomography, and high resolution CT (HRCT). They found HRCT allowed good depiction of the multiple cavitated pulmonary nodules often seen in Lemierre's disease, and that CDUS helped pinpoint the extent of internal jugular vein thromboses.

8. Treatment regimens and antimicrobial susceptibility of *F. necrophorum*

As the incidence of serious infections due to *F. necrophorum* are rare, it has not been possible to conduct statistically valid trials to evaluate optimum treatment regimens. Case histories of IFND often include outcomes of treatment commonly based on penicillin and metronidazole and this regimen is usually followed in the UK. Indeed, many authors recommend either this combination or monotherapy with clindamycin for 2–6 weeks [13,30,33,37,38,52]. Most treatment regimens are prolonged and the patients' temperature may remain elevated for several weeks and complete recovery is usually slow.

There is a paucity of susceptibility data in the literature on which to base empirical treatment. However, resistance to metronidazole has never been reported and susceptibility data from 100 human isolates of *F. necrophorum* submitted to the UK ARL identified 15% resistance to erythromycin, with 2% resistance to penicillin and 1% resistance to tetracycline. There was no resistance to metronidazole, co-amoxiclav, chloramphenicol, cefoxitin, clindamycin or imipenem [36]. The level of 15% resistance to erythromycin may be significant as this drug or its newer derivatives are ones that may commonly be prescribed by primary care physicians who may elect to treat upper respiratory tract infections with a drug other than penicillin. Other

fusobacteria such as *F. nucleatum* are also commonly resistant to erythromycin and this drug should not be considered for treatment of fusobacterial infections. In the series of 15 cases in the South West of England reported by Jones et al. [34], 6 had been given erythromycin prior to hospital admission. Hagelskjaer et al. [33] also reported that 33% of cases had received either a macrolide or penicillin before admission to hospital.

In the pre-antibiotic era, ligation of the internal jugular vein was a commonly attempted cure but had little success. Anticoagulant therapy has been advocated to treat suppurative thrombophlebitis in an attempt to remove a persistent septic focus that delays recovery. Goldhagen et al. [53] cite the potential for faster resolution of the thrombophlebitis with anticoagulants and limiting development of new metastatic abscesses. Others however, have pointed out the potential dangers of serious haemorrhage and there is little contemporary clinical data to support this form of treatment [54]. Surgical drainage of metastatic abscesses is an important part of the management of patients with IFND. Open drainage of anaerobic empyemas is associated with decreased morbidity and mortality compared with thoracentesis and is the optimal treatment for persistent fluid collections.

9. Conclusions

IFND is a serious disease that most commonly affects previously healthy young adults with symptoms that continue to confuse physicians primarily because of its rarity. Cases in the UK appear to have increased since 1999 but we can only speculate as to why. Is this due to increased ascertainment, i.e. better diagnosis? Or, if the increase is genuine, what could be contributing to it? Government reports such as that produced by the UK Standing Medical Advisory Committee entitled 'The Path of Least Resistance' [55] emphasised the need to control antibiotic resistance by restricting their use. In this report, general practitioners (GPs) are encouraged not to prescribe antibiotics for conditions such as sore throats that are primarily of viral origin. There has also been a UK government publicity campaign for the general public informing them not to expect an antibiotic when visiting their GP for upper respiratory tract infections such as coughs, colds and sore throats that are usually of viral origin. This is a laudable position, but adolescents and young adults, particularly males, should be aware that if their symptoms persist and general health worsens they should seek immediate help. Similarly, GP's should be aware that *F. necrophorum* can be a cause of either primary or persistent sore throats and that a small percentage of the former may progress to IFND and become severely ill. The author has had personal communication with case of IFND in a young adult female who displayed all the classical symptoms but who was only diagnosed after she became seriously ill and an isolate from her blood culture was identified. Her clinical history was of initially feeling

unwell and having a sore throat. Upon visiting her GP she was told her symptoms were of a viral aetiology and he did not intend to prescribe an antibiotic. Over the next 10 days however, despite a second GP consultation a week later she had deteriorated to such a point that she required immediate hospitalisation and was found to have bi-lateral pneumonia, was in septic shock, and in the early stages of renal failure. After admission, a preliminary diagnosis was Legionnaire's disease was made and it was not until a blood culture grew an anaerobic Gram-negative bacillus that was identified as *F. necrophorum* by referral to the Anaerobe Reference Laboratory that the correct diagnosis was made and a life potentially saved.

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