PILARZ, Anna, SOSIN, Julia, SALAMON, Dariusz, STACHOWIAK, Julia, ZWIERZCHOWSKA, Maria, SOJKA, Aleksandra and DOMAGAŁA, Wojciech. Lemierre's syndrome: a forgotten disease. Quality in Sport. 2024;36:56405. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.36.56405
https://apcz.umk.pl/QS/article/view/56405

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.11.2024. Revised: 15.12.2024. Accepted: 16.12.2024. Published: 18.12.2024.

Lemierre's syndrome: a forgotten disease

Anna Pilarz

Wojewódzkie Centrum Szpitalne Kotliny Jeleniogórskiej

anka.pilarz@gmail.com

https://orcid.org/0009-0003-8006-7191

Julia Sosin

SPZOZ Okręgowy Szpital Kolejowy w Katowicach

j.sosin99@gmail.com

https://orcid.org/0009-0009-1434-5038

Dariusz Salamon

SP ZOZ Brzesko

dareksal1@gmail.com

https://orcid.org/0009-0000-4107-4565

Julia Stachowiak
SP ZOZ MSWiA w Katowicach im. Sierżanta Grzegorza Załogi
julka.stachowiak96@gmail.com
https://orcid.org/0000-0001-6071-7642

Maria Zwierzchowska
SP ZOZ MSWiA w Katowicach im. Sierżanta Grzegorza Załogi
zwierzchowskam@gmail.com
https://orcid.org/0009-0009-6115-4197

Aleksandra Sojka
SP ZOZ MSWiA w Katowicach im. Sierżanta Grzegorza Załogi
aleksandra.sojka99@gmail.com
https://orcid.org/0009-0008-9428-7562

Wojciech Domagała
SZPITAL MIEJSKI NR 4 W GLIWICACH SP. Z O. O.
wojciech.domagalaa@gmail.com
https://orcid.org/0009-0001-8152-4521

Abstract:
Lemierre's syndrome or Lemierre's disease is septicemia in the course of angina. It is a rare disease that occurs during or after pharyngitis and appears as inflammation of the internal jugular vein and subsequent embolic abscesses in the lungs or viscera. It is most commonly seen in teenagers and young adults. Lemierre's syndrome has long been treated as a forgotten disease, but its incidence is now rising again.

Aim of the study:
Due to the high prevalence of benign oral and pharyngeal infections in adolescents, the diagnosis of Lemierre's syndrome is often difficult to catch initially. This can result in delays in treatment. This work describes the diverse presentation of Lemierre's syndrome, diagnostic options, and highlights the role of the interdisciplinary team in the care of these patients.

Materials and methods:
A systematic review of scientific and medical literature from the PubMed and Google Scholar databases was conducted.

Results:
Given the potential catastrophic consequences, including septicemia, multiple organ failure and death, it is imperative to quickly recognize Lemierre's syndrome based on the clinical picture, followed by targeted diagnostic testing and immediate initiation of broad-spectrum antibiotics. Increasing awareness of Lemierre's syndrome among physicians is key to facilitating rapid diagnosis and life-saving treatment.

Keywords: Lemierre's syndrome, Sepsis, Antibiotic therapy, *Fusobacterium nucleatum*

Introduction:
Lemierre's syndrome [LS] is a rare, potentially fatal complication of middle pharyngeal infections characterized by septic thrombophlebitis of the internal jugular vein. It mainly affects healthy adolescents and young adults. The incidence declined after the antibiotic era, but may have returned in recent decades, probably due to judicious use of antibiotics and increasing bacterial resistance. Prompt diagnosis and treatment are necessary to prevent significant morbidity and mortality [1].
The most common pathogen responsible for the onset of the disease is *Fusobacterium necrophorum* - the syndrome is also called necrobacillosis after this bacterium. LS has also been observed in *Fusobacterium nucleatum , Streptococci , Staphylococci* and *Klebsiella pneumoniae* [2].
Before the era of antibiotics, ushered in the 1940s by the introduction of penicillin into medicine, LS was more common and usually fatal after a few weeks. Over time, it became a “forgotten disease,” but nowadays, with the trend toward limiting antibiotic therapy for upper respiratory tract infections in young adults, the incidence of the syndrome is rising again [3].

Disease course:

LS usually develops in three main phases, beginning with a throat and mouth infection characterized by febrile episodes and chills within four to seven days after the initial illness. In most cases, LS results from oral infections such as pharyngitis, but can also be secondary to parotitis, otitis media, sinusitis and mastoiditis. It has also been reported that patients with confirmed Epstein-Barr virus infection and influenza A develop LS [4].

In the second phase, the infection spreads to the lateral pharyngeal space and soft tissues of the neck. Venous thrombosis begins locally in the periglottal veins, and then spreads to the internal jugular veins. *F. necrophorum* has been shown to aggregate human platelets in vitro, which then causes intravascular coagulation. In combination with venous stasis due to external compression and internal vascular obstruction secondary to inflammation and edema, this leads to the development of septic thrombosis of the internal jugular vein, which is marked as phase three of LS. The release of septic congestion into the systemic circulation results in the spread of *F. necrophorum* to the lungs, pleura, joints, bones, muscles, spleen, liver, kidneys and other circulatory endpoints. Direct extension or propagation of the clot can result in central nervous system abscess formation, as well as cavernous sinus thrombosis [5].

Complications

If *F. necrophorum* invades the jugular veins, septic congestion occurs. The most commonly affected organ is the lungs (85%), but the joints, liver, kidneys, brain, bones, heart and meninges can also be involved. Bacteremia is associated with fever, lethargy or shock, as well as end-organ damage. Septic shock occurs in about 7% of cases. Acute respiratory distress syndrome requiring mechanical ventilation can affect up to 10% of patients [5].

Researchers have also described atypical complications of LS that need to be kept in mind during diagnosis and therapy, as their consequences can be catastrophic. The case of a patient who lost her eyesight due to LS has been described. Ophthalmic complications of LS are rare and very few cases have been reported. Doctors must be aware that this is a serious condition that in some cases can lead to blindness [6].

Doctors have also reported a complication in the form of the development of a bronchopleural fistula in a young LS patient. The bronchopleural fistula may have developed due to a delay in starting drainage of the pleural abscess. Before performing a chest lavage, a CT scan of the chest should be performed to rule out a bronchopleural fistula, because if a bronchopleural fistula is present, a chest lavage should not be performed, as it can cause complications such as pneumonia on the opposite side due to reflux [7].

It has also been described that liver abscess can be associated with *Fusobacterium* species, in combination with a rare gastrointestinal variant of LS (pylephlebitis), which poses a significant risk of mortality. This case underscores the rarity and clinical challenges associated with these conditions. Increased awareness among physicians is crucial for early diagnosis and prompt intervention, potentially improving outcomes in such cases [8].

Diagnosis

Lemierre's syndrome is difficult to diagnose in its early stages. It should be suspected in patients with prolonged pharyngitis followed by unilateral neck swelling and fever. The diagnosis is often confirmed by identification of thrombophlebitis in the internal jugular vein and an increase in anaerobic bacteria in blood cultures [9]. Blood tests usually show elevated inflammatory markers and may show thrombocytopenia [10].

Cultures usually play a key role, and isolation of *F. necrophorum* from blood cultures can be the basis for diagnosis. However, blood cultures can take weeks to reveal anaerobic organisms and can be negative if empiric antibiotics were started before cultures. Therefore, culture alone cannot be relied upon, as patients may already have developed metastatic septic changes by the time results are received. The use of throat swabs in primary care may be one method of diagnosing LS at an earlier stage. However, this technique is limited by the fact that most throat swabs are cultured aerobically, and it can be difficult to distinguish
F. necrophorum from normal throat flora, even when swabs are cultured anaerobically [11].

Imaging diagnosis

Initial diagnostic clues often come from radiological findings, such as the presence of thrombophlebitis in the internal jugular vein (IJV), preceding the identification of positive bacterial growth in cultures. Imaging studies are key to visualizing thrombophlebitis and abscess formation in the neck. Although there are no specific guidelines in the literature, ultrasonography (USG) and chest X-rays have been suggested as initial diagnostic imaging modalities [12].

The preferred diagnostic method for Lemierre's syndrome is contrast-enhanced computed tomography of the neck and chest. This imaging technique is optimal for depicting the site of primary infection and revealing characteristic features, such as a filling defect in the internal jugular vein, variably associated with swelling in adjacent tissues [13]. It can also identify complications such as osteomyelitis, arthritis, abscesses and pulmonary emboli, providing information on their extent and distribution in the lungs. Typically, the latter show a classic

pattern, appearing as multiple peripheral, round, wedge-shaped areas that develop into cavities. The radiologic triad of pharyngitis, jugular vein thrombosis and cavitary pulmonary lesions is typical of this syndrome [14].

In special cases, magnetic resonance imaging has been used to detect internal jugular vein thrombosis. It provides high-quality images of the supratentorial abscess or brain [15].

Direct comparative studies are still needed. Both CT and MRI show high accuracy in detecting the characteristic feature of internal jugular vein thrombosis with sensitivity [16].

Antibiotic therapy

Long-term antibiotic therapy is the mainstay of treatment for LS in modern times. Because there are no controlled clinical trials to determine the optimal antibiotic regimen, decisions must be made based on known in vitro sensitivities along with anecdotal clinical evidence. While penicillin monotherapy has been used in the past, more recent antimicrobial studies have shown that many strains of *F. necrophorum* acquire beta-lactamase activity [17].

Currently, beta-lactams or carbapenems in combination with metronidazole are commonly prescribed. *F. necrophorum* is almost always sensitive to metronidazole, co-amoxiclav, clindamycin and imipenem, and less commonly to erythromycin and penicillin [18].

If there is any diagnostic doubt, timely therapy with intravenous broad-spectrum antibiotics should be initiated and further refinements made based on the results of available sensitivities. It should be noted that some authors advise against metronidazole monotherapy due to the frequent occurrence of mixed infections with other oral flora [19].

There is no consensus on the optimal duration of antibiotic treatment, and studies have shown that the average duration of treatment is approximately three to five weeks [20, 21].

Anticoagulant treatment

The role of anticoagulant treatment in LS has long been debated, and studies assessing the risks and benefits are lacking. Initial thromboembolic manifestations involve multiple sites and often include the cerebral veins, and the risk of new complications persists throughout hospitalization. Despite this, the use of any dose of anticoagulants was reported in only 56% of patients. This may have been due to the believed high risk of serious bleeding, but also to the concern that anticoagulants could break up a fresh septic clot and cause new septic lesions [22].

Various anticoagulants are used, including low-molecular-weight heparin, fondaparinux, unfractionated heparin, direct oral anticoagulants and vitamin K antagonists, with a reported duration of treatment ranging from 70 to 84 days [23].

The hypothesis behind the use of anticoagulant treatment is that bacteria may be hidden in the thrombus, so treatment to halt its progression may increase the availability of antibiotics to the source of infection, leading to faster resolution of the disease. In contrast, some argue that because the clot is secondary to an infectious process, simply resolving the infection with antibiotics would cause the clot to resolve [24].

Other researchers recommend the use of anticoagulants only in certain circumstances, such as when thrombosis has the potential for retrograde progression to the cavernous sinus, in the acute setting or in the context of extensive thrombosis. The use of anticoagulant therapy requires research and the development of guidelines for implementing therapy in patients with LS [25].

Surgical treatment

Surgical treatment of LS may include drainage of abscesses in the neck, most commonly peritonsillar or lateral pharyngeal abscesses. In the pre-antibiotic era, ligation or resection of the internal jugular vein was often performed to prevent septic emboli [26].

Although ligation or resection of the internal jugular vein was common before the use of antibiotics, this intervention is less common today. Only 8% of cases in a recent series required this intervention [27].

Ligation or resection of the internal jugular vein is indicated only in cases of uncontrolled sepsis or ongoing septic congestion despite antibiotic use [28].

Based on previous retrospective studies, systematic reviews and meta-analyses obtained through database searches, researchers [29] summarized the following points regarding surgical intervention in LS:

1. If patients fail to improve with conservative drug treatment and continue to have extensive septic thrombosis or uncontrolled severe sepsis, surgical treatment should be considered.
2. Abscess drainage is the most common and convenient method of surgical treatment for abscesses once they have formed.
3. Surgical treatment of the primary infection is an effective method of controlling the spread of infection and sepsis.

4. Ligation or excision of the internal jugular vein is indicated in patients with persistent septic embolism after treatment with antibiotics and anticoagulants.
5. Ligation or excision of the internal jugular vein is also indicated to prevent clot separation when anticoagulant treatment or transcatheter thrombolysis is ineffective [29].

Conclusions

A multidisciplinary approach is essential for effective treatment of LS. This approach should involve a range of specialties, including pediatrics, infectious diseases, otolaryngology and radiology, to ensure that all aspects of the disease are addressed.

Clinical pathways can streamline this approach, ensuring that each patient receives timely and comprehensive care. Education is another critical component in the fight against LS. Both healthcare providers and the public need to be aware of the signs and symptoms of the syndrome, as early recognition and intervention are paramount. Educational programs and campaigns can raise awareness and ensure that patients seek immediate medical attention for persistent throat infections.

Author's contribution:

Conceptualization: Anna Pilarz, Julia Sosin;
Methodology: Anna Pilarz, Julia Stachowiak;
Software: Dariusz Salamon, Maria Zwierzchowska;
Validation: Julia Sosin, Wojciech Domagała;
Formal analysis: Anna Pilarz, Maria Zwierzchowska;
Investigation: Aleksandra Sojka, Julia Sosin;
Resources: Anna Pilarz, Wojciech Domagała;
Data curation: Anna Pilarz, Julia Sosin;
Writing – Original Draft Preparation: Anna Pilarz, Julia Stachowiak;
Writing – Review & Editing: Anna Pilarz, Julia Sosin, Dariusz Salamon;
Visualization: Anna Pilarz, Aleksandra Sojka, Dariusz Salamon;
Supervision: Julia Sosin, Aleksandra Sojka;
Project administration: Anna Pilarz;
Funding acquisition: not applicable.

All authors have read and agreed with the published version of the manuscript.

Funding Statement:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:
Not applicable.

Acknowledgments:
Not applicable.

Conflict of Interest Statement:
Authors have declared no conflict of interests.

Bibliography:

1. Lavalle S, Masiello E, Cocuzza S, Pavone P, Di Nora A, Calvo-Henriquez C, Lechien JR, Yanez MM, Praticò A, Ceccarelli M, et al. Pediatric Lemierre's Syndrome: A Comprehensive Literature Review. *Pediatric Reports*. 2024; 16(1):201-213. https://doi.org/10.3390/pediatric16010018
2. Johannesen KM, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. *Infect Drug Resist*. 2016;9:221-227. Published 2016 Sep 14. doi:10.2147/IDR.S95050
3. Pychyński T, Bereza-Andrzejewska A, Milżyńska J, Pychyński W. Lemierre's syndrome – case report. Pol Otorhino Rev. (2024);13(1):48-53. https://doi.org/10.5604/01.3001.0054.3935.
4. Perez S, Shtanko Y, Del Pilar Bonilla L, Portnoy W. Case Report: An Unusual Case of Lemierre's Syndrome Presenting as Influenza B-Induced Myositis Complicated by Streptococcus intermedius Infection. *Cureus*. 2024;16(7):e64437. Published 2024 Jul 12. doi:10.7759/cureus.64437

5. Allen BW, Anjum F, Bentley TP. Lemierre Syndrome. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; July 31, 2023.
6. Suzuki T, Kojima M, Nakamoto R, et al. A case of blindness caused by Lemierre's syndrome. *Clin Case Rep*. 2023;11(12):e8327. Published 2023 Dec 13. doi:10.1002/ccr3.8327
7. Kodaka N, Nakano C, Oshio T, Matsuse H. Lemierre syndrome complicated by bronchopleural fistula. *J Postgrad Med*. 2024;70(1):50-52. doi:10.4103/jpgm.jpgm_722_22
8. Salam R, Verma A, Noeske M, Alnimer L, Sieloff EM, Piper MS. Gastrointestinal Variant of Lemierre Syndrome due to *Fusobacterium nucleatum*: A Case Report. *Case Rep Gastroenterol*. 2024;18(1):144-152. Published 2024 Mar 18. doi:10.1159/000536619
9. Eilbert W, Singla N. Lemierre's syndrome. *Int J Emerg Med*. 2013;6(1):40. Published 2013 Oct 23. doi:10.1186/1865-1380-6-40
10. Nygren D, Holm K. Invasive infections with Fusobacterium necrophorum including Lemierre's syndrome: an 8-year Swedish nationwide retrospective study. *Clin Microbiol Infect*. 2020;26(8):1089.e7-1089.e12. doi:10.1016/j.cmi.2019.12.002
11. Bank S, Nielsen HM, Mathiasen BH, Leth DC, Kristensen LH, Prag J. Fusobacterium necrophorum- detection and identification on a selective agar. *APMIS*. 2010;118(12):994-999. doi:10.1111/j.1600-0463.2010.02683.x
12. Nadir NA, Stone MB, Chao J. Diagnosis of Lemierre's syndrome by bedside sonography. *Acad Emerg Med*. 2010;17(2):E9-E10. doi:10.1111/j.1553-2712.2009.00644.x
13. Hong P, MacCormick J, Lamothe A, Corsten M. Lemierre syndrome: presentation of three cases. *J Otolaryngol*. 2005;34(5):352-358. doi:10.2310/7070.2005.34511
14. Morizono S, Enjoji M, Sonoda N, et al. Lemierre's syndrome: Porphyromonas asaccharolytica as a putative pathogen. *Intern Med*. 2005;44(4):350-353. doi:10.2169/internalmedicine.44.350
15. Lee WS, Jean SS, Chen FL, Hsieh SM, Hsueh PR. Lemierre's syndrome: A forgotten and re-emerging infection. *J Microbiol Immunol Infect*. 2020;53(4):513-517. doi:10.1016/j.jmii.2020.03.027
16. Johannesen KM, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. *Infect Drug Resist*. 2016;9:221-227. Published 2016 Sep 14. doi:10.2147/IDR.S95050

17. Appelbaum PC, Spangler SK, Jacobs MR. Beta-lactamase production and susceptibilities to amoxicillin, amoxicillin-clavulanate, ticarcillin, ticarcillin-clavulanate, cefoxitin, imipenem, and metronidazole of 320 non-Bacteroides fragilis Bacteroides isolates and 129 fusobacteria from 28 U.S. centers. *Antimicrob Agents Chemother*. 1990;34(8):1546-1550. doi:10.1128/AAC.34.8.1546
18. Walkty A, Embil J. Lemierre's Syndrome. *N Engl J Med*. 2019;380(12):e16. doi:10.1056/NEJMicm1808378
19. Riordan T, Wilson M. Lemierre's syndrome: more than a historical curiosa. *Postgrad Med J*. 2004;80(944):328-334. doi:10.1136/pgmj.2003.014274
20. Wright WF, Shiner CN, Ribes JA. Lemierre syndrome. *South Med J*. 2012;105(5):283-288. doi:10.1097/SMJ.0b013e31825581ef
21. Riordan T. Human infection with Fusobacterium necrophorum (Necrobacillosis), with a focus on Lemierre's syndrome. *Clin Microbiol Rev*. 2007;20(4):622-659. doi:10.1128/CMR.00011-07
22. Valerio L, Zane F, Sacco C, et al. Patients with Lemierre syndrome have a high risk of new thromboembolic complications, clinical sequelae and death: an analysis of 712 cases. *J Intern Med*. 2021;289(3):325-339. doi:10.1111/joim.13114
23. Tiwari A. Lemierre's Syndrome in the 21st Century: A Literature Review. *Cureus*. 2023;15(8):e43685. Published 2023 Aug 18. doi:10.7759/cureus.43685
24. Campo F, Fusconi M, Ciotti M, et al. Antibiotic and Anticoagulation Therapy in Lemierre's Syndrome: Case Report and Review. *J Chemother*. 2019;31(1):42-48. doi:10.1080/1120009X.2018.1554992
25. Kuppalli K, Livorsi D, Talati NJ, Osborn M. Lemierre's syndrome due to Fusobacterium necrophorum. *Lancet Infect Dis*. 2012;12(10):808-815. doi:10.1016/S1473-3099(12)70089-0
26. Lemierre A, Gregoire R, Laporte A, Couvelaire R. Les aspects chirurgicaux des infections a Bacillus funduliformis. Acad Med. 1938;6:352–359.
27. Chirinos JA, Lichtstein DM, Garcia J, Tamariz LJ. The evolution of Lemierre syndrome: report of 2 cases and review of the literature. *Medicine (Baltimore)*. 2002;81(6):458-465. doi:10.1097/00005792-200211000-00006
28. Moreno S, García Altozano J, Pinilla B, et al. Lemierre's disease: postanginal bacteremia and pulmonary involvement caused by Fusobacterium necrophorum. *Rev Infect Dis*. 1989;11(2):319-324. doi:10.1093/clinids/11.2.319

29. Pan Y, Shi Z, Ye B, et al. Surgical intervention of Lemierre's syndrome: a case report and review of the literature. *J Med Case Rep*. 2024;18(1):265. Published 2024 May 31. doi:10.1186/s13256-024-04584-2