Clinical characteristics of a large cohort of patients with positive culture of Fusobacterium necrophorum

Abstract

Background: *Fusobacterium necrophorum* is a rare pathogen, mostly affecting young adults, causing infections of the head and neck, typically described as the Lemierre’s syndrome. Today this symptom complex has become increasingly rare and has almost turned to a ‘forgotten disease’.

Methods: We performed a retrospective, descriptive study to identify the clinical features of patients with positive culture of *F. necrophorum*. Additionally, the antibiotic susceptibility profile of the pathogens was analysed.

Results: During a period of 22 years 36 patients with at least one isolate of *F. necrophorum* were identified. Mostly tonsillar and peritonsillar abscesses were found, 10 patients were identified with bacteraemia, but only 4 patients presented with symptoms like sore throat, fever and swollen cervical lymph nodes, which may suggest Lemierre’s. Most of the isolates (33/35) showed sensitivity to all tested antibiotics.

Conclusion: Appropriate techniques are needed to detect *F. necrophorum*, especially from throat swabs, in the microbiological laboratory. Current clinical and microbiological practice may lead to under-diagnosis of infections caused by *F. necrophorum*. Further research is needed to define the colonization rate and to optimize methods for detection as well as identification of virulence.

Keywords: *Fusobacterium necrophorum*, Lemierre’s disease, anaerobe, sepsis, thrombosis

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Background

Infections caused by Fusobacterium necrophorum may result in human necrobacillosis characterized as sore throat, bacteremia, multiple abscesses, jugular vein thrombosis and metastatic septic embolization [1]. This symptom complex was described first by André Lemierre in 1936 in a case series of 20 patients [2] where throat infections were followed by anaerobic septicaemia caused by Bacillus funduliformis (today: F. necrophorum). All but 2 of those initially described 20 patients died. In the 1960s and 1970s, possibly due to development of antibiotic therapy, Lemierre’s disease became increasingly rare and today has almost turned to a ‘forgotten disease’ [3].

Fusobacteria are Gram-negative, non-spore-forming anaerobic rods [4]. The taxonomy of the genus Fusobacterium includes 15 species, of which F. nucleatum and F. necrophorum are the species most frequently found in conjunction with clinical disease. F. necrophorum is a common inhabitant of the human digestive system and is found in the oral cavity, the upper respiratory tract as well as in the vaginal mucosa [5], [6]. F. necrophorum is divided in two subspecies: F. necrophorum ssp. necrophorum, which mostly causes infections in animals, and F. necrophorum ssp. fundiliforme causing infections in animals as well as humans [7]. F. necrophorum affects mostly young, healthy individuals [8], causing infections of the head like tonsillitis, peritonsillar abscess, post-anginal cervical lymphadenitis, otitis media in children, and sinusitis in adults [2], [9]. Furthermore, the pathogen may cause a persistent sore throat syndrome (PSTS) presenting with high fever, general malaise, lymphadenitis, tonsillar lesions and dysphagia during the acute phase [10].

A number of case series with F. necrophorum infections have been described in previous studies. Pett et al. [11] reported on a series of Fusobacterium spp. infection in 18 patients. This study, however, included also F. varium and F. nucleatum. Another study investigating Lemierre’s disease observed selectively F. necrophorum infection, which, however, included only 3 patients [12]. Here, we report on 36 patients with solely F. necrophorum infection, which may represent one of the largest case series on patients with F. necrophorum infection in the literature so far.

Methods

In order to identify all microbiological samples positive for F. necrophorum at the Vienna University Hospital, a 1,922-bed tertiary-care university teaching hospital, a retrospective search of all electronic records, obtained in the time period between June 1995 and January 2017, was performed. The clinical information and antimicrobial susceptibility test results were obtained from the Research, Documentation & Analysis (RDA) IT-platform and the hospital information system (HIS) of the Vienna General Hospital. The RDA platform is an IT system for the integrated support of medical research at the Medical University of Vienna (MUW), which provides the scientific research data in a highly structured form in a central database, which can be used for further specific queries and data download.

Samples were cultured following the standard operating procedures implemented at the Division of Clinical Microbiology. Samples consisted of blood cultures, swabs, and aspirates. Blood cultures were incubated for up to 7 days at 36.5–37 °C in the BacT/ALERT 3D system (BioMérieux, Marcy l’Etoile, France). Gram stains and subcultures were performed from positive blood cultures. Identification to the species level was done using the Vitek II system (BioMérieux) and after 2010 by the MALDI Biotyper instrument (Bruker Daltonics GmbH, Bremen, Germany). For the detection of Gram-negative, anaerobic bacteria in aspirates and swabs obtained from abscess areas, those were cultured under anaerobic conditions at 35–37 °C on Schaedler Kanamycin-Vancomycin plates (Becton Dickinson) for 48 h. From throat swabs cultures aiming at the detection of true anaerobes – as described above – were only conducted if the clinical information enclosed indicated the possible involvement of Fusobacterium (i.e. chronic tonsillitis). For antimicrobial susceptibility testing the minimum inhibitory concentration (MIC) was determined using the E-test (BioMérieux, Marcy l’Etoile, France and AB Biodisk, Solna, Sweden) following the manufacturer’s instructions. Since recurrent bacteraemia with an identical strain may have occurred and would have biased the cumulative susceptibility profile, only the first isolate per patient during the study period was included into this analysis.

Statistical analysis

Data and parameters were extracted from the RDA platform as *.csv file and collected in line-lists using MS Excel (Microsoft Excel 2010, version 14.0.4763.1150; Microsoft, Richmond, USA), which was also used to perform the descriptive statistics. Categorical data were expressed by percentage, continuous variables were expressed as mean and standard deviation (± SD) if normally distributed.

Results

During 1995 until 2017, 36 patients with at least one isolate of F. necrophorum were identified. Patient and specimen details are summarized in Table 1. The patients’ age ranged from 3 to 76 years (mean age ± sd: 36 ± 4 years). Among these patients, 14 were female and 22 were male. Eight patients presented with infections in the head and neck region. Sore throat, fever and swollen cervical lymph nodes, possible indicators of Lemierre’s disease, were found in 4 patients. Of these, one patient (female, 19 years of age) presented with an acute lymphadenitis on the face, head and neck. Furthermore,
Table 1: Samples with positive *F. necrophorum* culture categorized according to source and clinical characteristics

| Source               | No. of patients | Age range (min/max years) | Mean age (years) ± SD | Gender (female/male) | Clinical characteristics (No. of patients)                                                                 |
|----------------------|-----------------|---------------------------|-----------------------|----------------------|----------------------------------------------------------------------------------------------------------|
| Blood culture        | 10              | 14/76                     | 40 ± 8                | 1/9                  | Bacteraemia associated with tonsillitis (1), pneumonia (2), fever (4), cervical lymphadenitis (1), critical illness (1), periodontal disease (1), otitis media (1), cholangitis (1), phlegmon of the sternoclavicular joint (1) |
| Abdominal cavity     | 7               | 10/72                     | 37 ± 11               | 5/2                  | Surgical site infections (4), salpingitis (3)                                                            |
| Head and neck region |                 |                           |                       |                      | Peritonsillar abscess (4), chronic tonsillitis (1), abscess after dental extraction or dental disease (6), lymphadenitis/phlegmon (2), mastoiditis (1) |
| □ Peritonsillar      | 14 (5)          | 3/73                      | 32 ± 6                | 5/9                  |                                                                                                          |
| □ Oral cavity        | 6               |                           |                       |                      |                                                                                                          |
| □ Deep surgical      | 2 (1)           |                           |                       |                      |                                                                                                          |
| □ Ear/mastoid        |                 |                           |                       |                      |                                                                                                          |
| Thorax               | 3               | 20/55                     | 40 ± 13               | 3/0                  | Pleural empyema (1), abscessing pneumonia (1), colonization (1)                                           |
| Wounds               | 2               | 25/57                     | 41 ± 23               | 0/2                  | Gangrene (1), erythma (1)                                                                                 |

Discussion

Although there are several reports highlighting that *F. necrophorum* is an important cause of bacterial pharyngitis with prevalence as high as group A Streptococci in adolescents and young adults [13], [14], our investigation identified only 36 patients with positive *F. necrophorum* culture during a period of over 20 years. Only 8 of these 36 patients yielded *F. necrophorum* from clinical samples obtained from the upper respiratory tract. In our case series not a single case of jugular vein thrombosis was described, also none of the cases presented as typical Lemierre’s syndrome. However, 4 patients presented with neck swelling possibly suggestive for Lemierre’s syndrome, but the medical records of these patients did not contain information if Lemierre’s syndrome was suspected clinically.

Overall, the most common clinical features in younger patients were tonsillitis, peritonsillar abscess, post-angina cervical lymphadenitis, or otitis media. In older individuals *F. necrophorum* mostly was yielded in poly-microbial cultures from gingival and periodontal affections, but was also isolated from the abdominal cavity.

Interestingly, 22 of 36 of patients with *F. necrophorum* infection were male. This observation is in line with a previous case series published by Pett et al. [11] where 9 infections with *F. necrophorum* were reported, all in young, male patients. Patients with underlying diseases were more likely to be infected with *F. nucleatum* than *F. necrophorum*. This was demonstrated in a case series including 52 patients with *Fusobacterium* sp. bacteraemia, 23 of them infected with *F. necrophorum* [15]. Another case series, including 40 cases of *Fusobacterium* sp. bacteraemia (thereof 8 patients presenting with *F. necrophorum*), reported frequently nosocomial infec-

Table 2: Antibiotic susceptibility profile

| Antimicrobial agent                      | % (n/n tested) of isolates |
|-----------------------------------------|---------------------------|
| Penicillin                              | 97% (34/35) 3% (1/35)    |
| Amoxicillin and clavulanic acid         | 100% (35/35) 0%          |
| Imipenem                                | 100% (35/35) 0%          |
| Clindamycin                             | 100% (35/35) 0%          |
| Metronidazole                           | 97% (34/35) 3% (1/35)    |
tions, occurring mostly in males with underlying diseases [16]. Afra et al. [8] estimated the overall annual incidence of bacteremia due to *Fusobacterium* sp. at 0.55 cases per 100,000 populations and identified *F. necrophorum* in 18 cases out of 72 cases of *Fusobacterium* spp. bacteremia. Other case series included a very small number of patients (3 to 9 cases), with little information to draw further conclusions [17], [18], [19], [20]. A similar incidence for *F. necrophorum* infection was reported in a prospective study reporting rates of 0.31–0.83 cases per 100,000 inhabitants per year [21], suggesting *F. necrophorum* being the second most common bacterial cause of pharyngo-tonsillitis [22]. In several studies isolation of *F. necrophorum* followed in 10–48% of cases of persistent, recurrent and chronic sore throats [1], [23], [24] and was isolated in 28% in patients subjected to tonsillectomy [25]. The prevalence of *F. necrophorum* in children was significantly higher among young adults aged 14 to 20 years (14%), than in patients younger than 14 years (2%) [26]. According to the “UK Standards for Microbiology Investigations B9/Investigation of throat related specimens” bacteriologic work-up of specimens for *F. necrophorum* is only recommended in the clinical cases of persistent sore throat or quinsy [27]. Based on our results it may be questioned if such microbiological processing algorithm represents an effective and reliable method to detect *F. necrophorum* in the upper respiratory tract, and hence early detection of Lemierre’s Syndrome. Centor [14] highlighted that the risk for the Lemierre’s syndrome after *F. necrophorum* pharyngitis greatly exceeds the risk for acute rheumatic fever after group A beta-haemolytic streptococcal pharyngitis. Therefore the diagnostic paradigm of pharyngitis in adolescents and young adults should be expanded and improved detection methods should be considered. Another important aspect is the fact that *F. necrophorum* is able to aggregate platelets and causes thrombosis. In a study published by Forrest et al. [28] the ability of *F. necrophorum* (strains 3080 and 5018) to induce platelet aggregation was demonstrated. Interestingly, in this study aggregation was demonstrated only in biotype A (subsp. *necrophorum*) and could not be demonstrated in biotype B (subsp. *funduliforme*) or the AB biotype, indicating a strain-dependent virulence [28]. In literature subspecies *necrophorum* is described as more virulent, but the isolation mainly follows from infections in animals [29]. In this context, it is worth to highlight the importance of diagnostic methods, including PCR based methods, for reliable identification of *F. necrophorum* to subspecies level. Jensen et al. [30], [31] demonstrated in detailed investigations that all isolates except for 1 were identified as *F. necrophorum* subsp. *funduliforme*. The determination of the species and subspecies together with their potential virulence, as well as the effect on blood platelets aggregation, should be considered in order to identify potential serious complications at an early stage. It might not be sufficient to solely detect *F. necrophorum* in clinical samples. The identification of the subspecies present and its potential to influence the kinetics of aggregation might be more important for the prevention of complications.

Our case series is limited by the fact that only patients with positive microbiological identification of the pathogen were included, while patients with no microbiological investigation or false negative results were not noted even though they might have had clinical symptoms suggesting Lemierre’s syndrome. Therefore, the number of clinical cases diagnosed as Lemierre’s syndrome without microbiological identification remains unknown. Furthermore, the identification of *Fusobacterium* sp. did also not include the identification of the subspecies, since this was and is not routine microbiological procedure.

In conclusion further research is needed to optimize the identification of *F. necrophorum* from throat swabs, to discriminate between virulent species and to identify their role in causing complications or as colonizing organisms. In the group of adolescents and young adults with sore throat targeted investigation for the presence of *F. necrophorum* should be considered for routine diagnostics. In addition, due to the possible complication of thrombosis and abscess formation, imaging in all infections with *Fusobacterium* sp. should be considered.

### Notes

#### Competing interests

The authors declare that they have no competing interests.

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### References

1. Betty A, Wren MW, Gal M. Fusobacterium necrophorum as the cause of recurrent sore throat: comparison of isolates from persistent sore throat syndrome and Lemierre’s disease. J Infect. 2005 Nov;51(4):299-306. DOI: 10.1016/j.jinf.2004.09.013
2. Lemierre A. On certain septicemias due to anaerobic organisms. Lancet. 1936 Mar;227(5874):701-3. DOI: 10.1016/S0140-6736(00)57035-4
3. Weesner CL, Cisek JE. Lemierre syndrome: the forgotten disease. Ann Emerg Med. 1993 Feb;22(2):256-8. DOI: 10.1016/S0196-7059(05)80218-1
4. Citron DM. Update on the taxonomy and clinical aspects of the genus fusobacterium. Clin Infect Dis. 2002 Sep;35(Suppl 1):S22-7. DOI: 10.1086/341916
5. Huggan PJ, Murdoch DR. Fusobacterial infections: clinical spectrum and incidence of invasive disease. J Infect. 2008 Oct;57(4):283-9. DOI: 10.1016/j.jinf.2008.07.016
6. Goldberg EA, Venkat-Ramani T, Hewit M, Bonilla HF. Epidemiology and clinical outcomes of patients with Fusobacterium bacteraemia. Epidemiol Infect. 2013 Feb;141(2):325-9. DOI: 10.1017/S0950268812000660
7. Nagaraja TG, Narayanay SK, Stewart GC, Chengappa MM. Fusobacterium necrophorum infections in animals: pathogenesis and pathogenic mechanisms. Anaerobe. 2005 Aug;11(4):239-46. DOI: 10.1016/j.anaerobe.2005.01.007

8. Afra K, Laupland K, Leal J, Lloyd T, Gregson D. Incidence, risk factors, and outcomes of Fusobacterium species bacteremia. BMC Infect Dis. 2013 Jun;13:264. DOI: 10.1186/1471-2334-13-264

9. Hagelskjær Kristensen L, Prag J. Localised Fusobacterium necrophorum infections: a prospective laboratory-based Danish study. Eur J Clin Microbiol Infect Dis. 2008 Aug;27(8):733-9. DOI: 10.1007/s10096-007-0497-3

10. Goldberg EA, Venkat-Ramani T, Hewit M, Bonilla HF. Epidemiology and clinical outcomes of patients with Fusobacterium necrophorum bacteraemia. Epidemiol Infect. 2013 Feb;141(2):325-9. DOI: 10.1017/S0950268812000660

11. Pett E, Saeed K, Dryden M. Fusobacterium species infections: clinical spectrum and outcomes at a district general hospital. Infection. 2014 Apr;42(2):363-70. DOI: 10.1007/s15010-013-0564-2

12. Lu MD, Vasavada Z, Tanner C. Lemierre syndrome following oropharyngeal infection: a case series. J Am Board Fam Med. 2009 Jan-Feb;22(1):79-83. DOI: 10.3122/jabfm.2009.01.070247

13. Jensen A, Hansen TM, Bank S, Kristensen LH, Prag J. Fusobacterium necrophorum tonsillitis: an important cause of tonsillitis in adolescents and young adults. Clin Microbiol Infect. 2015 Mar;21(3):266.e1-3. DOI: 10.1016/j.cmi.2014.09.020

14. Centor RM. Expand the pharyngitis paradigm for adolescents and young adults. Ann Intern Med. 2009 Dec 1;151(11):812-5. DOI: 10.7326/0003-4819-151-11-200912010-00011

15. Nohrström E, Mattila PS. ClinicalspectrumofbacteraemicFusobacteriumnecrophorumsubsp.funduliformeinchildren. J Clin Microbiol. 1985 Aug;22(2):245-9.

16. Bourgaut AM, Lamothé F, Dolcé P, Saint-Jean L, Saint-Antoine P. Fusobacterium bacteraemia: clinical experience with 40 cases. Clin Infect Dis. 1997 Sep;25 Suppl 2:SI81-3. DOI: 10.1086/516181

17. Goldenberg NA, Knapp-Clevenger R, Hays T, Manco-Johnson MJ. Lemierre’s disease: Lemierre’s-like syndromes in children: survival and thromboembolic outcomes. Pediatrics. 2005 Oct;116(4):e453-8. DOI: 10.1542/peds.2005-0433

18. Ramírez S, Hild TG, Rudolph CN, Sty JR, Kehl SC, Havens P, Henrickson K, Chud M. Increased diagnosis of Lemierre syndrome and other Fusobacterium necrophorum infections at a children’s Hospital. Pediatrics. 2003 Nov;112(5):e380. DOI: 10.1542/peds.112.5.e380

19. Seidenfeld SM, Sutker WL, Luby JP. Fusobacterium necrophorum septicemia following oropharyngeal infection. JAMA. 1982 Sep;248(11):1348-50. DOI: 10.1001/jama.1982.03330110044024

20. Creemers-Schild D, Grontfouhd F, Spanjaard L, Visser LG, Brouwer CN, Kuiper EJ. Fusobacterium necrophorum, an emerging pathogen of otogenic and paranasal infections? New Microbes New Infect. 2014 May;2(3):52-7. DOI: 10.1002/mm2.39

21. Hagelskjær Kristensen L, Prag J. Localised Fusobacterium necrophorum infections: a prospective laboratory-based Danish study. Eur J Clin Microbiol Infect Dis. 2008 Aug;27(8):733-9. DOI: 10.1007/s10096-008-0497-3

22. Holm K, Bank S, Nielsen H, Kristensen LH, Prag J, Jensen A. The role of Fusobacterium necrophorum in pharyngotonsillitis - A review. Anaerobe. 2016 Dec;42:89-97. DOI: 10.1016/j.ananebo.2016.09.006

23. Amess JA, O’Neill W, Goliariabhaigh CN, Dytrych JK. A six-month audit of the isolation of Fusobacterium necrophorum from patients with sore throat in a district general hospital. Br J Biomed Sci. 2007;64(2):63-5.

24. Jensen A, Hagelskjær Kristensen L, Prag J. Detection of Fusobacterium necrophorum subsp. fuluduliforme in tonsillitis in young adults by real-time PCR. Clin Microbiol Infect. 2007 Jul;13(7):695-701. DOI: 10.1011/jcm.1469-0691.2007.01719.x

25. Björk H, Bieber L, Hedin K, Sundqvist M. Tonsillar colonisation of Fusobacterium necrophorum in patients subjected to tonsillectomy. BMC Infect Dis. 2015 Jul;15:264. DOI: 10.1186/s12879-015-0975-z

26. Van TT, Cox LM, Cox ME, Dien Bard J. Prevalence of Fusobacterium necrophorum in children Presenting with Pharyngitis. J Clin Microbiol. 2017 04;55(4):1147-1153. DOI: 10.1128/JCM.02174-16

27. Public Health England. UK Standards for Microbiology Investigations B 9: Investigation of throat related specimens. 2015. Available from: https://www.gov.uk/government/publications/smi-b-9-investigation-of-throat-swabs

28. Forrester LJ, Campbell BJ, Berg JN, Barrett JT. Aggregation of platelets by Fusobacterium necrophorum. J Clin Microbiol. 1985 Aug;22(2):245-9.

29. Tadepalli S, Narayanay SK, Stewart GC, Chengappa MM, Nagaraja TG. Fusobacterium necrophorum: a ruminal bacterium that invades liver to cause abscesses in cattle. Anaerobe. 2009 Feb-Apr;15(1-2):36-43. DOI: 10.1016/j.anaerobe.2008.05.005

30. Jensen A, Hagelskjær Kristensen L, Nielsen H, Prag J. Minimum requirements for a rapid and reliable routine identification and antibiogram of Fusobacterium necrophorum. Eur J Clin Microbiol Infect Dis. 2008 Jul;27(7):557-63. DOI: 10.1007/s10096-008-0468-8

31. Jensen A, Hagelskjær Kristensen L, Prag J. Detection of Fusobacterium necrophorum subsp. fuludulforme in tonsillitis in young adults by real-time PCR. Clin Microbiol Infect. 2007 Jul;13(7):695-701. DOI: 10.1111/j.1469-0691.2007.01719.x

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