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ARTICLE

Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey

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Abstract In a 3-year prospective study, all cases of disseminated *Fusobacterium necrophorum* infections found in Denmark from 1998 to 2001 were analysed, with the aim of describing the epidemiology and clinical features of the variants of Lemierre's syndrome and disseminated non-head-and-neck-associated *F. necrophorum* infections. Fifty-eight cases of Lemierre's syndrome were reported in previously healthy persons, with an incidence of 14.4 cases per million per year in youngsters aged 15–24 years old. There was no increase during the study period. Lemierre's syndrome originating from an oropharyngeal infection was seen in 37 youngsters. An otogenic variant of Lemierre's syndrome was seen in 5 children with dissemination to nearby regions, and other variants of Lemierre's syndrome, e.g. from the sinuses and teeth, were seen in 16 adults. Patients often had metastatic infections already on admission and needed prolonged hospitalisation. The overall mortality of Lemierre's syndrome was 9%. Forty-two elderly patients had disseminated *F. necrophorum* infections originating from foci in lower parts of the body. They frequently had predisposing diseases, e.g. abdominal or urogenital cancers, which contributed to the high mortality of 26%. This study shows that the incidence of Lemierre's syndrome is higher than that previously found and has a characteristic age distribution. Early suspicion of the diagnosis, several weeks of antibiotic therapy, often combined with surgical drainage, is mandatory to lower the mortality. In disseminated non-head-and-neck-associated *F. necrophorum* infections, underlying cancers must be considered.

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Introduction

Fusobacterium necrophorum causes the rare, life-threatening Lemierre's syndrome, described in 1936 by Lemierre as "anaerobic postanginal septicaemia" [1]. It was not until the early 1980s that the name "Lemierre's syndrome" was introduced by Shannon et al. in a case of oropharyngeal septicaemia, ironically caused by *Bacteroides melaninogenicus* and not by *F. necrophorum* [2]. Typical Lemierre's syndrome begins with pharyngotonsillitis, followed by unilateral swelling and tenderness along the sternocleidomastoid muscle, owing to septic thrombophlebitis of the internal jugular vein [1, 3–9]. Postanginal *F. necrophorum* septicaemia with high fever and metastatic lung abscesses often develops within a week [1, 3, 5–8, 10–12]. Lemierre claimed that the syndrome is so characteristic, that the clinical diagnosis is nearly impossible to mistake [1]. He also wrote that anaerobic septicaemia arising from otitis media and buccal suppuration following from infected teeth had clinical manifestations very similar to postanginal septicaemias, and that these infections were remarkably similar, irrespective of the primary focus [1].

The definition of Lemierre's syndrome is not yet clear in the literature. Some authors only include disseminated *F. necrophorum* infections originating from the throat, while we and others include all disseminated cases with primary foci in the head and neck, as they have much in common, even though they may originate from different head foci and have different age distributions [1, 3–8, 11, 13]. We require a septic case of documented *F. necrophorum* infection by, e.g. the growth of *F. necrophorum* in blood cultures, dissemination to nearby regions, e.g. mastoiditis in otitis media, and/or dissemination to remote regions, e.g. metastatic pulmonary infections. We choose to name them

all as variants of Lemierre's syndrome, appreciating that the oropharyngeal variant of Lemierre's syndrome is the most common. We believe that this definition gives clinicians, who rarely come into contact with Lemierre's syndrome, the must useful description of the clinical spectrum of Lemierre's syndrome. Basically, the clinicians must be reminded that Lemierre's syndrome is a life-threatening but curable *F. necrophorum* infection originating in the head, attacking healthy children and youngsters.

This prospective study is a follow-up of an earlier retrospective study in which we described the epidemiological and clinical features of disseminated *F. necrophorum* infections [7]. We pay special attention to the variants of Lemierre's syndrome, but disseminated non-head-and-neck-associated *F. necrophorum* infections will also be described briefly.

Patients and methods

From July 1998 to June 2001, all 16 departments of clinical microbiology in Denmark sent their human *F. necrophorum* isolates to our department. The isolates were identified as *F. necrophorum* in the local laboratories, mostly following the guidelines at http://www.tagejustesen.dk/anaerobebakterier/ and reidentified phenotypically to the subspecies level in our laboratory, as described by Jensen et al. [14]. Isolates received as *Fusobacterium* spp. were identified in our laboratory and included in the study if they were identified as *F. necrophorum*. Audits were performed to check whether all *F. necrophorum* isolates were sent to us during the study period, and *F. necrophorum* infections that had been forgotten were found and included.

All patients with disseminated *F. necrophorum* infections were included and their clinical records reviewed one year after the infective episode. Age, sex, predisposing diseases, origin of infection, presenting symptoms, clinical chemistry test results, microbiological findings, metastatic abscesses, therapy and the clinical outcome were recorded.

The cases were classified according to the primary infectious foci as variants of Lemierre's syndrome or disseminated non-head-and-neck-associated *F. necrophorum* infections.

Mortality was defined as death within one month after admission.

Statistical analyses were performed by using SPSS® for Windows® version 13.0 (SPSS Inc., Chicago, Illinois). The χ^2-test, Wilcoxon's test and Mann-Whitney's test were used for the statistical calculations. Statistical significance was defined as $p<0.05$. Data from http://www.statistikbanken.dk were used to describe the total background population and age distribution in Denmark during the study period.

Results

We found 100 cases of disseminated *F. necrophorum* infections during the 3-year period. Fifty-eight cases were variants of Lemierre's syndrome, 37 oropharyngeal cases and 21 cases with other head-and-neck-associated foci. Forty-two cases were disseminated non-head-and-neck-associated *F. necrophorum* infections.

Isolates from 52 of the head-and-neck-associated cases and 31 of the non-head-and-neck-associated cases were sent to us as *F. necrophorum* and were reidentified to the subspecies level in our department as *F. necrophorum* subsp. *funduliforme*, except for one isolate from a disseminated gastrointestinal infection in a farmer, which was *F. necrophorum* subsp. *necrophorum* [14]. The remaining isolates were only identified once; in the original laboratory to subspecies level as *F. necrophorum* in 11 isolates and in our laboratory to the subspecies level as *F. necrophorum* subsp. *funduliforme* in six isolates. These isolates were included, as we did not find that any of the isolates which had been identified twice had been wrongly identified as *F. necrophorum* in the original laboratories.

Epidemiology of Lemierre's syndrome

With a total population of 5.33 million in Denmark, the 58 cases of Lemierre's syndrome corresponded to an incidence of 3.6 cases per million inhabitants per year (95% confidence interval [CI] 2.8–4.7). The incidence was 14.4 cases per million per year (95% CI 9.5–21.1) in youngsters 15–24 years of age. Lemierre's syndrome was rare in adults over 40 years of age, with an incidence of 1.4 cases per million per year (95% CI 0.7–2.6). The detection rates varied among the departments of clinical microbiology from 0 to 6.1 cases of Lemierre's syndrome per million per year.

There was no increase in incidence during the study period. There seemed to be a slight seasonal variation, with an accumulation of cases in the late winter and early autumn months, but fewer cases in the summer months.

The characteristics of the variants of Lemierre's syndrome are shown in Table 1. The patients were in generally previously healthy without recurrent complaints from the primary foci. Sixty-five percent of patients developed symptoms less than one week before hospitalisation, and 21% within one to two weeks and 14% had symptoms for more than two weeks. More than half were admitted immediately after the first medical contact.

Microbiology in Lemierre's syndrome

Eighty-one percent of patients had not received antibiotic therapy before admission, 14% had received oral penicillin and 5% had received macrolides. In only a few cases, the

Table 1 Variants of Lemierre's syndrome in Denmark, 1998–2001; demography, microbiology, clinical chemistry, metastatic infections, antibiotic therapy and outcome

Primary infectious foci	Ear *N*=5	Throat *N*=37	Other foci in the head* *N*=8	Presumable foci in the head *N*=8	Total number *N*=58
Demography					
Age in years, median (range)	2 (0–16)	20 (6–66)	24 (7−84)	55 (24−89)	20 (0−89)
Male/female ratio in no.	2/3	22/15	5/3	4/4	33/25
Predisposing diseases in no.	0	1**	0	1***	2
Microbiology with *F. necrophorum* in no.					
In blood, as the only pathogen/in mixed culture	1/0	22/7	1/0	3/2	27/9
In pus or swabs only, as the only pathogen/in mixed culture	4/0	4/4	3/4	3/0	14/8
Metastatic infections in no.					
Pleuropulmonary infection	1	21	3	8	33
Pneumonia complicated by pleural empyema	0	8	2	3	13
Pneumonia complicated by lung abscesses	0	10	0	3	13
Pneumonia complicated by mediastinitis	0	1	1	0	2
Parapharyngeal abscess	0	0	4	0	4
Meningeal empyema or meningitis	2	4	1	0	7
Mastoiditis	5	1	0	0	6
Subcutaneous abscesses	0	5	1	1	7
Positive blood culture as the only dissemination	0	11	1	0	12
Clinical chemistry findings on admission, median (range)					
White blood cell count, normal level $4–10\times10^9$/l	12 (9–20)	15 (2–44)	12 (5–53)	17 (14–19)	15 (2–44)
Band neutrophilia, normal level <5%	31 (13–43)	24 (0–78)	–	–	25 (0–78)
C-reactive protein, normal level <10 mg/l	119 (63–192)	223 (34–396)	140 (33–424)	238 (104–364)	193 (33–424)
Thrombocyte count, normal level $150–450\times10^9$/l	203 (129–249)	136 (28–526)	184 (142–335)	405 (53–811)	161 (28–811)
Bilirubinaemia, normal level 20–28 μmol/ml	–	23 (5–157)	10 (7–18)	–	18 (5–157)
Course of the infection in days, median (range)					
Duration of relevant antibiotic therapy	30 (18–90)	27 (5–181)	16 (2–61)	10 (0–56)	21 (0–181)
Duration of fever during antibiotic therapy	14 (2–20)	8 (1–55)	9 (1–39)	5 (3–20)	9 (1–55)
Admission time	17 (4–27)	21 (1–151)	13 (0–30)	11 (0–30)	17 (0–215)
Course of the infection in no.					
Admission to intensive care unit	0	11	5	1	17 (30%)
Ventilator assistance	0	7	3	0	10 (17%)
Surgical incision (e.g. drainage)	5	16	8	2	31 (53%)
Recovery without sequelae, but often long convalescence	5	33	5	5	48 (83%)
Permanent cerebral and/or pulmonary sequelae	0	3	2	0	5 (9%)
Deaths in no.	0	1	1	3	5 (9%)

– No data available
*Four parapharyngeal abscesses, two dental infections, one meningitis and one sinusitis
**Intravenous drug abuse
*** Diabetes mellitus

primary focus was noted to be foul smelling, e.g. as the characteristic butyric acid smell of *F. necrophorum*.

In 22 patients, *F. necrophorum* was not found in the blood, but was cultured from one or more of the following foci: pleural empyemas, bronchoalveolar lavage, meningitis, cerebral empyemas, parapharyngeal abscesses, mastoiditis and sinusitis. Exclusively, *F. necrophorum* subsp. *funduliforme* was identified.

The median time that elapsed before the first microbiological report was available was two days, range 0–6 days. The first report was often made by telephone, reporting the growth of Gram-negative rods in anaerobic blood culture

and, in a few cases, findings by the direct microscopy of pus. Judged from the clinical records, there were rarely any reports of the characteristic pleomorphic shape of *F. necrophorum* which could lead to the suspicion of Lemierre's syndrome. The median time for the microbiology departments to send a final response was six days, range 3–31 days. In 14% of the cases, a final microbiological report could not be found in the clinical records, but only in the records from the departments of clinical microbiology.

In the polymicrobial cases, *F. necrophorum* was found in mixed culture with group C streptococci (GCS) in five cases, non-haemolytic streptococci in five, *Prevotella* sp. in three and group A streptococci (GAS), *Eikenella corrodens*, *Bacteroides* sp., *Staphylococcus areus*, *Haemophilus influenzae* and microaerophilic streptococci in one case each.

Otogenic variant of Lemierre's syndrome

All five patients were treated by ear, nose and throat (ENT) specialists. All presented with acute otitis media, fever and acute mastoiditis. None had recurrent otitis media. One had concomitant sinusitis. None had sore throat or abdominal pain, but one showed unilateral swelling of the neck. *F. necrophorum* was grown from the mastoid in all of the patients. All five had the mastoid drained and received a prolonged antibiotic therapy with penicillin and/or metronidazole. Although two cases were complicated by meningitis, they all recovered completely after a long convalescence.

Oropharyngeal variant of Lemierre's syndrome

Seventy-nine percent of the 37 patients were initially admitted to the departments of internal medicine, 14% to ENT departments and 7% to paediatric departments. All cases were septic, 97% had fever, 95% had non-GAS tonsillitis, 76% had respiratory complaints and 63% had unilateral swelling of the neck on admission. The unilateral swelling was often mistaken as lymphadenitis or peritonsillar abscess. Only very few cases had ultrasound scanning of the neck performed to confirm the clinical findings of septic thrombophlebitis of the internal jugular vein. Abdominal pain was reported from 10 patients, which, in some cases, led the clinicians to search for an abdominal focus. Two patients had concomitant tonsillitis and sinusitis. One intravenous drug abuser developed Lemierre's syndrome following a spontaneous perforation of a peritonsillar abscess complicated by the aspiration of pus while sleeping. One more case of peritonsillar abscesses developed into Lemierre's syndrome after a difficult tonsillectomy complicated by the aspiration of pus into the lungs. Both patients developed bilateral pulmonary infiltrates within the next 24 h.

There was an overall male predominance, but females dominated in patients below 20 years of age with a male/female ratio of 6/12, while males dominated above 20 years of age with a ratio of 16/3 ($p<0.01$). The median age for females was 18 years, range 6–41 years, while it was 23 years, range 15–66 years for males ($p<0.01$).

Three patients had acute infectious mononucleosis diagnosed by heterophilic antibodies, in one case, confirmed by increased specific IgM. *F. necrophorum* was found as the monoculture in most blood cultures. Concomitant GCS was found in five out of seven polymicrobial blood cultures.

In a quarter of patients, a positive blood culture with *F. necrophorum* was the only documented sign of dissemination. In this septicaemic, non-metastatic group, all but one had complaints for less than one week before hospitalisation and none developed sequelae. By contrast, almost half of the cases with documented metastatic abscesses had symptoms for more than one week and all cases of permanent sequelae and death were found in this group. Four of the five patients with polymicrobial blood culture with concomitant GCS were in the metastatic group. There was no difference between the metastatic and non-metastatic groups concerning doctors' delay before starting antibiotic therapy, in white blood cell count (median 16 versus 13×10^9/l), band neutrophilia or C-reactive protein (median 207 versus 231 mg/l). The non-metastatic group was significantly older than the metastatic group, with median age 32 years, range 15–66 years, versus 19 years, range 6–41 years ($p<0.01$). The non-metastatic patients were hospitalised for a significantly shorter period, median 6 versus 26 days ($p<0.001$), needed less antibiotic therapy, median 14 versus 31 days ($p<0.001$), and had less fever, median 2 versus 13 days ($p<0.01$). There was an even male/female ratio (13/13) in the metastatic group, while there were 9 men and 2 women in the non-metastatic group ($p=0.132$). None of the patients were screened for thrombophilia. There was no difference between the two groups concerning the clinical description of unilateral swelling of the neck, an indirect indicator of possible thrombophlebitis of the internal jugular vein.

The metastatic abscesses were mainly in the lungs and were often detected at admission, with rapid development within the first few hours of admission. A young female with multiple round pulmonary infiltrates and neutropaenia was initially suspected to have lymphoma. Three patients developed acute respiratory distress syndrome (ARDS). Disseminated intravascular coagulation was rare and was only present in a mild degree.

A 25-year-old male died 50 days after admission. He had metastatic lung abscesses harbouring *F. necrophorum* and an initial blood culture where only pneumococci was reported. He was started on antibiotic therapy on the fourth

day, received inefficient antibiotic treatment in several periods, was moved several times between different hospitals, causing a loss of clinical information, and he was finally discharged on insufficient antibiotic monotherapy with grepafloxacin (Raxar) six days before he died. At the medico-legal autopsy, the monoculture of *F. necrophorum* was found in his blood, cerebrospinal fluid and lung tissue.

Other variants of Lemierre's syndrome

Parapharyngeal abscesses were found in four patients, dental infection in two, meningitis and sinusitis in one each. These patients were predominantly admitted to ENT departments. All had fever, four had pulmonary complaints and three developed ARDS. Abdominal pain was not reported. The four cases of parapharyngeal abscesses had recent complaints of sore throat and unilateral neck swelling. A 62-year-old woman died after rapid progression of a parapharyngeal abscess. She had sterile blood culture, but *F. necrophorum* and non-haemolytic streptococci were cultured from the parapharyngeal abscess. She received appropriate antibiotic therapy with β-lactam and metronidazole and immediate surgery, but died within 24 h from septic shock and ARDS.

Presumed Lemierre's syndrome with primary foci probably in the head

Pulmonary symptoms dominated in eight middle-aged patients, who were predominantly admitted to medical departments with fever and pneumonia; one also voiced abdominal complaint. From the sparse information contained in the records, it was not possible to find the primary focus of these patients, but they all had recent head and neck complaints, although without recorded signs from the head on admission, and they all presented with metastatic pulmonary infection. Thus, the primary focus was presumably the head and neck region.

A 24-year-old male had backache for one to two weeks and, on deterioration, he sought a chiropractor, where he collapsed and died before receiving any treatment. Medico-legal autopsy revealed bilateral pulmonary empyema and pneumonia. Concomitant growth of *F. necrophorum* and haemolytic streptococci group A was found in the heart blood, empyema and lung tissue.

A 33-year-old diabetic male with a toe ulcer died suddenly whilst on holiday, with no preceding infective illness. Autopsy showed that he suffered from pneumonia and lung abscesses. Growth of *F. necrophorum* was found in the heart blood, lung abscesses and skin ulcer of the toe.

A 73-year-old female died after 30 days in hospital. She was initially suspected to have pulmonary cancer because of round infiltrates on the lungs. She began receiving metronidazole on the 12th day of admission after the monoculture of *F. necrophorum* was found in pleura-empyema and the cancer diagnosis was cancelled.

Diagnosis of Lemierre's syndrome

In one third of the cases, the term "Lemierre's syndrome" was not mentioned anywhere in the records. In the cases, where "Lemierre's syndrome" was mentioned, it was usually proposed by the microbiologists, who recognised the characteristic morphology of *F. necrophorum*. In a few cases, the clinicians or the microbiologists familiar with Lemierre's syndrome voiced their suspicion on the clinical findings alone.

Wrong differential diagnosis was common, such as legionellosis in cases with severe pulmonary infection, intra-abdominal infections based on the finding of positive anaerobic culture and immunosuppression, e.g. HIV or malignancy based on the severity of the infection. Weeks of fever, despite appropriate antibiotic therapy, also confused the clinicians.

Treatment of Lemierre's syndrome

The majority of cases were initially treated with a β-lactam, plus an aminoglycoside and metronidazole on suspicion of septicaemia, but a few were started on macrolide on suspicion of legionellosis. The median time before adequate antibiotic therapy with β-lactam and/or metronidazole was initiated was less than 1 day, range 0–9 days, for the surviving patients. Later on, most of the patients were shifted to penicillin G and/or metronidazole, based on susceptibility results.

Necessary surgical drainage was often delayed. The lack of awareness and knowledge regarding Lemierre's syndrome and its treatment was evident in patients who were repeatedly transferred between departments and hospitals during the week-long hospitalisation. Only a few patients with septic thrombophlebitis received anticoagulation therapy. None received hyperbaric oxygen.

Disseminated non-head-and-neck-associated *F. necrophorum* infections

The characteristics of these 42 cases are shown in Table 2. They were significantly older than patients with Lemierre's syndrome, and were mainly elderly males with predisposing diseases. None of them had symptoms from the head and neck. Four developed septic shock. Pulmonary infection was rare. The majority had spread of the infection to regions near the primary focus. A positive blood culture with *F. necrophorum* was the only sign of dissemination in 11 of the gastrointestinal patients and three urogenital patients, of whom, four and one died, respectively. In the

Table 2 Non-head-and-neck-associated disseminated *Fusobacterium necrophorum* infections in Denmark, 1998–2001; demography, predisposing diseases, microbiology, clinical chemistry, antibiotic therapy and outcome

Primary infectious foci	Gastrointestinal tract *N*=30	Urogenital tract *N*=6	Unknown foci *N*=6	Total *N*=42
Demography				
Age in years, median (range)	61 (5–89)	78 (25–96)	76 (66–87)	66 (5–96)
Male/female ratio in no.	20/10	4/2	5/1	29/13
Predisposing disease, cancer related to primary focus in no.	11	3	0	14
Predisposing diseases, others*, in no.	7	1	5	13
Microbiology with *F. necrophorum* in no.				
In blood, as the only pathogen/in mixed culture	13/3	1/2	4/1	18/6
In pus or swabs only, as the only pathogen/in mixed culture	1/13	2/1	1/0	4/14
Metastatic infections in no.				
Pneumonia	1	0	–	1
Intra-abdominal/urogenital abscesses	19/0	0/3	–	19/3
Subcutaneous abscesses	1	0	1	2
Positive blood culture as the only dissemination	11	3	–	14
Clinical chemistry findings on admission in median (range)				
White blood cell count, normal level 4–10×10^9/l	18 (7–73)	17 (8–29)	10 (4–22)	17 (4–73)
Band neutrophilia, normal level <5%	8 (0–54)	–	1 (0–5)	5 (0–54)
C-reactive protein level, normal level <10 mg/l	170 (7–379)	247 (110–330)	115 (10–322)	170 (7–379)
Thrombocyte count, normal level 150–450×10^9/l	252 (72–679)	330 (199–500)	162 (58–508)	263 (58–679)
Bilirubinaemia, normal level 20–28 μmol/ml	18 (7–324)	9 (9–11)	14 (9–20)	12 (7–324)
Course of the infection in days, median (range)				
Duration of antibiotic therapy	7 (0–41)	10 (2–13)	13 (0–37)	10 (0–41)
Duration of fever during antibiotic therapy	5 (0–52)	3 (2–13)	11 (0–44)	5 (0–52)
Admission time	16 (0–60)	11 (3–35)	10 (1–69)	15 (0–69)
Deaths in no.	8	2	1	11 (26%)

– No data available

*Other predisposing diseases were immunosuppressive therapy, intravenous drug or alcohol abuse, diabetes and cancers not related to primary infectious focus

polymicrobial cases, *F. necrophorum* was found, together with *Escherichia coli*, *Proteus vulgaris*, *Bacteroides* sp., microaerophilic streptococci, GCS, group F or G streptococci. Except for one gastrointestinal case of *F. necrophorum* subspecies *necrophorum*, only *F. necrophorum* subspecies *funduliforme* was found.

One third of the gastrointestinal patients had a gastrointestinal cancer and one half of the urogenital patients had a urogenital cancer. Seven patients died immediately related to the infection; four of them had underlying cancers. Three patients, all with cancers, died within a month following the infective episode: two of them had terminal cancers and one developed recurrent *F. necrophorum* infection.

These patients did not receive week-long antibiotic therapy to control the infection, and did not have long-term fever, in contrast to the patients with Lemierre's syndrome. The age and predisposing diseases, e.g. cancers, contributed to the high mortality rate in these patients.

Disseminated *F. necrophorum* infection of unknown origin

In six patients, it was not at all possible to find the primary focus of the infection or the extent of the metastatic complications from the sparse information in the records, but two patients were immunosuppressed following chemotherapy for underlying cancers and one of them died.

Discussion

Epidemiology of Lemierre's syndrome

There are many case reports about Lemierre's syndrome, but only a few retrospective reviews have been undertaken [3, 5–7, 9, 15–21]. To our knowledge, this study is the first attempt to describe Lemierre's syndrome in a prospective

way. The overall incidence of 3.6 cases per million inhabitants per year in Denmark is higher than the incidence of 0.8 cases per million per year found in our retrospective study from 1998, which is not surprising [7]. The true incidence is probably even higher, as some departments never found any cases at all. We were later informed of eight more cases of clinical Lemierre's syndrome during the study period without growth of *F. necrophorum*, which were, therefore, not enrolled in the study.

We presume that *F. necrophorum* is involved in most cases, but is not always detected in the blood culture, e.g. because of prior antibiotic therapy or because the growth of *F. necrophorum* is slower than most facultative aerobes in anaerobic blood culture bottles. *F. necrophorum* subsp. *funduliforme* is the common subspecies in human infections, irrespective of the primary infectious focus and irrespective of whether the infection remains localised or is disseminated [14, 22].

It is unsolved whether there is a seasonal variation, but we found a tendency of accumulation of cases in the late winter and early autumn, while there were fewer cases in the summer. Brazier et al. have also reported an accumulation of cases in the late winter months [16].

Otogenic variant of Lemierre's syndrome

In accordance with the literature, we found that Lemierre's syndrome with a primary otogenic focus predominantly occurred in otherwise completely healthy children, who mainly developed a spread of the infection into neighbouring regions, e.g. mastoiditis, meningitis and meningeal empyaemas [23–29]. In the era of antibiotics, acute mastoiditis has become a rare complication to acute otitis media, but it has developed into a "first appearance" disease in children with a median age of 16 months, and no previous middle-ear infections [30]. Our children with *F. necrophorum* mastoiditis also tended to be younger than children with localised *F. necrophorum* infection in the ears, and it seemed to be a "first appearance" disease [4, 31]. The immune system of children matures within the first few years of life, and children may also develop specific immunity over time, which may prevent dissemination from the ear in older children.

In Denmark, we have about 40 cases of acute mastoiditis per year, of whom, 10% develop meningitis or intracranial abscesses [30]. Almost half of our patients with *F. necrophorum* mastoiditis developed meningitis or meningeal empyemas. None of our patients developed permanent sequelae or died. Patients with the otogenic variant of Lemierre's syndrome may have a less severe course than the oropharyngeal cases of Lemierre's syndrome, at least as long as they remain at the mastoiditis stage and do not yet have developed into meningitis, which is reported to have a mortality of up to 31.5% [25, 29, 32].

The oropharyngeal cases of Lemierre's syndrome

The present study confirms that oropharyngeal infection is the most common variant of Lemierre's syndrome [4–7, 9, 18, 19]. The majority of our patients were healthy adolescents with acute non-GAS tonsillitis as the primary infectious focus, as found in other studies, including our former retrospective study [1, 5–7, 16, 18]. They were septic with fever and had painful unilateral swelling of the neck, probably due to septic thrombophlebitis of the internal jugular vein. Thrombophlebitis can be diagnosed by ultrasound or, better, by computerised tomography (CT) scanning of the neck, but this was rarely performed in our patients and, therefore, was not of any help as a diagnostic tool in our study [7, 33–44]. There are casuistic reports of Lemierre's syndrome developing from a peritonsillar abscess [45, 46]. However, this current study seems to indicate that peritonsillar abscesses do not normally develop into Lemierre's syndrome, except under extraordinary circumstances, e.g. accidental direct aspiration to the lungs from the abscess, which is a completely different pathogenic process compared to septic thrombophlebitis propagating from the tonsillar veins, resulting in septic infarcts in the lungs [47–49].

Lemierre's syndrome is sometimes preceded by concomitant infections, which may break the mucosal barrier of the tonsils, e.g. Epstein-Barr virus (EBV) [7, 46, 50–54]. We found only a few cases with documented acute infectious mononucleosis in our study. It is probably of more interest that we found that GCS was the predominant concomitant bacterium in the polymicrobial blood cultures of the oropharyngeal cases of Lemierre's syndrome and it was mainly found in manifest metastatic cases. This may indicate that concomitant GCS infection is a risk factor in itself. Both the role of EBV and GCS in *F. necrophorum* infections needs further investigation [22].

This study confirms that the age group from 15 to 24 years has the highest risk of Lemierre's syndrome, whereas it is rare above the age of 40 years [3, 5–7, 55]. The same age distribution is seen in patients with tonsillitis and peritonsillar abscesses caused by *F. necrophorum* [31].

We found an even male/female distribution among the metastatic patients, while the non-metastatic patients were predominantly men, older than the patients with metastasis, which may indicate that Lemierre's syndrome has a milder course in the older population. It is known that the tonsils only grow until puberty, which, perhaps, means that they become less attractive to anaerobes in older age groups, whose tonsils have decreased in size. The size of tonsils remains enlarged until an older age in males than in females, which may explain the finding that males attract Lemierre's syndrome until an older age than females [56]. Protective antibodies may also develop over time.

The non-metastatic group in this study had less marked band neutrophilia and C-reactive protein, and needed a shorter duration of antibiotic therapy and hospitalisation than the metastatic group, but they were obviously more sick and needed more therapy than the cases of localised *F. necrophorum* tonsillitis [31]. Thus, the non-metastatic group may present early stages of Lemierre's syndrome, where the metastatic abscesses are small and/or remain undiagnosed [57]. Manifestly, our non-metastatic patients had less prehospital delay and none developed sequelae, as opposed to the metastatic patients, which we think emphasises the importance of early diagnosis and therapy [7, 8, 57, 58]. Based on the findings in this study, we believe that non-metastatic patients represent early stages of Lemierre's syndrome, but the possibility of "a pure bacteraemic manifestation of *F. necrophorum* infections" without the development of metastatic abscesses has been suggested, e.g. explained by host factors [4, 59, 60].

It has been hypothesised that the tendency to develop thrombophlebitis of the internal jugular vein and, thereby, disseminate from a localised infection is host-related, e.g. caused by underlying thrombophilia [4, 61–66]. Further studies are needed to elucidate whether thrombophilia has any part in the dissemination of *F. necrophorum* infections and to whether "a pure bacteraemic manifestation" exists.

We found that metastatic abscesses were often present on admission, especially as pulmonary metastasis, and they were frequently associated with pleural empyemas and pulmonary abscesses, and, occasionally, mediastinitis, as found in other studies [3, 7, 17]. Septic arthritis, osteomyelitis and liver abscesses have become infrequent in the antibiotic era, which is in accordance with our findings [67–69]. Similar to other studies, we found that disseminated intravascular coagulation and septic shock were rare, but some patients had subclinical hyperbilirubinaemia [5, 7]. The mechanism behind the hyperbilirubinaemia is not known, but it may be a direct effect of the haemolytic activity of *F. necrophorum* [14, 70].

Differential diagnoses in the oropharyngeal cases of Lemierre's syndrome are legionellosis, other severe pulmonary infections, leptospirosis, but also intra-abdominal infections. As earlier described in our retrospective study and a few case reports, we found that abdominal pain was a common complaint [7, 71, 72]. Abdominal pain, in combination with the information regarding anaerobic Gram-negative rods in the blood culture, often misled the clinicians to search for an intra-abdominal focus.

Other variants of Lemierre's syndrome

Adults with other primary foci in the head, e.g. sinusitis and gum boils, seem to be older than the oropharyngeal cases. Some may have had an undiagnosed tonsillitis. Our four cases of parapharyngeal abscesses most likely originated from the throat, as they all had a recent history of a sore throat. Parapharyngeal abscesses are said to originate from the tonsils in 60% of patients, an infected wisdom tooth in 30% and of unknown origin in the last 10% [73–76]. The percentage of dental infections have declined over the last few decades, along with improved dental care and oral hygiene [77, 78]. This group demonstrates some of the diagnostic challenges of Lemierre's syndrome, e.g. when backache is the dominating symptom, as seen in one of our patients and reported in one case report [79].

Therapy and outcome of Lemierre's syndrome

Lemierre's syndrome is rare and unfamiliar to most medical practitioners in its most frequent manifestation originating from a pharyngotonsillitis, as well as in its variants from other head foci. It is, therefore, important that the clinical microbiologists inform the clinicians as soon as possible about the characteristic pleomorphic bacteria seen by microscopy indicative of *F. necrophorum* and Lemierre's syndrome [14].

Early diagnosis, adequate drainage and appropriate antibiotic therapy in an intensive care setting is essential in the management of patients with Lemierre's syndrome.

The optimal antibiotic regimen has not yet been found in any controlled study, but most authors recommend a combination of penicillin and metronidazole for several weeks [3, 5, 6, 8, 20]. Based on our findings, our standard recommendation is intravenous penicillin G 2–5 MIE four times daily combined with metronidazole 500 mg three times daily for at least two weeks, followed by oral amoxicillin 500 mg three times daily combined with metronidazole 500 mg three times daily for several weeks until the inflammatory parameters have been normalised for at least two weeks [14]. Whereas *F. nucleatum* is often resistant to penicillin, *F. necrophorum* is almost always susceptible to penicillin [14, 80, 81].

Clindamycin 1,800 mg divided into three or four doses daily is recommended as a good alternative, e.g. in cases with penicillin allergy [14]. Three doses are probably sufficient in *F. necrophorum* infections, even though its half-life is 2.4 h, as *F. necrophorum* has a minimum inhibitory concentration (MIC)<0.064 mg/l to clindamycin [14]. Clindamycin may even be a better first choice. *F. necrophorum* is not susceptible to macrolides and quinolones, which may have contributed to the fatal outcome in one of our patients, who was treated with grepafloxacin [14, 82].

Metastatic cases involve lengthy hospitalisation, many weeks of antibiotic therapy and the patients are subjected to the risk of permanent sequelae or death. Repeated CT scans of the thorax are often needed for the early detection of extension of the infections, e.g. mediastinitis, and as a follow-up during treatment. Drainage of empyemas and

large abscesses is an important supplement to antibiotic therapy. We found that slow clinical response and weeks of fever was common, despite appropriate antibiotic treatment, probably due to the development of multiple abscesses [7].

Anticoagulation therapy is problematic in patients requiring surgery and is not recommended, except in cases of sinocavernous thrombosis [26, 62, 83–85]. None of our patients received hyperbaric oxygen therapy, which has been reported to be beneficial in a recent report [86].

In accordance with prior studies, this study confirms that patients with Lemierre's syndrome still have a considerable mortality rate of 4–12%, correlated to the extent of metastatic infections and not related to underlying diseases, immunodeficiency or cancers [3, 5–7, 10, 11, 17, 18, 20, 55].

Disseminated non-head-and-neck-associated *F. necrophorum* infections

It is obvious that the same subspecies, *F. necrophorum* subsp. *funduliforme*, is responsible for the majority of infections in both these patients and in patients with Lemierre's syndrome [14].

These patients are not well described in the literature. Contrary to the cases of Lemierre's syndrome, these patients were elderly, mainly men, who frequently had cancers related to the primary infectious focus, as we have already reported in an earlier retrospective study [7]. These findings stress the importance of examining these patients for cancer. This study shows that these patients rarely developed pulmonary infection and that the infection, per se, was relatively easy to control, contrary to the cases with Lemierre's syndrome. Age and predisposing diseases contribute to the high mortality in these patients [7, 8].

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