



A Review of *Fusobacterium necrophorum* Infections in Humans

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Authors' contributions

This review was carried out in collaboration among all authors. Author EEC designed the review and wrote the drafts of the manuscript. Authors FON and AOC reviewed the drafts and provided suggestions. All authors contributed to the literature searches and approved the final manuscript.

Review Article

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ABSTRACT

The incidence of human infections caused by *Fusobacterium necrophorum* is recently on the increase and this is attributed largely to alteration in antibiotic usage pattern, malnutrition and poor oral hygiene. These infections are usually acquired exogenously from animals such as dogs, livestock or humans and ranges from mild sore throat to severe infections like Lemierre's syndrome and *Cancrum oris* (NOMA). *Fusobacterium necrophorum* species produce characteristic toxins and virulent factors which are responsible for the severity of infections. Confirming the presence of these species is recommended during suspected infections. It would help in providing information on the antimicrobial sensitivity pattern so as to guide treatment and control of these severe infections as well as for epidemiological purposes. This review summarizes human infections associated with *F. necrophorum* providing information on their epidemiology, risk factors, pathogenicity, diagnosis and treatment.

Keywords: *Fusobacterium necrophorum*; Sore throat; Lemierre's syndrome; *Cancrum oris*; Noma.

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1. INTRODUCTION

Fusobacterium necrophorum is a gram negative, non-spore forming, obligate anaerobe that was first described in animals as far back as 1884 by Loeffler and was later isolated from humans in 1898 by Jean Halle [1]. This anaerobic organism causes a wide variety of infections ranging from septic arthritis [2], peritonsillar abscess [3], *Cancrum oris* [4,5], to the most fatal conditions such as endocarditis [6], Meningitis [7] and Lemierre's syndrome [8]. This specie can be responsible for any of these infections either as a sole agent or in combination with other potential pathogens [9]. Previously, it was difficult to associate *F. necrophorum* with some of these conditions. However, the increased awareness of the infections as well as improved anaerobic diagnostic techniques have accounted for the high incidence and understanding of *F. necrophorum* infections [9]. Furthermore, due to concerns on the increasing levels of multidrug resistance among most human pathogens, there is judicious use of antibiotics for the prevention and treatment of sore throat and tonsillitis and this is believed to have contributed to high rate of infections [8,9].

Fusobacterium necrophorum is able to initiate these infections due to their ability to produce leukotoxins that are active against a variety of white blood cells, especially polymorphonuclear neutrophils [10,11]. In addition, they can recruit host plasminogen to the bacteria surface which is converted to active plasmin and aids in cell invasion [12]. Apart from *Cancrum oris* [13,14], other Infections associated with *F. necrophorum* are not well documented in sub-Saharan African region. Adequate knowledge on the predisposing factors, symptoms of infection, diagnosis and management would provide information on clinical conditions involving the presence and activities of strains of *F. necrophorum*. Therefore, this paper gives a review of the variety of infections caused by *F. necrophorum*, their pre-disposing factors, pathogenesis, diagnosis and treatment.

1.1 *Fusobacterium necrophorum*

Fusobacterium necrophorum belongs to the family *Fusobacteriaceae*. They are gram negative pleomorphic anaerobic species, with filaments, short rods and coccoid elements [15]. Among the different species of Fusobacteria, *F. nucleatum* and *F. necrophorum* are the most pathogenic [15]. *Fusobacterium necrophorum* is classified into two subspecies namely *F. necrophorum subspecies necrophorum* and *Fusobacterium necrophorum funduliforme*. *F. necrophorum* subsp *funduliforme* are responsible for human infections while *F. necrophorum* subsp *necrophorum*, causes infection in animals [15].

While *Fusobacterium nucleatum* is associated with oro-facial infections, cases of post-surgical sepsis of odontogenic tumors [16] and periodontitis [17], *Fusobacterium necrophorum* is mainly implicated in Lemierre's syndrome [18]. However, they are also pathogens in *Cancrum oris*, endocarditis, meningitis, peritonsillar abscess and sore throats [4,7,19,20]. In some cases, they have been isolated in Lemierre's syndrome as a sole agent or in association with other *Fusobacterium* species notably *F. mortiferum* and *F. varium*. [21-24].

1.2 Epidemiology

Fusobacterium necrophorum infection occurs mainly in healthy individuals [25]. The most common are necrobacillosis which is a term used to describe group of infections caused by *F. necrophorum* [26] and post-anginal sepsis also known as Lemierre's syndrome. These

infections occur worldwide [22,27-29]. During the 1990s, the incidence of Lemierre's syndrome in Denmark was estimated to be 0.8 to 1.5 per million persons per year [26]. Between 1990 and 1995, the incidence of necrobacillosis in Denmark was also reported to be 1.5 per million persons per year with a mortality rate of about 24% [26]. In a follow up study from 1998 to 2001, the number of cases of Lemierre's syndrome rose to 14.4 per million per year with a mortality rate of 9% [30]. Similarly Jones et al. [31] reported an incidence of 0.9 per million persons per year in southwest England between 1994 and 1999. The Lemierre syndrome infection is common in young healthy adults especially those aged 15-24 years with mean age of 20 affecting both males and females [18,21,24,28,32].

Cancrum oris (NOMA) infection is a well recognized disease of the poor, occurring and being fatal in children especially those aged 0-7 years [33]. The incidence of Noma varies from one country to another but the majority of cases occur in sub-Saharan Africa. The current global incidence is uncertain. However, it was estimated to be between 100 000 and 140 000 cases per annum in 1998 [34]. Extrapolated data from a few referral centers within the same period estimated the incidence to be 0.8 per 1000 person in Nigeria, 4.0 per 1000 in Niger and 2.1–3.6 per 1000 in Senegal [35]. Subsequently, Finger et al. [13] studied a larger population of patients and placed the incidence of Noma in North-west Nigeria at 6.4 per 1000 children with estimated 25 600 Noma patients in the savannah region south of the Sahara Desert and a global incidence of 30 000–40 000 per annum. Noma infections have also been reported in other parts of Africa and Asia [36-39]. In Nigeria, it is common in the Northern part of the country especially Sokoto and Kaduna Table 3. It is also responsible for a greater percentage of children dropping out from schools [10,40]. Although Noma is recorded in eastern and western part of the country, the incidence is relatively low [41,42]. It is believed that the recorded incidence in these areas is as a result of the Hausa indigenes migrating from the North due to communal clashes and growing unrest. However, *F. necrophorum* tonsillitis has been shown to be more prevalent in older patients and those with persistent or recurrent sore throat than in individuals with uncomplicated tonsillitis [43].

1.3 Source of Infection

Though *F. necrophorum* was suggested to be a normal flora in the oral cavity [44], data supporting this is unconvincing with several authors insisting that *F. nucleatum* rather than *F. necrophorum* is more likely to be isolated from oral cavity of healthy individual [15]. Riordan concluded that the infection is acquired exogenously through human to human and animal to human transmissions [15]. *Fusobacterium necrophorum* is acquired by children via fecal contamination resulting from sharing household and domestic facilities with animals [33]. Under favorable conditions, it invades the tonsils and deeper tissues, causing serious life threatening conditions. In the case of Noma and other disease conditions, *F. necrophorum* is able to enter children's mouths through water and food contaminated with animal feces [45]. Similarly, in Lemiere syndrome, they can either be acquired by feaco-oral transmission, or inoculated directly during routine dental procedure and at the site of injection in healthy intravenous drug users (IVDU) with no previous history of sore throat or pharyngitis [46].

1.4 Predisposing Factors

Poverty remains the single most important predisposing factor for Noma [33]. Thus the disease is frequently seen in malnourished children with poor oral hygiene, poor environmental sanitation, unsafe drinking water and in those with underlying disease such as measles [33,47]. Furthermore, close proximity to unhealthy livestock and pets in the case of children playing with animals can lead to infection [47]. It is also a serious complication of

routine dental procedure and tonsillectomy [48]. Recent reports indicate that intravenous drug users are liable to septic thrombophlebitis with high mortality rate [46].

1.5 Virulence Factors

Fusobacterium necrophorum has the ability to invade as primary pathogen without an underlying illness as a result of several virulence factors and toxins it produces [49]. They possess classic endotoxins such as lipopolysaccharide which causes secretion of cytokines by white blood cells leading to symptoms of sepsis. Production of haemagglutinin causes platelet aggregation that leads to diffuse intravascular coagulation and thrombocytopenia responsible for the formation of a thrombus containing the bacteria [50]. The rapid progression of the lesion is presumed to be due to *F. necrophorum* producing a leukotoxin which is active against a variety of white blood cells [10]. The organism is also capable of producing dermonecrotic toxin, a cytoplasmic toxin as well as a hemolysin. These toxins initiate the production of a low oxidation-reduction potential resulting in varying degrees of tissue destruction typically seen in Noma infections [33]. It also produces substances such as volatile sulfur compounds and proteolytic enzymes like phosphatase B which are destructive to tissues [51]. Plasmin activity at the bacterial surface is also considered to be important for bacterial invasion [12]. The roles of key virulence factors in the pathogenesis of *F. necrophorum* infections are summarized in Table 1.

1.6 Pathogenesis

Major sources of infection include human to human transmission and animal to human. In relation to NOMA, Falkler and workers [45] postulated that *F. necrophorum* is able to enter children's mouths through water and food contaminated with animal faeces. The mucous membranes of the mouth develop ulcers which progresses rapidly. This is followed by painless tissue degeneration and goes on to degrade tissues of the bone in the face [4] Fig. 2.

Disease process varies among individuals, but generally it usually begins with a sore throat, fever, and general body weakness in most of the infections. This may be due to the fact that its mode of entry is mainly feaco-oral. Depending on the patient's immune status, the infection may be localized or become systemic. After colonization of the infection site, the infection spread to the parapharyngeal space from where the bacteria invade the peritonsillar blood vessels and move on to the internal jugular vein in Lemierre's syndrome [52]. Also the internal jugular vein becomes inflamed and this septic thrombophlebitis can give rise to septic microemboli that disseminates to other parts of the body where they can form abscesses and septic infarctions [53]. Following systemic infection, *F. necrophorum* can be carried to the lungs, causing abscesses, nodular and cavitory lesions [54]. It can also penetrate the joints causing arthritis; liver and spleen causing nuchal rigidity, photophobia, enlarged liver and splenomegaly; with meningitis [52]. When *F. necrophorum* finds its way into the pulmonary systems, they cause shortness of breath, cough and painful breathing (pleuritic chest pain) and septic shock presents with hypotension, tachycardia, oliguria and tachypnea. Other signs and symptoms that may occur include headache, muscle pain, jaundice and trismus [52].

Table 1. *Fusobacterium necrophorum* virulence factors and their role in the Pathogenesis of infections

| Virulence factors | Role in the pathogenesis of infection | References |
|----------------------------|---|------------------------------|
| Hemagglutinin | Causes platelet aggregation, inducing thrombocytopenia and diffuse intravascular coagulation which is responsible for formation of thrombus | Forrester <i>et al.</i> [50] |
| Leukotoxin | Active against a variety of white blood especially Polymorphonuclear neutrophils causing cell death by apoptosis. Overcomes host defense mechanism to establish infection and protects the organism from phagocytosis | Tadepalli <i>et al.</i> [11] |
| Synergy | Synergistic relationship with facultative bacteria that utilize oxygen and lower the redox potential creates an anaerobic environment which protects <i>F. necrophorum</i> . The leukotoxin produced by <i>F. necrophorum</i> on the other hand protects these bacteria from phagocytosis | Tan <i>et al.</i> [86] |
| Hemolysin | Responsible for the lysis of cells and release of iron which plays a central role in bacterial pathogenesis and contributes to abscess formation | Kanoe, [55] |
| Endotoxin | <i>Fusobacterium necrophorum</i> Lipopolysaccharide causes stimulation of pro-inflammatory cytokines responsible for the inflammatory and endotoxic effects. | Tan <i>et al.</i> [56] |
| Dermonecrotic toxin | Cell wall dermonecrotic toxin induces haemorrhagic necrosis in the skin of humans and is responsible for tissue destruction | Kanoe <i>et al.</i> [57] |
| Adhesin | Aids attachment and subsequent penetration of the host cell and this contributes to the establishment of infection | Tan <i>et al.</i> [56] |
| Recruitment of plasminogen | <i>F. necrophorum</i> recruits host plasminogen to the surface of the bacteria cell. Surface bound plasminogen is converted to plasmin and protected from inactivation by α 2-antiplasmin, thus promoting fibrinolysis | Holm and Rasmussen [11] |

2. FUSOBACTERIUM NECROPHORUM INFECTIONS

2.1 Lemierre's Syndrome

Lemierre's syndrome was initially described in the early nineteen century by Lemierre [44]. There were few reported cases in the 60's and 70's and it was then seen as a "forgotten

disease". Interestingly, this infection re-emerged in the early 1990s, and since then there have been increasing reports indicating that the disease may not be so uncommon [8,58] Table 2. For instance, Denmark witnessed a surge of *F. necrophorum* infections in the 90's, with eighty-two cases of Lemierre's syndrome reported in previously healthy individuals within 1990-1995 and 1998-2001 [26,30]. The authors concluded that delay in diagnosis was responsible for increased mortality and risk of disseminated infections [26]. A study by Ramirez and workers brought to attention the increased diagnosis of Lemierre syndrome in Children's Hospital of Wisconsin [8]. Since then, several authors have also reported cases of Lemierre's syndrome and within the last 10 years more than 80 cases have been recorded worldwide [22,29,53,59-61]. While some investigators are of the opinion that the re-emergence is due to the restricted use of penicillin, a drug with strong antibacterial activity on *F. necrophorum*, as an anti-streptococcal agent for sore throats and tonsillitis, others attributed it to increased awareness of the disease as well as the improvement in the laboratory diagnosis of anaerobic pathogens [52]. Lemierre's syndrome is characterized by thrombosis of internal or external jugular vein Fig. 1. Bilateral and sigmoid sinus, painful facial and neck swelling, multiple lung abscess, persistent sore throat and pharyngitis [21,23,32]. Common symptoms of infection include extreme lethargy, spiked fevers, rigors, swollen cervical lymph nodes and tender or painful neck. Often there is abdominal pain, diarrhea, nausea and vomiting during this phase. These symptoms are usually observed within 2 weeks after the initial exposure [54]. In complicated conditions there is a chronic dissemination of emboli to pulmonary and systemic sites. [8,58]). Clinical diagnosis is usually challenging due to the diverse clinical presentations and symptoms. Some clinically confusing cases have been reported involving unusual symptoms such as acute paresis of the abducens and oculomotor nerve [28], thrombosis of the intracranial, extracranial, subclavian and brachiocephalic vein [49].

Table 2. Global Reports of Lemierre's Syndrome

| Location | No of cases | Implicated organism(s) | References |
|----------------|-------------|---|-------------------------------|
| UK | 4 | Case 1: <i>F. necrophorum</i> , 2: <i>F. necrophorum</i> , 3: <i>Enterococcus</i> spp., 4: <i>Fusobacterium</i> spp. | Screaton et al. [53] |
| Spain | 6 | <i>Fusobacterium</i> spp. | Gargallo et al. [63] |
| Seattle, USA | 3 | Case 1. <i>F. necrophorum</i> . 2. <i>Fusobacterium</i> spp., 3. <i>Fusobacterium</i> spp. | Lu et al. [64] |
| Ottawa, Canada | 1 | <i>F. necrophorum</i> | Aljohaney and MacCarthy, [18] |
| UK | 1 | <i>F. necrophorum</i> | Khan et al. [61] |
| Cameroun | 1 | Patient refused laboratory investigation | Uduma et al. [32] |
| Columbia | 1 | <i>F. nucleatum</i> | Williams et al. [21] |
| Germany | 1 | <i>F. necrophorum</i> | Kisser et al. [58] |
| New York, USA | 1 | <i>F. varium</i> | Kushawaha et al. [22] |
| South Africa | 1 | <i>Escherichia coli</i> , No anaerobic cultivation done | Such and Joseph, [65] |
| Japan | 1 | <i>F. necrophorum</i> | Murata et al. [29] |
| Greece | 1 | <i>F. necrophorum</i> | Dimitropoulou et al. [46] |

Although *F. necrophorum* is implicated as the major anaerobic pathogen in Lemierre's syndrome and has been reported as a sole pathogen in several cases [23,28,61], other bacteria of the same genus especially *F. nucleatum*, *F. mortiferum* and *F. varium* have also been isolated [21-24]. The paucity of data on Lemierre's syndrome in sub-saharan Africa may not necessarily mean that the disease is not present in this sub region. This is likely due to lack of proper and adequate diagnostic facilities, skilled manpower to diagnose anaerobic infections [62], adequate surveillance system and good record keeping. It is important to consider Lemierre's syndrome in susceptible individuals with recurrent sore throats and those with predisposing conditions in Africa.

Table 3. Nigerian Reports on *Cancrum oris*

| State | Period of review | Age range (years) | No of cases | References |
|---------|------------------|-------------------|-------------|---------------------|
| Sokoto | 1996-1997 | 2-16yrs | 129 | Enwonwu et al. [33] |
| Ile-ife | 1982-1996 | 2-16yrs | 152 | Ogini et al. [14] |
| Enugu | 1992-2001 | 5-28yrs | 2 | Oji [41] |
| Ibadan | 1986-2000 | 1-16yrs | 45 | Denloye et al. [42] |
| Kaduna | 1991-2001 | 3-6yrs | 252 | Adeola et al. [40] |

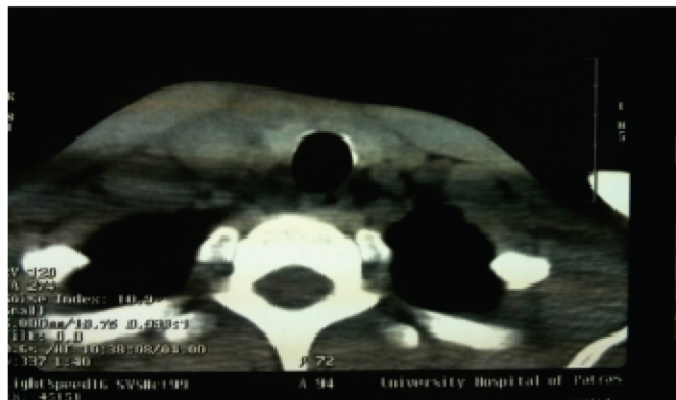


Fig. 1. A 31year-old female presenting with Lemierre's syndrome who admitted to intravenous drug abuse. Computed Tomography scan shows thrombosis in the right internal jugular vein (Reproduced from Dimitropoulou et al. [46])

2.2 *Cancrum* (NOMA)

Noma is an overwhelming infectious disease which destroys the soft and hard tissues of the oral and para-oral structures [10] Fig. 2. It is common in those aged between 2 to 16 years particularly in sub-Saharan Africa. The mortality rate varies but can be as high as 70-90% especially in untreated cases [45,66]. Though the infection is usually polymicrobial with several opportunistic pathogens [47], the major pathogens are *F. necrophorum* and *Prevotella intermedia* with an isolation rate of 87.5% and 75.0% respectively. These two organisms are believed to be involved in the initiation and progression of the disease [45,67]. However, recent reports on the microbiota of Noma lesions using culture independent molecular methods have shown a diverse array of microorganisms and queried the role of *F. necrophorum* as causative agent of the disease [68,69]. In many instances, the infection starts as necrotizing ulcerative gingivitis [67]. Acute necrotizing gingivitis (ANG) is a severe and painful form of gingivitis characterized by necrotizing inflammation of the gingival. This

condition is believed to precede Noma, though not in all cases [33,68]. The infection usually begins as an ulcer of the mucous membrane followed by edema of the face, which extends and rapidly destroys the soft parts and the bones [10]. Noma is preventable and can be eradicated with adequate antibiotic therapy in combination with good nutrition especially when detected on time [5]. Although the progression of the disease can be halted, it usually leaves a permanent physical effect on the victim that can only be repaired by reconstructive plastic surgery [67]. Even with that, those who survive Noma are often not able to eat, speak or breathe normally coupled with the social stigma of being branded as an outcast by some communities where the disease is considered a curse. Due to the public health importance of this infection, a few treatment centers have been organized in some countries like Nigeria and Ethiopia where survivors of Noma infection receive treatment and corrective surgery. These health centers which are exemplified by Noma Children's Hospital Sokoto receive team of professional surgeons at intervals and are sponsored by international charitable organizations. However, it is unfortunate that this condition is still largely unrecognized at the early stage by many health personnel's. In addition, due to the social stigma associated with the disease, some families tend to hide the patients from public view to avoid embarrassment.



Fig. 2. Faces of Noma infection showing varying degrees of soft and hard tissues destruction (A) A 6-year-old boy with Noma after first debridement showing extensive penetrating hemifacial defect including soft tissues and bony layers. (B) Fresh Noma at first clinical presentation in a 5-year-old boy (C) Seven- year-old girl with fresh Noma, destruction of 50% upper lip and nose, requiring extensive and complex reconstructive surgery. (Images provided by Dr Ralf Sautter former CMD Noma Children's Hospital, Sokoto, Nigeria)

Noma infection is common in malnourished children with poor oral hygiene and underlying illnesses such as human immunodeficiency syndrome (HIV) and measles [33,40], and is common in African and Asian countries as well as Latin America [36-39]. Human Immunodeficiency virus (HIV) is suspected to play a role in the pathogenesis of Noma in South Africa though the epidemiology of the infection in this area is still unknown [70].

2.3 Sore Throat

Fusobacterium necrophorum is well established as the main causative agent of Lemierre's disease; a syndrome characterized by severe sore throat [15]. Available evidence suggests that the organism can be limited to the throat without reaching the blood causing acute or recurrent sore throat [71]. The role of *F. necrophorum* in uncomplicated tonsillitis remains unclear. Nevertheless, there is increasing evidence that *F. necrophorum* causes pharyngitis like group A *Streptococcus* [72] and both species have been isolated in polymicrobial sore throat infection. *Fusobacterium necrophorum* tonsillitis has been shown to occur in older patients and those with persistent or recurrent sore throat [43]. Suggesting that the organism can occur as a sole agent in non streptococcal tonsillitis that may or may not result into Lemierre's syndrome [15,59,73].

2.4 Peritonsillar Abscess

Peritonsillar abscess (PTA) is a collection of pus between the tonsillar capsule and the pharyngeal constrictor muscle [3]. Most peritonsillar abscesses are polymicrobial involving both aerobic and anaerobic organisms [74]. Brook [75] investigated the role of anaerobic bacteria in tonsillitis and suggested that gram-negative anaerobic bacilli play an important role in the pathogenesis of recurrent non-streptococcal tonsillitis with possible immune response. Similarly, Jensen and workers [43] concluded that *F. necrophorum* could be a cause of acute tonsillitis and may account for some of the cases initially assumed to be of viral origin. Other studies have also implicated *Fusobacterium necrophorum* in tonsillitis and subsequent pathogenesis of peritonsillar abscess [20,43,76]. In a study by Klug and colleagues [3], *F. necrophorum* was reported as the most prevalent pathogen in PTA patients in Denmark and this contrasted with the commonly held opinion that group A Streptococci (GAS) are the most prevalent cause of bacterial tonsillitis. Management of peritonsillar abscess requires surgical drainage and antimicrobial therapy and penicillin is the primary drug of choice. However, the growing inability of penicillin to treat recurrent and chronic tonsillitis is a clinical problem [77]. Brook and Gober [78] evaluated the efficacy of metronidazole on the management of acute episodes of non-Streptococcal tonsillitis and discovered that it alleviated the symptoms and shortened the duration of fever in patients.

2.5 Meningitis

Meningitis is inflammation of the protective membranes covering the brain and spinal cord, known collectively as the meninges [71]. Meningitis due to *F. necrophorum* is a significant cause of mortality and several cases have been reported in both young and old adults [79-82]. *Fusobacterium necrophorum* finds its way to the meninges during pharyngitis, lung and middle ear infections [83,84]. Garimella and workers in 2004 observed a fatal case of meningitis due to a complicated case of otitis media caused by *F. necrophorum* in a 51 year-old patient [7] Fig. 3. The authors recommended that anaerobic culture, using appropriate technique, should be carried out when gram stain of cerebrospinal fluid shows gram-negative bacilli. Where these infections are not properly managed it may result to life threatening infections of the central nervous system, cranial nerve palsy, sinus venous thrombosis, and brain abscess [82].

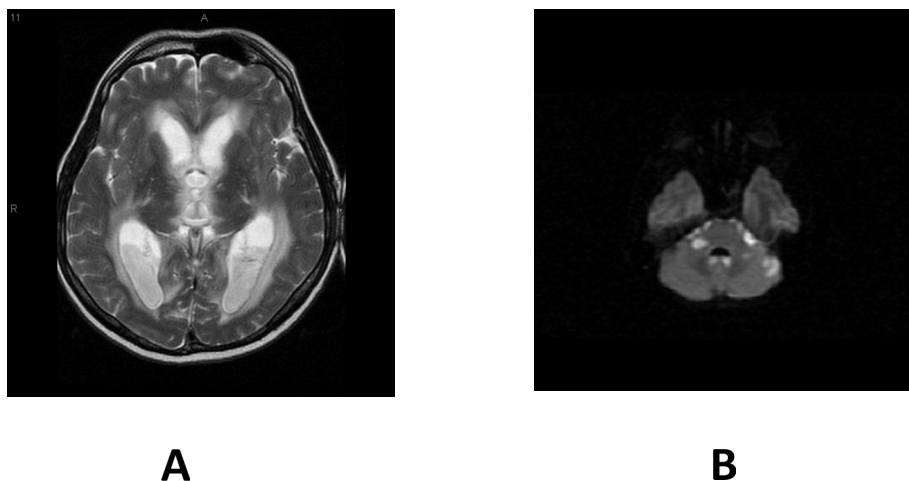


Fig. 3. Meningitis due to *F. necrophorum* in a 51-year-old male. Magnetic resonance imaging of the brain (A) weighted image showing obstructive hydrocephalus and ventriculitis (B) Diffusion image showing acute infarcts in the cerebellum. (Reproduced from Garimella et al. [7])

2.6 Endocarditis

Anaerobic endocarditis due to *F. necrophorum* is very rare but has a high mortality rate [6]. It may cause the initiation and progression of infective endocarditis as a sole agent or in conjunction with other anaerobes [6,19,85]. In most cases, the clinical condition may be bad or the patients may have died before accurate diagnosis is made [86,87]. Thus early diagnosis by monitoring fevers greater than 38.3°C is important. Also evidence of aortic valve insufficiency as well as positive blood cultures are clear indications of infective endocarditis infections due to *Fusobacterium* species.

3. DIAGNOSIS OF *F. NECROPHORIUM* INFECTIONS

In patients presenting with persistent sore throat, it is necessary to screen for Lemierre's syndrome. Throat swabs, cerebrospinal fluids (CSF), aspirates and blood are all ideal specimen for the laboratory diagnosis of *F. necrophorum* infections, [88]. *Fusobacterium* species grows well on blood agar media supplemented with vitamin K, hemin menadione and a reducing agent such as cysteine hydrochloride in anaerobiosis at 35-37°C for 3-7 days. Morphologically, they form characteristic large cream yellow colonies with smooth round and entire edge. They produce an odor similar to smell of cabbages. Although they show narrow zone of complete haemolysis on horse blood agar, this feature vary between strains [9]. Gram staining reaction shows that they are pleomorphic filamentous short rods and coccoid elements [15]. Like other *Fusobacteria*, *F. necrophorum* produces indole, a metabolite that can be readily detected directly from colonies on agar plate.

Cultural Isolation of *F. necrophorum* is tedious; however they can be easily identified to species level by molecular methods [89]. Though this technique is expensive, it is simple, rapid, accurate, more convenient and has been a major contributing factor in recent increase in diagnosis and reported cases of *F. necrophorum* infections worldwide.

Radiological diagnosis is vital to the confirmation of most *F. necrophorum* infection and this can be accomplished using ultrasonography, magnetic resonance imaging (MRI), X-ray or Computed tomography (CT) scans [60,90,91]. Ultrasonography can be used in screening for internal jugular vein thrombosis [60]. Also Chest X-ray films may be used but they do not show definite abnormality [91]. Computed tomography (CT) scanning gives better pictures, are more sensitive and will detect the lesions earlier than plain X-rays [92]. For better comparative confirmation both method can be applied [18,59,61]. However, Nakamura *et al.* [90], suggested that magnetic resonance imaging is the most accurate and reliable method of detecting the presence and extent of deep venous thrombosis.

3.1 Treatment

Fusobacterium necrophorum is generally highly susceptible to beta-lactam antibiotics, metronidazole, clindamycin and third generation cephalosporins [93]. Since they are found in polymicrobial infections, the use of single therapeutic agent is not advisable. Most reports recognized the use of Penicillin in combination with a beta-lactamase inhibitor such as clavulanic acid [52,94]. Intravenous clindamycin has been suggested for patients with penicillin allergy [93]. Nevertheless, metronidazole remains the drug of choice for the treatment of *F. necrophorum* infections. It has excellent activity against all strains of *Fusobacterium* spp. with good tissue penetration [95,96]. There are controversies on the use of anticoagulants in severe cases of thrombosis in patients with Lemierre's syndrome. Some studies suggested that it increases the rate of resolution of internal jugular vein thrombosis [21,28] while others believed that it should not be recommended since there are no clear evidence to show that they can be used in the management of thrombosis [95].

Initial treatment of Noma is focused on correct nutrition with adequate balance of ionic and acid-base elements followed by the administration of vitamins aimed at improving the overall health status of the patient and then broad spectrum antibiotics to control the infection [97]. If there are no clinical improvements following antibiotic therapy, definitive surgical drainage and evacuation may be quite useful especially in patients with pulmonary abscess and empyema or ligation of the internal jugular vein to permit the penetration of antibiotic to the desired sites [94,98]. Depending on the site of infection, the duration of treatment ranges from 9 to 84 days. A complete antibiotic dose with an average period of 2-6 weeks has been recommended to avoid relapses [23,59,61].

3.1.1 Antimicrobial resistance and treatment failure

There are limited data on the antibiotic sensitivity pattern of human isolates of *F. necrophorum* in literature; therefore empirical treatment is not advised [15]. Though penicillin is commonly used in the treatment of *F. necrophorum* infections, clinical resistance has been reported despite *in-vitro* activity [15]. In a study by Brazier and workers [9], of the 100 human isolates of *F. necrophorum* analyzed, 15% were resistant to erythromycin, 2% to penicillin and 1% to tetracycline. *Fusobacterium necrophorum* is essentially resistant to gentamycin and quinolones, with poor susceptibility to tetracyclines [15]. However, resistance to metronidazole has not been recorded [99]. A combination therapy including lincomycin, clindamycin or amoxicillin clavulanic acid plus metronidazole is shown to be superior over penicillin and is effective against aerobic as well as anaerobic organisms [77].

4. CONCLUSION/RECOMMENDATION

Fusobacterium necrophorum has been reported to be responsible for a range of diseases including Lemierre's syndrome, *cancreum oris*, recurrent tonsillitis and necrobacillosis complex. They are able to initiate the disease process due to the toxins they produce. Source of infection include acquisition from animals such as dogs or human to human transmission. Therefore these infections can be prevented by controlling contact between children and animals, proper oral-hygiene as well as environmental sanitation and improvement of the nutritional and health status of children, pregnant and lactating mothers. Irrespective of the fact that Noma is frequently reported in Nigeria, cases of Lemierre syndrome caused by same organism are quite rare. It would be important to screen for Lemierre's syndrome in susceptible individuals. Clinicians need to be conscious of the increasing clinical importance of *F. necrophorum* infections and its life threatening nature and the need for early detection to avoid fatality. Similarly, microbiologists should be more aware of this group of anaerobes as potential pathogens in severe infections. In addition, surgery and/ or antibiotics therapy can be used to prevent and treat these systemic and localized infections. Isolation of these species is recommended during suspected infections and would also help in detecting the antimicrobial sensitivity pattern and providing epidemiological information so as to guide treatment and control of these severe infections caused by *F. necrophorum*.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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