From rare to aware: confronting Lemierre syndrome

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Lemierre syndrome is a life-threatening condition characterized by an acute head/neck bacterial infection due to anaerobes (namely *Fusobacterium necrophorum*), local septic vein thrombosis and distance septic embolism.[1] The venous thromboembolic manifestations of the disease are well known and it is only recently that other features, including arterial thromboembolic complications and long-term sequelae, have been reported in up to 10% of the patients.[2] First described a century ago, Lemierre syndrome remains poorly studied, frequently underdiagnosed, and still burdened with a high fatality and morbidity rate.[2]

With approximately 800 cases indexed in PubMed as of 2024, one wonders why the syndrome is so poorly known to even the physicians most directly involved, namely infectious disease, vascular, and ear, nose and throat specialists. Despite being considered a rare disease, Lemierre syndrome predominantly affects young and healthy individuals and its incidence may be on the increase (from 2.9 to 5.0 cases per million per year from 2010-13 to 2014-17), particularly in teenagers, among whom the incidence rate may be as high as 1 per 100,000 population years.[1,3-6] Whether this trend is due to increasing antibiotic resistance, improved diagnostics, increased reporting, or a combination thereof remains unclear.

If not promptly recognized and treated, the syndrome can lead to life-threatening complications. Its diagnosis can be challenging even for experienced clinicians due to the often ambiguous clinical presentation, the absence of specific laboratory markers, and the lack of widely accepted diagnostic criteria.[7] The traditional criteria as summarized by Riordan included i) history of pharyngotonsillitis; ii) internal jugular vein thrombosis and/or evidence of septic embolism; and iii) isolation of *Fusobacterium necrophorum* from cultures.[8] However, more liberal criteria are currently discussed to increase diagnostic sensitivity. It is now generally accepted that primary infectious foci can be localized beyond the oropharyngeal district in other parts of the head and neck region. Thrombosis can involve other vessels than the internal jugular vein, such as the facial and external jugular veins, cerebral sinuses, and even the carotid arteries. The microbiological criterion may also be too restrictive: isolating *F. necrophorum*, an anaerobic Gram-negative bacterium typically associated with the disease, can be difficult and time-consuming, potentially leading to delays in diagnosis. Additionally, other bacteria, including *Staphylococcus spp*., *Streptococcus spp*., and *Bacteroides spp*. are now considered to be possibly associated with this syndrome.[9-13]

Indeed, the largest analysis to date (712 cases reported in the literature from 2000 to 2017) included patients with primary infections of the head or neck and septic thrombosis or embolism and revealed that only 46% met the "historical" definition of Lemierre syndrome.[1,14] Therefore, the notion has developed that Lemierre syndrome should rather be considered a specific manifestation within the spectrum of bacterial thrombophlebitis, encompassing conditions with vascular dissemination associated with various primary infections caused by multiple microbial agents.[14]

Although the prognosis of Lemierre syndrome has significantly improved compared to the pre-antibiotic era, when it was

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mostly fatal, it still carries a current mortality rate of 4-9%.[1,5] In the retrospective review of 712 cases previously mentioned, septic shock and complications related to cerebral infarction or intracranial septic emboli emerged as the primary causes of mortality. Severe early complications, including new or recurrent venous thromboembolism and peripheral septic lesions, affected more than 14% of patients. Furthermore, over 10% of the survivors experienced long-term neurological sequelae, such as cranial nerve palsy, blindness or reduced visual acuity, and peripheric paralysis or paresis, or orthopedic and functional limitation.[1]

As for diagnosis, also for its management there are no standardized guidelines. Antibiotic therapy remains the cornerstone of treatment, whereas the role of anticoagulant therapy remains controversial. There is concern that anticoagulation may promote thrombus fragmentation and its peripheral embolization. Although the use of anticoagulants has not been proven to reduce mortality, retrospective analyses did not show it to increase the risk of bleeding, septic embolization, or primary thrombus extension. Therefore, anticoagulation can be considered acceptably safe in those patients without absolute contraindications to anticoagulant therapy, according to current guidelines and practice in venous thromboembolism.[1,15]

To address the current evidence gap, the BATTLE registry (https://lemierre-syndrome.org/) was established in 2022 as the first global network dedicated to studying Lemierre syndrome and septic thrombophlebitis. This disease-specific, multicenter clinical registry of global reach and multidisciplinary scope is designed to provide clinically relevant information to patients and physicians and to evaluate management strategies.[14]

Raising awareness and enhancing the understanding of Lemierre syndrome are crucial steps in improving its diagnosis, management, and outcomes, with the ultimate goal of reducing mortality, minimizing long-term complications, and enhancing patient quality of life.

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