Head, Neck, and Abdominopelvic Septic Thrombophlebitis: Current Evidence and Challenges in Diagnosis and Treatment

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Abstract

Septic thrombophlebitis (STP) is a complex, cross-disciplinary clinical condition that combines a localized infection with a neighboring venous thrombosis. STP can occur at several possible anatomic sites, such as dural sinuses, jugular vein (Lemierre syndrome), portal vein (pylephlebitis), and pelvic veins. Its high mortality in the preantibiotic era improved considerably with the introduction of modern antibiotics. However, little evidence exists to date to guide its clinical management. The incidence of STP or its risk factors may be increasing, and its mortality may still be considerable. These trends would have far-reaching implications, especially in the setting of increasing resistance to antimicrobial agents. No clinical assessment tools exist to support patient screening or guide treatment in STP. Few interventional studies exist on the efficacy and safety of anticoagulation. Recommendations on its indications, duration, and the agents of choice are mostly based on evidence derived from small observational studies. While all forms of STP pose similar challenges, future research may benefit from the distinction between bacteria-associated, virus-associated, and mycosis-associated thrombophlebitis. Addressing these gaps in evidence would enhance our ability to diagnose this condition and treat patients effectively.

Keywords

- septic thrombophlebitis
- venous thromboembolism
- Lemierre syndrome
- pylephlebitis
- bacterial infection
- anticoagulant

Introduction

Septic thrombophlebitis (STP) can be defined as venous thrombosis resulting from local bacterial infection or colonization. This common pathogenesis encompasses a group of clinical conditions with specific anatomic localizations, risk factors, and prognoses.

The idea that some venous thromboses have an infectious origin originated from the observation that a thrombus may co-occur with local infection and inflammation. Historically, this pathogenesis was reflected in the anatomic-pathological demonstration of (1) perivascular inflammation and (2) vein-wall suppuration (which, together, define *phlebitis*) contiguous to the thrombus; (3) bacteremia; or (4) suppuration or microorganisms in the thrombus itself.[1] Hence, the notion of STP.[2]

The bacteria themselves or the inflammation that they elicit acts on the Virchow triad's component of vascular damage.[3] Indeed, the other two components of the triad, hypercoagulability and venous stasis, often explain the association of STP with specific sites and risk factors. The oldest example is pelvic thrombophlebitis: hypercoagulability is provided by pregnancy/puerperium, stasis by the dilation of the ovarian veins.[4]

However, the term STP is often referred to two groups of conditions with overlapping but different etiology (►Fig. 1). The first group includes thrombi resulting from vascular

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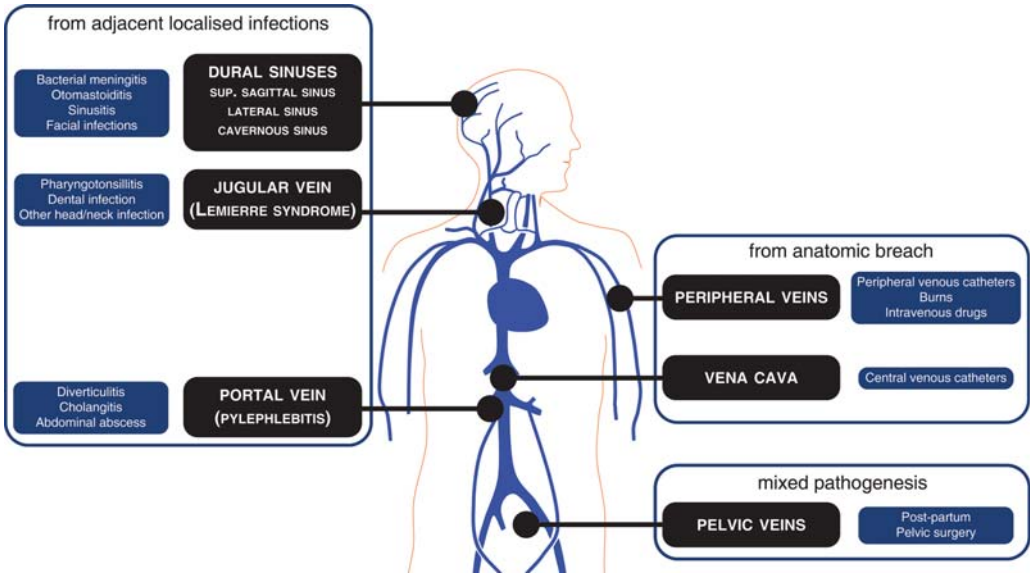

Fig. 1 Major risk factors and sites of septic thrombophlebitis.

involvement in the context of a localized infection. Dural STP can involve the sagittal sinus, the lateral sinus, or the cavernous sinus, typically as a complication of meningitis, otitis media, or facial and sinusal infections, respectively. Lemierre syndrome, a STP of the jugular vein, usually follows an acute pharyngotonsillitis in children and young adults. STP of the portal vein (pylephlebitis) is associated with abdominal infections (diverticulitis, cholangitis, appendicitis). The second group of STP includes conditions associated with septic colonization through a *porte d'entrée*—a breach of anatomic continuity through which bacteria enter the vascular system even in the absence of an overt primary local infection. This mechanism explains all catheter-associated thrombophlebitis, including inferior vena cava thrombosis, and peripheral vein thrombophlebitis, often found in intravenous drug users and burn patients. STP of the pelvic veins can accompany either local infections or septic colonization following delivery or surgery. Both groups may evolve into sepsis, and the distinction between infection and colonization is not always clear-cut. Yet, it sets apart catheter-associated thrombophlebitis, which affects a relatively well-defined patient population with specific implications for clinical management, and has been thus addressed by considerable research and long-standing international guidelines.[5]

This article focuses on the forms of STP associated with local infection. While these conditions affect different patient populations, they are all treated in relatively similar ways and present the physician with the same management problems. Their common pathophysiology provides the rationale for a unified view of all STPs as a single entity in clinical practice. We will review available evidence and current challenges in the epidemiology and management of STP associated with head/neck, abdominal, and pelvic infections.

Epidemiology

All STPs are rare. Estimates of their incidence in the general population amount to 1 to 2 per million population-years for dural sinus STP[6] and 1 per million population-years for Lemierre syndrome.[7] Incidences are often produced for specific age groups at risk: the yearly incidence of dural sinus STP is then estimated to be 13 to 16 cases per million adults,[6] and that of Lemierre syndrome over 10 per million children and adolescents.[7] Pelvic STP has been reported to occur in 1:3,000 overall deliveries and 1:800 caesarean deliveries.[8] No reliable estimates of the incidence of pylephlebitis exist; in a single-center retrospective study, it complicated 0.6% of all intra-abdominal infections.[9]

Pathophysiology

Coagulation plays a defensive role during infections by limiting the dissemination of pathogens and contributing to their destruction.[10] The systemic inflammatory response during sepsis includes the increased expression of procoagulant cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α,[11] which also activate platelets.[12] Locally, bacteria and viruses elicit a prothrombotic environment both indirectly, through endothelial damage and inflammation,[13] and directly, by inducing the expression of tissue factor on monocytes and endothelial cells,[14] activating the intrinsic coagulation pathway,[10] inhibiting the physiologic anticoagulation mechanisms,[15] and promoting platelet aggregation,[16] particularly via complement activation.[17] Antiphospholipid antibodies generated during bacterial and viral infections[18] may result in thrombotic syndromes clinically indistinguishable from the classic antiphospholipid antibody syndrome.[19] Gram-negative

bacteria may elicit the formation of antibodies that cross-react with platelet factor 4 (PF4), possibly leading to a procoagulant state and even to "spontaneous heparin-induced thrombocytopenia."[20]

Thrombotic complications can derive either from the excessive activation of coagulation or from the evasion of host defenses by the pathogen. Prolonged sepsis damages endothelial cells, leading to microvascular dysfunction and loss of antithrombotic properties,[11] while sepsis-associated neutrophil extracellular traps (NETs) and neutrophil-derived extracellular vesicles also contribute to coagulation activation and platelet aggregation.[21] Some bacteria seem to have developed the ability to turn coagulation to their advantage. A well-documented example is the streptococcal ability to inhibit plasminogen and use the fibrin clot to shield themselves from the immune system.[22] The combination of these mechanisms ultimately results in clinically significant thrombotic phenomena such as disseminated intravascular coagulation (DIC) and local venous thrombosis in the form of STP.

Diagnosis

Unlike their risk factors, the common principles for clinical suspicion, diagnosis, and management of STPs are remarkably similar across all venous sites.

Because of its anatomical location, only cavernous sinus STP is associated with relatively specific symptoms (headache, eye swelling) and signs (diplopia), which should raise suspicion in patients with sinusitis or other facial infections. Most other forms of STP are suspected based on the persistence of fever, leucocytosis, or positive blood cultures despite appropriate antibiotic therapy in patients at risk. For Lemierre syndrome, traditionally associated with *Fusobacterium* spp., a positive culture of *Fusobacterium* from blood or pus in patients with recent pharyngotonsillitis has been used as a criterion for clinical suspicion or even diagnosis. However, this has been challenged. Fusobacteria are difficult to grow, and reports are common of patients who, despite blood cultures being negative or growing bacteria other than *Fusobacterium* spp., satisfy all other criteria for Lemierre syndrome.[23] The absence of bacteremia should not be used to exclude pelvic STP, as blood cultures are negative in most cases.[24] The main risk factor is caesarean delivery, but a 2017 case–control study of a multicenter registry of caesarean deliveries has identified potential novel risk factors, including black ethnic background, age <20 years, preeclampsia, and multiple gestation.[25] No specific risk factors or clinical findings exist for pylephlebitis. Once most commonly associated with appendicitis and abscesses, after 2000 it has been more often reported in patients with diverticulitis and biliary infections.[9,26]

In cases suggestive of STP, thrombus visualization strongly supports a conclusive diagnosis. Both ultrasound and computed tomography (CT)/magnetic resonance imaging (MRI) are used, the former ensuring lower costs and larger availability, and the latter higher accuracy. The supposed recent increase in the incidence of several forms of STP may be explained by the increased use of CT/MRI and diagnosis of subclinical cases. In contrast, increased imaging specificity may have lowered the estimated incidence of some conditions. This is the case for septic pulmonary embolism as a complication of pelvic STP: its high incidence described in the 1970s may have been partly due the exclusive use of the poorly specific plain chest radiographs in the earliest diagnoses.[27] While thrombus demonstration is generally required for a diagnosis of dural STP and pylephlebitis, Lemierre syndrome and pelvic STP can be diagnosed even with negative imaging tests. In Lemierre syndrome, ultrasound, readily available in emergency settings, may miss the hallmark jugular vein thrombosis. In early stages, thrombi may be fresh and poorly echogenic; in advanced stages, by the time *Fusobacterium* or septic emboli are found, they may have resolved.[23] Pelvic STP presents even more difficulties for the radiologist: no imaging techniques identify thrombi with sufficient accuracy in the ovarian veins. They all lack sensitivity, as clots are often too small to be visible, and specificity, as small thrombi in ovarian veins can be present in healthy postpartum women. Therefore, a presumptive diagnosis can be made and even anticoagulation considered in patients in whom no thrombus has been visualized.[8]

Treatment

Antibiotic Therapy

The mainstay of management of STP is antibiotic therapy. The empiric regimens recommended for each form are based on the sensitivity of the bacteria that most commonly cause the underlying infection (►Table 1). In most cases, third to fourth-generation cephalosporins are the agent of choice. They are combined with vancomycin to target *Staphylococcus aureus* (dural STP), with metronidazole or clindamycin (or replaced by a carbapenem) to target anaerobes (Lemierre syndrome, pylephlebitis). As in usual stewardship, antibiotic management should be subsequently guided by blood cultures. However, several STPs are characterized by persistently negative cultures, including most cases of pelvic STP[24] and a considerable minority of those of Lemierre syndrome.[23] This finding poses considerable management challenges in the case of insufficient clinical response, as the only option is broadening the antibiotic coverage blindly.

Interventional Treatment

In the preantibiotic era, invasive interventions (such as venous excision or venous ligation) were often the only options for severe STP.[23,28] Since the introduction of modern antibiotic therapy, surgery has been increasingly reserved for complicated cases refractory to antibiotics.[8,23] Over the last few years, the successful application of endovascular therapies has been described in case reports of septic thrombosis of large-diameter veins such as the vena cava,[29] but no study has systematically explored their risk-benefit profile.

Anticoagulation

The use of anticoagulation in STP is a matter of ongoing controversy. Because STP is rare, few clinical trials have been conducted, precluding the exploration of all possible efficacy

Table 1 Common etiologic agents and treatment recommendations for septic thrombophlebitis by site

Site		Common etiologic agents[23,26,85]	Empiric antibiotic therapy[23,26,27,85]	Anticoagulation[23,26,37,62]
Dural sinuses	Superior sagittal sinus	As in bacterial meningitis: *Streptococcus pneumonia, Neisseria meningitidis*.	Vancomycin + 3rd–4th generation cephalosporin	Not recommended because of high risk of hemorrhage
	Lateral sinus	*Proteus* spp. *Staphylococcus aureus* *Escherichia coli* *Bacteroides fragilis*	Metronidazole + 3rd–4th generation cephalosporin OR carbapenem	Considered in patients who fail to improve clinically despite antibiotics and surgical drainage
	Cavernous sinus	*Staphylococcus aureus* *Streptococcus* spp. If dental infection/sinusitis: anaerobes	If no associated dental infection/sinusitis: vancomycin + 3rd–4th generation cephalosporin If associated dental infection/sinusitis: metronidazole + 3rd–4th generation cephalosporin	Early heparinization is standard of care
Jugular vein		*Fusobacterium* spp.	Beta-lactamase-resistant antibiotics with anaerobic activity (metronidazole, clindamycin, Tazocin)	No consensus. Often suggested for patients with thrombus extension or recurrence despite antibiotic therapy
Portal vein		Frequently polymicrobial Common: *Streptococcus viridans* *Escherichia coli* *Bacteroides fragilis*	Metronidazole + 4th generation cephalosporin OR piperacillin–tazobactam OR ticarcillin–clavulanic acid OR ampicillin–sulbactam OR carbapenem	Often suggested for patients with thrombus extension or recurrence despite antibiotic therapy
Pelvic veins		Blood cultures negative in the majority of cases. When positive: *Streptococcus* spp. *Enterobacteriaceae* Anaerobes	Vancomycin + 3rd–4th generation cephalosporin	Considered in patients with clear visualization of thrombus and no alternative explanation for persisting symptoms

and safety outcomes or of subpopulations in whom benefits may overweigh risks. In this context, statements on the potential benefit of anticoagulation in a specific form of STP have often been based on questionable analogies with evidence collected in other forms. ►Table 1 provides an overview of current practice at each site of STP.

One of the earliest reports of anticoagulation for any STP was the retrospective series of 46 patients with pelvic STP treated with heparin described by Josey and Staggers in 1974.[30] Although noninterventional, this study guided practice until the small-scale clinical trial published by Brown et al in 1999.[8] This trial compared six patients randomized to heparin treatment in addition to standard antimicrobial therapy with eight patients with standard antimicrobial therapy only and found no difference in the duration of fever or hospitalization length. The study, however, was only powered to identify differences in the duration of fever, and did not consider several other outcomes of clinical interest, such as survival, thrombus resolution, or bleeding.

Considerable evidence exists on the use of anticoagulation for sinus vein thrombosis, which includes dural STP as a subgroup. Two small trials conducted in the 1990s[31,32] found that anticoagulation seemed to lower the overall risk of death, leading to its adoption in international guidelines.[33] After 2000, two additional small trials suggested that low-molecular-weight heparin (LMWH) was superior to unfractionated heparin (UFH).[34,35] Unfortunately, this evidence cannot be applied as such to the subgroup of dural STP. One of the two original trials excluded dural STP[31]; the two more recent trials included it, but did not provide specific results for this patient subgroup.[34,35] Only two observational studies have specifically addressed anticoagulation in dural STP. A single-center analysis of 19 cases seen over 44 years suggested that heparin may reduce mortality in selected cases of septic cavernous sinus thrombosis.[36] A more recent analysis of prospective data on 77 patients with dural SPT did not find evidence of adverse safety outcomes in patients treated with heparin, but the small sample size prevented firm conclusions.[37]

International guidelines on the management of portal vein thrombosis recommend anticoagulation in most patients, although with several exceptions and differences between countries.[38] However, no studies or guidelines specifically address pylephlebitis.

Similarly, neither reliable evidence nor consensus exists on the use of anticoagulation in Lemierre syndrome. The main concern is the possible hemorrhagic transformation of the frequent peripheral septic emboli.[7] A single-center retrospective study on 18 patients seen over 17 years, six of whom received at least 4 weeks of LMWH, UFH, or warfarin, found no association between anticoagulation and either radiologic thrombus resolution or bleeding. In the absence of a consensus, the general rule is often cited that anticoagulation should

only be considered in cases of retrograde thrombus extension from the internal jugular vein to the cerebral veins.[39] However, the only rationale for this rule is the analogy with lateral sinus thrombosis in children, a form of dural STP in which anticoagulation has been considered since the 1990s.[40,41]

Prognosis

Most STPs were first described between the end of the 19th century and the mid-20th century. At that time, therapeutic options were few and usually limited to surgical venous excision; case series published until the 1960s reported death rates close to 100%. The introduction of venous ligation resulted in significantly improved survival compared with venous excision, but most of the subsequent reduction in mortality can be attributed to modern antibiotics.[23,26,42,43]

Along with infective endocarditis, STP is the only condition that can be complicated by septic embolism,[44] especially in the case of Lemierre syndrome and pelvic STP. Unlike thromboembolism, septic embolism does not exclusively lead to venous infarct or ischemia, but can present as abscess at locations not amenable to surgical treatment, including lungs, bone and joints, soft tissue, and the central nervous system. Embolization also reflects the continuous bacterial spread in the circulation, leading to a bacteremia difficult to control by medical therapy only. As such, septic embolism poses serious treatment challenges and severely affects prognosis. Septic pulmonary embolism is considered to be particularly specific for STP, as its only alternative cause is right-sided infective endocarditis.[45] As this form of embolism is most typically associated with Lemierre syndrome[7] and vena cava STP,[45] the diagnosis of these conditions should prompt a low index of suspicion for pulmonary involvement. Because septic pulmonary emboli can mimic lobar pneumonia, standardized radiological criteria have been proposed for their diagnosis: multiple, bilateral peripheral pulmonary nodules often with cavitations. CT can identify emboli with partial or complete abscess formation and remains more sensitive than chest X-rays.[44]

Knowledge Gaps

Trends in the Incidence and Mortality of STPs

Estimates on the incidence of most STPs are heterogeneous. What little information is available is limited to small case series. Inaccuracy because of rarity is compounded by detection bias in both directions. Their true incidence can be underestimated because, in clinical practice, STP is not actively searched unless several alternative diagnoses have been excluded; even when searched, it is difficult to confirm conclusively; and even when confirmed, it may not be characterized as septic, as this label rests on the concomitant finding of a systemic inflammatory reaction or a frank infection that may both be missing in mild cases or have subsided by the time the thrombus is found. Conversely, overestimation can result from small thrombi being present in patients with no clinical symptoms and having been increasingly detected as imaging techniques became more sensitive.

Several claims have been made that the incidence of dural, jugular, and portal STPs has increased over the past 30 years.[6,7,46] Commonly alleged reasons include increasing bacterial antibiotic resistance or, in the case of Lemierre syndrome, strict adherence to the guidelines that limit antibiotic use in acute pharyngotonsillitis, possibly leaving some nonviral cases untreated. However, this trend is difficult to substantiate. An apparent increase in incidence may originate from higher diagnostic sensitivity (detection bias) or even an increase in published case reports (publication bias). In contrast, death rates and case fatality rates in STP series described since the 1980s have clearly decreased compared with earlier series of the 20th century.[23,27,43] However, some reviews suggest that death rates are still considerable in pylephlebitis (11%)[26] and Lemierre syndrome (4%).[42]

More detailed information on the incidence trends of STPs and their death rates or case fatality rates in the contemporary era would have far-reaching implications for both clinical practice and public health. Increasing incidence of some forms of STP would mandate changes in the empirical management of infections or prophylaxis of patients at risk: acute pharyngotonsillitis for Lemierre syndrome,[47] the use of caesarean section for pelvic STP, or the management of the aging human immunodeficiency virus (HIV)-infected population.[48] If death rates or case fatality rates are still high, new therapeutic options should be found, as increasing antibiotic resistance may otherwise preclude further reduction.

While viruses and fungi can also be associated with thrombophlebitis, all epidemiological information on STP associated with these pathogens is limited to case reports and case series. The potential to cause clinically relevant thrombophlebitis has been attributed to both long-known viruses, such as HIV,[48] and newly recognized ones, including COVID-19.[49] As viral infections remain a difficult challenge for public health and clinical practice, international longitudinal studies are needed and should clearly distinguish STP associated with viral versus bacterial or fungal infections. This approach would also clarify whether the rarity of fungal STP reflects the rarity of mycosis, compared with bacterial or viral infections, rather than a lower thrombogenic potential of fungi. Specific analyses should address whether fungi may only be associated to thrombosis in rare, yet clinically relevant populations.[50]

Risk Estimation and Pathogen-Specific Thrombogenic Potential

STP is often diagnosed with a considerable delay, limiting management options and compromising patient prognosis. While the risk factors of most STPs are well known nowadays, STP is so rare that patients at risk are not systematically screened or monitored. Several STPs with no specific clinical manifestation remain a diagnosis of exclusion. This problem disproportionately affects conditions with potentially unfavorable prognosis such as cavernous sinus thrombosis from sphenoidal sinusitis, lateral sinus thrombosis from otitis media, and Lemierre syndrome after pharyngotonsillitis.

No guidelines exist to identify those patients in whom these rare complications are likely enough to warrant additional monitoring by hospital admission or early imaging. Evidence on risk factors and epidemiology, as well as the accuracy of imaging techniques, may now be sufficient for the development of classification tools sensitive enough to identify patients with no need for monitoring or specific enough to identify those at high risk of already having developed STP. Promising candidates for inclusion in these tools could be suggested by high-quality observational data including prospectively collected data or disease registries and based on hypotheses generated by case reports or case series; they may include hypercoagulation states, immune deficiencies, and anatomic variation. An example is the alleged role of the Epstein–Barr virus (EBV) infection in the pathogenesis of Lemierre syndrome, based on small case series that cannot rule out detection bias determined by the similar age range and initial symptoms of the two conditions.[23]

In this perspective, the question of whether specific infectious agents cause thrombophlebitis more often than others is intriguing. This is almost certainly the case for Lemierre syndrome, which has traditionally been associated with *Fusobacterium* spp., and pylephlebitis, commonly caused by *Bacteroides fragilis*: both pathogens have been attributed marked procoagulant properties.[51–53] These associations may even have implications for management choices, such as the decision to initiate anticoagulation and the type of antimicrobial agent. The impact of the pathogen on the occurrence and features of thrombophlebitis may extend to nonbacterial STP. Mycotic thrombophlebitis from *Candida* spp. almost exclusively involves the vena cava,[54,55] but was reported also at other sites, such as the internal jugular vein.[56] Similarly, not all viruses seem to be equally thrombogenic. Clinically serious thrombophlebitis has been reported in association with viral infections both acute, such as varicella zoster virus[57–59] and COVID-19,[49] and chronic, such as cytomegalovirus in HIV patients[60] and hepatitis B virus.[61] These considerations suggest that it would be meaningful to distinguish, in future research, three groups of STP defined by the major microbiological agents definitely or potentially associated with it: bacteria-associated thrombophlebitis, mycosis-associated thrombophlebitis, and virus-associated thrombophlebitis.

Treatment Choices: Antibiotic Therapy and Anticoagulation

While antibiotic therapy is the mainstay of the treatment of STP, recommendations are limited to the empiric regimes and subsequent reliance on antibiotic sensitivity testing. Little or no evidence supports other key aspects of management, such as the duration of therapy or the criteria for escalation: available studies either did not compare alternative durations of therapy or had no comparable endpoints.

The greatest unsolved issue is the role of and optimization of anticoagulation. No trial so far was sufficiently powered to explore all the efficacy outcomes of clinical interest: death, thrombus extension and recurrence, embolization rate, time to fever resolution, time to discharge, and possibly time to recanalization (insofar as this is clinically relevant). Safety outcomes should include not only bleeding, but also distant embolization from rupture of the primary thrombus and hemorrhagic transformation of abscesses, since these risks are often mentioned as reasons to avoid anticoagulation in STP. The decision to start anticoagulation depends on the identification of subgroups of patients in whom the benefits of anticoagulation outweigh risks, beyond the poorly substantiated rule of only considering anticoagulation in case of thrombus extension or recurrence despite antibiotic therapy. The alternative merits of different anticoagulation agents, dosages, and treatment durations should be evaluated.

This paucity of evidence results in great variation across STPs in the recommendations provided by the scientific literature. The indication for anticoagulation varies from the extreme of superior sagittal sinus thrombosis, in which anticoagulation is always contraindicated because of the high risk of bleeding, to pelvic STP, a unique case in which it is considered acceptable to start anticoagulation even without radiological evidence of thrombosis.[62]

Due to the important contribution of inflammation to both sepsis and venous thromboembolism,[12,63] heparin may be the anticoagulant of choice in the acute phase of STP due to its intrinsic anti-inflammatory properties.[64,65] It is still controversial whether nonsteroidal anti-inflammatory drugs, often used in the treatment of superficial thrombophlebitis,[66] might play a role, given the increased risk of venous thromboembolism suggested by some observational studies.[67]

Ongoing Research

Epidemiology and Clinical Outcomes

The first results of an individual patient level analysis of all cases of Lemierre syndrome reported since 2000[7] have shed light on the prognosis of this condition in the antibiotic era, revealing a possibly decreasing mortality and a still considerable burden of complications despite treatment.[42] Additional analyses will provide information on the clinical profile, treatment patterns, and long-term prognosis in these patients. In addition, a systematic review aiming to clarify the role of EBV infection in the development of Lemierre syndrome is currently registered on the online PROSPERO database.[68]

Anticoagulation

The EXCOA-CVT study is evaluating the optimal duration of anticoagulation in cerebral vein thrombosis.[69] As the study does not formally exclude cases of infectious pathogenesis, subgroup analysis in patients with dural STP may shed light on the efficacy and safety of anticoagulation in this condition. To the best of our knowledge, no other clinical trials on the treatment of a form of STP are currently planned or ongoing.

A recent animal study has shown that the synthetic pentasaccharide fondaparinux improves survival in sepsis induced by *Escherichia coli* by inhibiting the activation of both the intrinsic and extrinsic coagulation pathways.[70] All attempts to modulate coagulation in DIC using antithrombin, activated protein C, and their combination with heparins had

so far failed because of excessive bleeding. In this setting, the advantage of fondaparinux over heparins may lie in its ability to inhibit factor Xa but not thrombin, which is necessary to generate the antithrombotic activated protein C. Future studies should further investigate the properties of fondaparinux before it is possibly considered as anticoagulant of choice in a septic or inflammatory setting.

Combining Anticoagulation and Antimicrobial Activity

Recent preclinical studies suggest that several anticoagulant agents or platelet aggregation inhibitors, as well as natural proteins involved in both coagulation and inflammation, have marked antimicrobial properties. As such, they represent viable candidates for use in STP, in which thrombosis accompanies an acute infection.

The direct thrombin inhibitor dabigatran successfully inhibited staphylococcal coagulase and was clinically safe in a randomized clinical trial in humans with staphylococcal sepsis.[71] This study suggested that direct thrombin inhibitors are at least as safe as standard thromboprophylaxis with LMWH in patients with a severe infection, and provides a rationale to test the efficacy of these agents in preventing thrombus extension and septic embolization of staphylococcal STP. After clinical observations that platelet aggregation inhibitors seemed to improve survival and inflammatory biomarkers during infection,[72,73] a recent study on mice has shown that ticagrelor may indeed have antimicrobial properties against several gram-negative bacteria, including multiresistant strains, and even display synergistic activity with several commonly used antibiotics.[74]

Similar properties are increasingly reported in several natural proteins. The hßAT isoform of antithrombin has displayed marked antibacterial properties in mice, and is depleted in the plasma of patients with severe infectious diseases.[75] These findings may lead to a resurgence in the clinical application of antithrombin. In addition, in a study prompted by a previous incidental finding, the light chains of coagulation factors VII, IX, and X exhibited in vitro antibacterial activity against several gram-negative bacteria, including extensively drug-resistant pathogens.[76]

Targeting Sepsis and Inflammation

As sepsis and inflammation are key pathophysiological mechanisms in STP, nonanticoagulant agents that primarily act on the molecular pathways shared by sepsis, inflammation, and thrombosis may be able to modify the course of STP by either preventing thrombus formation or promoting its dissolution.

Because of the role of NETs in the development of thrombosis during sepsis, agents that prevent their formation are being explored as therapeutic options. An example of this approach is blockade of either complement factor C5a or its receptors C5aR1 and C5aR2 on neutrophils. However, complement activation seems to be more specific to infection by gram-negative than gram-positive bacteria, and some gram-positive bacteria, such as *S. aureus*, are able to inhibit it.[17] An alternative is pharmacologically targeting cytokines that sustain NET formation with pathways different from complement activation. Experimental blockade of interleukins IFNγ, IL-17, IL-1β, and IL-9 reduces formation of venous thrombi in animal models.[77] Recently, agonism of the adenosine A2A receptor has been shown to reduce the generation of NET and venous thrombosis mediated by antiphospholipid antibodies.[78] This finding may be especially relevant to STP because of the evidence on the association between infection, antiphospholipid antibodies, and thrombosis.[19]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may increase the clearance of bacterial endotoxin during sepsis; at the same time, studies on knockout mice suggest that blocking PCSK9 may reduce activity against venous thrombosis.[79] However, an animal study showed that neither anti-PCSK9 antibodies nor germ-line deletion of *pcsk9* improved mortality in mice exposed to endotoxins,[80] and observational analyses have shown the relationship between endotoxin-associated inflammation and PCSK9 in humans to be complex.[81] More evidence is needed before a therapeutic role for PCSK9 inhibitors in STP is considered.

Thrombus dissolution is also increasingly considered as a treatment strategy. The role of circulating inflammatory cytokines in the remodeling and resolution of venous thrombi is well established; IL-2 seems to be the most viable for testing in humans, as it is already used for other indications and is considered safe.[77,82] Noncirculating molecules may also provide targets: a recent study showed that blockage of endothelin receptors prevents TGFβ1-mediated thrombofibrosis and improves venous thrombus resolution in murine pulmonary circulation. This finding may be relevant to STP to the extent this pathway is involved in the endothelial dysfunction caused by a localized infection or sepsis.[83] Finally, as NETs are responsible not only for thrombus formation, but also for thrombus stability, thrombus dissolution by direct targeting of NETs via DNAses has been preliminarily tested in vitro and ex vivo.[84]

Time capsule

We hope that

- In the next 30 years, international registries will provide accurate data on the incidence trends and the case fatality rate of septic thrombophlebitis.
- Microbiologists will be able to identify individual pathogens with high thrombogenic potential and notify the clinician upon their isolation, prompting a screening for septic thrombophlebitis in patients with refractory infection.
- In addition to anticoagulants and antibiotics, natural or synthetic compounds will provide innovative treatments that combine antimicrobial or anti-inflammatory activity with the modulation of coagulation and platelet aggregation.
- Specific guidelines will guide the indication, agent choice and duration of anticoagulant and antibiotic treatment for septic thrombophlebitis of dural sinuses, jugular vein, and portal and pelvic veins.

Authors

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Conflict of Interest

The authors declare, that they have no conflict of interest.

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