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Johannesen, Katrine M; Bodtger, Uffe

Published in:
Infection and Drug Resistance

DOI:
[10.2147/IDR.S95050](https://doi.org/10.2147/IDR.S95050)

Publication date:
2016

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Johannesen, K. M., & Bodtger, U. (2016). Lemierre's syndrome: current perspectives on diagnosis and management. *Infection and Drug Resistance*, 2016(9), 221-227. <https://doi.org/10.2147/IDR.S95050>

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Lemierre's syndrome: current perspectives on diagnosis and management

Katrine M Johannesen¹
Uffe Bodtger¹⁻³

¹Department of Lung Medicine, Naestved Hospital, Naestved,

²Institute for Regional Health Research, University of Southern Denmark, Odense, ³Department of Pulmonology, Zealand University Hospital, Roskilde, Denmark

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Abstract: This is a systematic review of cases with Lemierre's syndrome (LS) in the past 5 years. LS is characterized by sepsis often evolving after a sore throat or tonsillitis and then complicated by various septic emboli and thrombosis of the internal jugular vein. Symptoms include sepsis, pain, and/or swelling in the throat or neck, as well as respiratory symptoms. Laboratory findings show elevated infectious parameters and radiological findings show thrombosis of the internal jugular vein and emboli in the lungs or other organs. The syndrome is often associated with an infection with *Fusobacterium necrophorum*. We found a total of 137 cases of LS, of which 47 were infected with *F. necrophorum* and others with *Staphylococcus* and *Streptococcus*. Complications of this rare but severe disease included osteomyelitis, meningitis, and acute respiratory distress syndrome. Mortality was extremely high in the pre-antibiotic era but has diminished with the advent of antibiotics. This review showed a mortality rate of only 2% of which none of the cases involved fusobacteria. Duration of treatment varied; a 4–6-week course of carbapenem or piperacillin/tazobactam in combination with metronidazole was optimum. Other treatment options included anticoagulants in 46% of cases, which is unwarrantedly high, as to date, no evidence of the positive effects of anticoagulants in LS exists. Only two cases had ligation of the internal jugular vein performed. This review confirms the rare, but severe aspects of LS. Mortality from LS in this day and age appears to be low, however the syndrome is difficult to recognize, and still requires the full attention of the clinician.

Keywords: Lemierre's syndrome, fusobacteria, postanginal sepsis

Definition

Lemierre's syndrome (LS) takes its name after the French bacteriologist André-Alfred Lemierre, who first described the syndrome in 1936.¹ The syndrome is defined by a pharyngeal infection, complicated by septicemia and internal jugular vein thrombosis followed by septic emboli. Due to the introduction of antibiotics, LS has aptly been referred to as "the forgotten disease". The most commonly involved bacteria is *Fusobacterium necrophorum* but other bacteria such as fusobacteria, *Streptococcus*, *Staphylococcus*, and *Enterococcus* are commonly found in cultures.² Other bacteria, such as *Klebsiella Pneumoniae* have rarely been described in middle-aged persons with newly diagnosed type 2 diabetes.³

Patients with LS present with a prolonged sore throat, neck pain, and often with fever.⁴ Patients are often young (age 16–30 years) and otherwise healthy, but appear acutely ill with tachycardia, tachypnea, hypotension, and a poor saturation (often <95%).^{2,3,5,6} Laboratory findings showed leukocytosis with dominating neutrocytosis and elevated C-reactive protein as well as signs of organ failure, such as elevated

Correspondence: Katrine M Johannesen
Department of Lung Medicine, Naestved Hospital, 61, Ringstedgade, DK-4700 Naestved, Denmark
Email kamaa@regionsjaelland.dk

liver enzymes. Imaging of the internal jugular vein showed thrombosis.^{2,5}

Complications to this severe syndrome include a mortality rate as high as 10%,³ especially when antibiotic treatment is delayed.⁷ Other less severe complications include metastatic infections in joints, internal organs (often lungs), and/or the brain.⁶

Fusobacterium necrophorum has a reputation for being resistant to penicillin, thus the drugs of choice have primarily been β -lactamase-resistant β -lactams, such as piperacillin–tazobactam, even though many strains are sensitive to penicillin in combination with metronidazole.^{4,7}

The syndrome remains difficult to diagnose due to its low incidence and absence of pathognomonic symptoms. Thus, symptoms mimic other common diseases. Botros et al⁸ have described this dilemma in an excellent manner.

The present study is a review of the publications in the past 5 years concerning LS. A PubMed search was carried out

using the MeSH terms “Lemierre Syndrome/classification”, “Lemierre Syndrome/diagnosis”, “Lemierre Syndrome/etiology”, and “Lemierre Syndrome/therapy”. Inclusion criteria were: studies published in English language, dealt with human subjects, and a publication date within the last 5 years. The search elicited 121 papers, of which the abstracts were read, and 18 papers were excluded as they did not concern LS. The full text of 103 papers was read, after which seven were excluded, since they did not include any data on patients/cases. A total of 137 cases were included for this review (Figure 1).

Diagnosis

A definite diagnosis of LS should be made based on the following findings:^{7,9}

- 1) a recent pharyngeal illness,
- 2) complicated by septic emboli,
- 3) as well as either thrombosis of the internal jugular vein or findings of *F. necrophorum* in blood cultures.

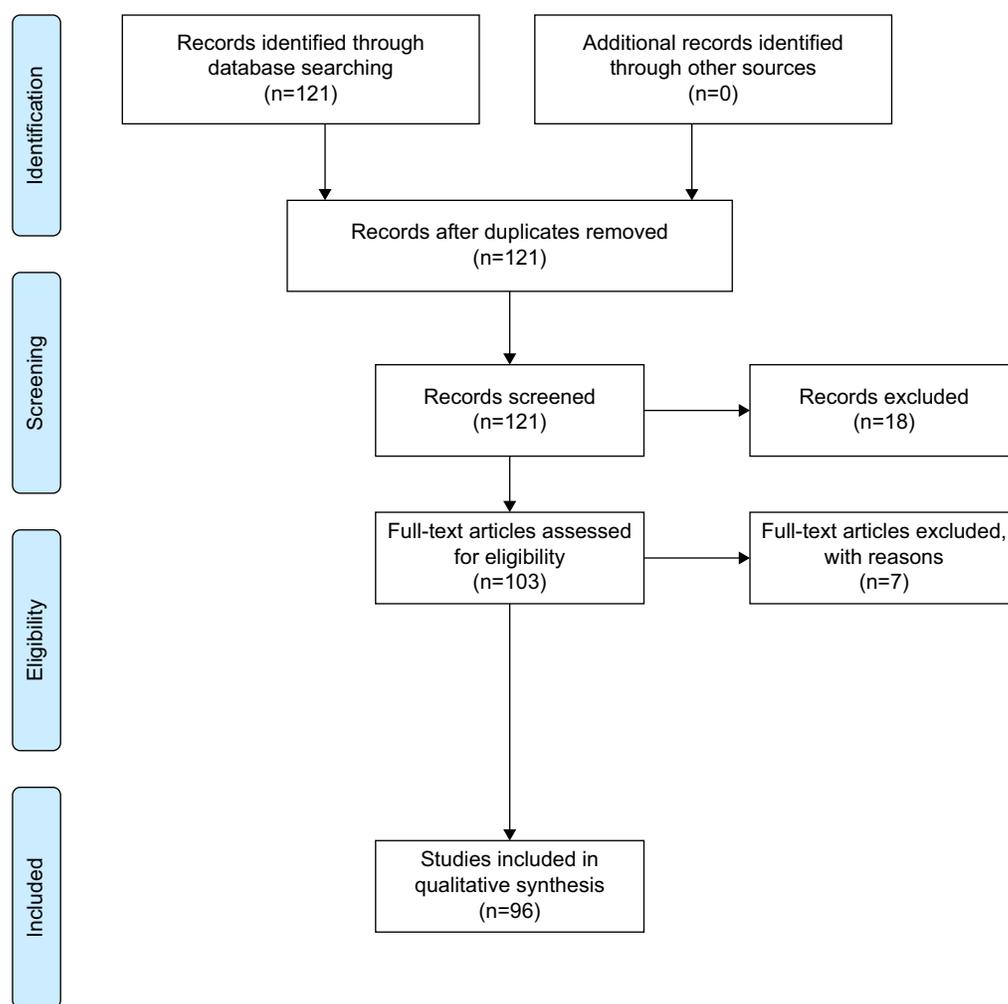


Figure 1 Lemierre's syndrome review: study inclusion and exclusion flow diagram.

Notes: Figure created using PRISMA 2009 flow diagram software from Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7):e1000097 doi: 10.1371/journal.pmed.1000097. For more information, visit www.prisma-statement.org.⁹⁴

Clinical

This review yielded at total number of 137 cases^{2,3,5,6,8,10-90} including both case reports and minor reviews. The major clinical characteristics of LS are reported in Table 1. Twenty-four percent of the cases were presented with a complaint in the pharyngeal area (tonsillitis, pharyngitis, common sore throat), whereas a few came with an initial complaint of a swelling of the neck,^{37,61,64-66,73,82} due to either the thrombus itself or an abscess located in the neck region. Only eleven cases were described with initial difficulties in the dental region,^{6,16,18,42,46} the otogenic region,^{18,19,68,77} or the central nervous system.^{29,45} Atypical presentations included seizures⁹⁰ and blindness.^{60,63} Half the cases were presented with sepsis at their first evaluation in the hospital, and at least 17 cases were intubated (not reported in all articles), underlining the severity of LS. Interestingly, the location of the primary infection is an important prognostic factor: infection in the oropharyngeal location (compared to other sites) was associated with a higher risk of longer intensive care unit stays due to complications such as respiratory problems.¹⁸ At least 37 of the cases in this review were not in the age group usually associated with LS, rather they were older than 30 years or younger than 15 years. Eleven were children younger than 15 years, who presented with a variety of symptoms, including pharyngitis⁵⁹ and/or pneumonia⁴³ and also more severe symptoms such as meningitis⁴⁵ or febrile seizures.⁵⁸ None of the children in this review died. In the older age group too, common complaints such as pneumonia⁴⁰ dominated, but also here more severe symptoms/illnesses were seen, such as multiple emboli.³⁸ It had previously been found that other diseases underlie LS in these older patients, such as diabetes or cancer.⁹¹

The overall mortality was 2%, death was reported only in two of 137 cases. This is considerably less than previously reported.⁹¹ Briefly, no fusobacteria were cultured in the following two cases: 1) a diabetic patient with tonsillitis and peritonsillar abscess (*K. pneumoniae* positive culture)³ and 2) a 79-year old with tonsillitis and multiple septic emboli in lungs, liver, heart, kidney, and joints (*Streptococcus anginosus* positive culture).³⁸ In a previous study, we presented

morbidity and mortality in patients with positive cultures in blood, sputum, or pleural effusion with fusobacteria versus *Staphylococcus aureus* and showed that infections with fusobacteria were associated with a significantly lower 1-year mortality.⁹² Only one patient in the fusobacteria group in that study had LS,⁴⁹ but generally mortality in the fusobacteria group was due to comorbidity and not due to severity of the infection itself. It could be speculated that publication bias plays an important role when trying to estimate the mortality in this rare syndrome. It could go both ways: fatal cases with a lesser likelihood to be published due to the simple fact that these cases could be missed and not diagnosed at all; or fatal cases could have a higher likelihood to be published due to the interest in why these cases become fatal.

Microbiological

In this review, 96 cases reported a causative microbiological agent; the majority of the cases were infections with *F. necrophorum* (41), *Fusobacterium nucleatum* (6), and unspecified fusobacteria (3), others were infections with microbiological agents such as *Streptococcus* (17), including *methicillin-resistant S. aureus*, and *S. aureus* (six cases) (Figure 2). These findings suggest that *F. necrophorum* is still the major microbiological agent in LS, but it could also be due to reporting bias, as clinicians and/or editors only approve “the forgotten disease” when fusobacteria is present in relevant cultures. *Fusobacterium necrophorum* (and other fusobacteria) is an obligate anaerobic bacterium and is notoriously difficult to culture, requiring a longer incubation period than other bacteria.⁹² A large proportion of the cases did not report a microbiological agent (n=40). As with other bacteria, cultures can be false negative if antibiotics are administered before sample collection. Whether the cases without a positive culture of *F. necrophorum* (or other fusobacteria) are true cases of LS is debatable. In the review by Riordan,⁹ it was suggested that *F. necrophorum* is in fact present in all patients with LS but goes undetected due to various circumstances and that the bacteria detected would be unable to cause LS on its own. However, this quite stern conclusion has not been accepted as a common rule in the clinical community, and so far a clinical diagnosis of LS is still valid if the bacteria either go undetected or turn out to be *Streptococcus* or some other known pathogenic bacteria.

Imaging

Concerning the diagnosis of the infectious thrombosis, the optimal imaging tool is still debated. Ultrasonography is a radiation-free and easily available bedside tool, but it has the disadvantage of being less sensitive for recently formed

Table 1 Common clinical characteristics of Lemierre's syndrome

Symptom	Percentage
Septic emboli	100
Thrombosis of the internal jugular vein	84
Sepsis	50
A sore throat	24
Swelling of the neck	5
CNS affection	3.6

Abbreviation: CNS, central nervous system.

- *Fusobacterium necrophorum*
- *Fusobacterium nucleatum*
- *Fusobacteria* spp.
- *Klebsiella pneumoniae*
- *Streptococci*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- MRSA
- Other bacteria
- Not found

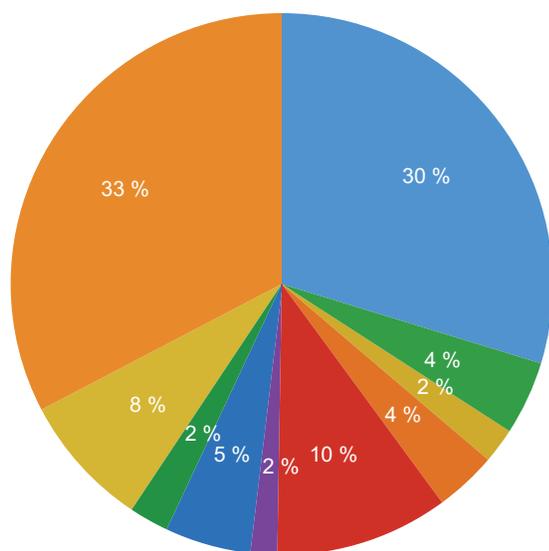


Figure 2 Distribution of bacterial agent.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

thrombosis material, with a lesser echogenicity, as well as difficulties in the deeper tissue areas around the clavicle and mandible.⁹³ Magnetic resonance imaging (MRI) is an excellent method for visualizing all anatomic structures as well as the thrombosis and/or septic emboli. However, MRI is expensive and usually not readily available. Computed tomography (CT) scans are cheaper and available in most hospitals, but it involves radiation exposure. In this review, the vast majority of cases (95%) with thrombophlebitis of the internal jugular vein were diagnosed by CT scans. Ultrasonography was used by the remaining cases, but none used MRI.

In total, ten cases (7%) had no or unknown thrombus during their disease. The majority of cases (84%) had thrombosis of the internal jugular vein, while a few (9%) cases had thrombosis of other veins, such as the facial vein, sinus transversus, or vena ophthalmicus.^{47,60}

A larger proportion of cases (71 cases) had septic emboli in the lungs, but septic emboli were also seen in other organs, such as the liver,^{12,38,87} spleen,⁸¹ joints,^{38,70} heart,³⁸ and the central nervous system,^{29,31} even though in smaller numbers.

Management

Antibiotics

All but a few rare cases received antibiotic treatment during their hospital stay. Multiple different regimens of the

antibiotic of choice were used. Resistance to penicillin was not found at an increased frequency. However, carbapenem and piperacillin/tazobactam were commonly used, either as monotherapy or in combination with metronidazole, and 98% of the cases (mortality $n=2$) were treated successfully. The mean duration of antibiotic treatment was 4 weeks, but it ranged from 10 days to 8 weeks. The reason for the choice of a particular duration was not explained in any of the included papers. Riordan⁹ highlights the features of metronidazole and also recommends it as monotherapy, which was not seen in any of the cases in this review. He especially praises metronidazole for its profound activity against all strains of *Fusobacterium* spp., its good penetration within the tissue, and its good oral availability. Regarding treatment duration, Riordan⁹ and others have, similar to this review, found a wide range of treatment duration; however, it seems that there is no justified reason for prolonged intravenous treatment in cases of LS, and thus, if the patient responds well to treatment, he/she could be switched to oral treatment after the first 2 weeks of intravenous antibiotics.⁹

Anticoagulation

Anticoagulation is still a controversial issue, with no proper studies carried out on the issue. In this review, we found that 87 cases (64%) received anticoagulation treatment, often with low-molecular-weight heparin. Treatment duration varied between 2 weeks and 6 months. A few ($n=2$) patients suffered from side effects (hemorrhage or disseminated intravascular coagulation) and were treated accordingly without serious adverse effects.^{32,87} In the review by Riordan and also previous reviews, the frequency of patients treated with anticoagulants was 21%–23%. The high prevalence in this study might be due to the widespread, unconfirmed hypothesis regarding the positive effects of anticoagulants, which seem to have gained a favorable position in the clinic. Also, within this review, we have not subdivided the patients receiving anticoagulation treatment regarding thrombosis solely in the jugular vein and thrombosis involving sinus cavernosus. The latter is a more severe situation and thus requires a more aggressive treatment strategy.

Other forms of treatment

A substantial number of cases ($n=17$) had abscesses in various anatomical locations: lungs, liver, epidura, and neck. Generally, accessible abscesses were treated by drainage. Rarely, other surgical procedures were performed: tooth extraction,⁸⁴ craniotomy,⁶⁹ and ligation of the occluded vein,^{18,65,68} in order to prevent further septic emboli. Common for these cases

were severe illness, and all other treatment modalities were already initiated, ligation seems to be reserved exclusively for extremely ill patients.

Conclusion

Given that we identified only 30 case reports from 2012, 27 from 2014, and ten from 2015, it does not seem that the incidence of LS is increasing. However, these are speculations, and evidently publication bias is unavoidable, and the “market” might be saturated with case reports on the subject. The syndrome still deserves the name “the forgotten disease”, and most fusobacterial infections are not LS. A fatal outcome is rare.

Diagnosing LS still requires thorough clinical examination and awareness of the association between current acute medical illness and a recent pharyngeal infection; yet, there is a need for studies on the diagnostic outcomes when LS is suspected.

Furthermore, early collection of blood samples and microbiology cultures in severely ill patients are required to establish a microbiological diagnosis. Symptoms of possible thrombosis need evaluation by an early CT scan or ultrasonography. The former has a better diagnostic capability, including intrathoracic vessels and septic emboli.

Treatment is efficacious and follows the general principles: systemic antibiotics, drainage of abscesses, and, perhaps, anticoagulation. Antibiotic treatment is crucial and should be corrected according to microbiological results on drug resistance. Penicillin, carbapenem, or piperacillin/tazobactam – often in combination with metronidazole – is efficacious. The optimal duration of treatment is not established, but 2 weeks of intravenous antibiotics with a total of 4–6 weeks seems sufficient. However, duration needs individualization according to disease severity and follow-up results, including imaging and serological inflammatory markers.

Based on the current evidence, it is still unknown whether anticoagulation therapy is mandatory. There were no apparent differences in mortality or course between the 64% cases treated with anticoagulants versus the 36% who were not. However, confounding by indication is most likely. Unfortunately, no randomized studies on this controversy are available.

Overall, LS is characterized by the absence of large-scale studies, but hopefully the future will witness a pragmatic multicenter approach to address the various controversies of this intriguing disease.

Disclosure

The authors report no conflicts of interest in this work.

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