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The long shadow of Lemierre's syndrome

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Summary Lemierre's syndrome is a rare and feared complication of pharyngitis, occurring most commonly in adolescents and young adults. It is typically defined by the constellation of septic internal jugular vein thrombophlebitis, pulmonary and other septic emboli, and sterile-site infection by *Fusobacterium necrophorum*. The rarity and severity of Lemierre's syndrome has made it an attractive subject for case reports but there is a paucity of evidence to inform areas of persistent uncertainty. In recent years, heightened attention and controversy has focused upon speculation that a purported rise in the incidence of Lemierre's syndrome is due to reduced antibiotic prescribing for respiratory tract infections, that *F. necrophorum* is an under-appreciated cause of acute tonsillopharyngitis and that testing and targeted treatment would prevent cases of Lemierre's syndrome.

Introduction

In 1936 in The Lancet, André Lemierre described the syndrome which would eventually carry his name and concluded that it was, "relatively easy to make a diagnosis on the simple clinical findings…a syndrome so characteristic that a mistake is almost impossible".[1] Although Lemierre broadly addressed "certain septicaemias due to anaerobic organisms" what is best remembered is his illustrative focus on post-anginal septicaemia due to *Bacillus fundiliformis* (known today as *Fusobacterium necrophorum*) in which he described the progression from focal suppurative (peritonsillar) infection to local septic (internal jugular) thrombophlebitis and distant septic (pulmonary) emboli. As familiarity with the most advanced and characteristic elements of Lemierre's syndrome has diminished in the antibiotic era, it has assumed a classical and almost mythical status, attested to by a proliferation of case reports portraying it as a "forgotten" and "sinister" enigma, contrasting the historical diagnostic confidence

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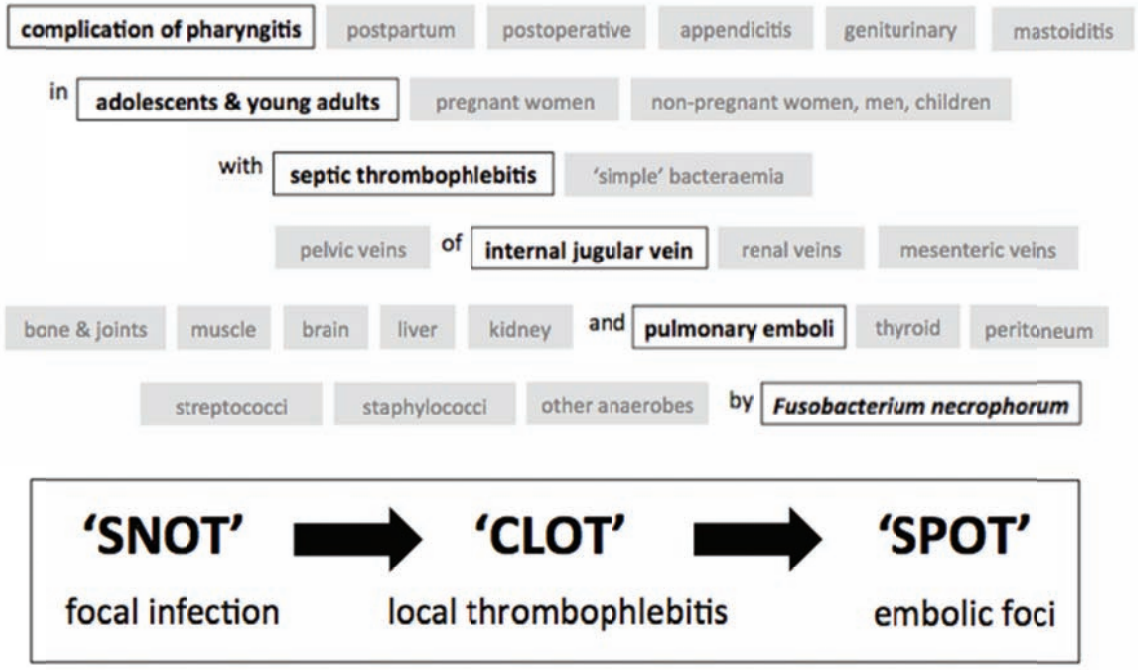

Figure 1 Lemierre's syndrome — an eponym with many synonyms. The classic syndrome (black text) with variations recognised by André Lemierre in his 1936 paper (grey boxes).

of Lemierre.[2,3] Rather than subjecting the syndrome to further review and report, we point instead in this article to previous outstanding reviews[4,5] and will concentrate on areas of confusion, contention, and controversy which have emerged in relation to its definition, microbiology, epidemiology, pathogenesis, and management.

Definition

The term Lemierre's (or simply Lemierre) syndrome has been applied broadly and often interchangeably since the 1980s to cases including any one or more of *F. necrophorum* infection, septic thrombophlebitis, and distant metastatic septic emboli (Figure 1). André Lemierre himself emphasised that the pathway from focal suppurative infection to local thrombophlebitis, generalised sepsis, and distant embolic phenomena could originate: "1) From inflammatory lesions of the nasopharynx, particularly tonsillar and peritonsillar abscesses; 2) From similar lesions of the mouth and jaws; 3) In connexion with otitis media or mastoiditis; 4) From purulent endometritis following parturition; 5) From appendicitis; 6) From infections of the urinary passages".[1]

In a meticulous 2007 review of 393 reported cases, including a comprehensive and engaging examination of the historical aspects of Lemierre's syndrome, Riordan tested various case definitions and arrived at a clinical-microbiological hybrid requiring: a history of "anginal illness" within the preceding four weeks *or* compatible clinical findings *and*; evidence of remote metastatic lesions *and*; internal jugular thrombophlebitis *or* isolation of *F. necrophorum* or *Fusobacterium* sp. from blood cultures or other sterile site.[4] Though this definition does not fit with Lemierre's original concept of an ominous pathological sequence common to "certain anaerobic septicaemias", it conforms (by design) to modern usage. Use of the antiquated term "anginal illness" was somewhat unfortunate but should be understood to encompass pharyngo-tonsillitis and its attendant local suppurative complications. Taking into account new molecular diagnostic techniques, the final microbiological criteria should be amended to include identification in blood or other sterile site of *F. necrophorum* or *Fusobacterium* sp. by culture *and/or* non-culture-based diagnostics (e.g. polymerase chain reaction, PCR).[6–8] This definition notably excludes otogenic *Fusobacterium* sp. infections, which disproportionately affect young children and can also cause thrombophlebitis and serious intracranial complications.[4,9]

Epidemiology

Efforts to fully appreciate the epidemiology of Lemierre's syndrome are confounded by its rarity, conflicting definitions, and multiple aliases. Qualified estimates of Lemierre's syndrome incidence derived from English and Danish retrospective case series from the 1990s were approximately one per million persons per year.[10,11] A subsequent prospective study from Denmark reported an annual incidence of 3.6 per million persons per year.[12] By any definition and for unexplained reasons, Lemierre's syndrome predominantly affects young adults. The prospective Danish study found an annual incidence of 14.4 cases per million for persons aged 14–24 years, and in Riordan's 2007 review of 222 previous cases meeting his restricted case definition, the median age was 19 years and 89% of patients were aged 10 to 35 years.[4] Other enigmatic epidemiological observations are a male:female ratio of approximately 2:1 in most series and a concentration of cases in autumn and winter in some series.[5]

Of greatest epidemiological relevance and resonance is the contention by some authors that the incidence of Lemierre's syndrome is increasing.[10,13,14] Authors of case