

Editorial Focus

Thromboembolic complications of sepsis: What is the incidence and pathophysiological mechanisms involved?

Michal Holub

3rd Department of Infectious and Tropical Diseases, First Faculty of Medicine, Charles University in Prague, Czech Republic

The original article published in this issue of *Thrombosis and Haemostasis* by Levin et al. (1) presents a retrospective analysis of a pooled database of three placebo-controlled clinical trials with two novel antithrombotic drugs for the treatment of severe sepsis and septic shock, in which 3.2% incidence of venous and arterial thrombosis was reported. The authors evaluated data from 2,649 patients enrolled in the drug trials strongly supporting their findings. However, there are some potential concerns regarding the study design that should be further discussed.

The incidence of thromboembolic (TE) disease reported in critically ill patients (i.e. patients with sepsis, major trauma or surgery) ranging between 9.6 and 33% is much higher than 3.2% detected in the Levin's et al. retrospective analysis (2, 3). Moreover, a higher incidence of TE disease (15.5%) was previously found even in the patients who received antithrombotic prophylaxis (4). The Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial with a novel antithrombotic and anti-inflammatory drug drotrecogin alpha (recombinant human activated protein C – rhAPC) was one of the studies analyzed by the authors. This drug demonstrated a beneficial effect in severe sepsis significantly improving its survival (5). It is worth noting that rhAPC has strong antithrombotic, fibrinolytic and anti-inflammatory effects, which reduce a risk of TE disease development. Also, a relatively high percentage of patients enrolled in the PROWESS trial received TE prophylaxis – 60.4% in the treatment arm versus 64.3% in the control group. Therefore, it is not surprising that the incidence of TE disease in both groups of subjects enrolled in the PROWESS trial was much lower than that demonstrated in previous studies.

It has been widely accepted that sepsis is associated with hyperinflammation and procoagulant responses, which are closely linked. Systemic inflammation elicited during an early stage of sepsis is associated with activation of many physiological responses including the coagulation pathway and the innate immunity. Proinflammatory cytokines such as tumor necrosis factor α and interleukin (IL)-1 β induce expression of tissue factor

(TF) on endothelial cells and monocytes leading to coagulation factor IX and X activation and subsequent thrombin production (6). Similarly, IL-6, which is usually intensively produced during the course of sepsis, increases synthesis of fibrinogen, factor VIII as well as plasminogen activator inhibitor 1 (PAI-1). On the other hand, synthesis of important factors with anticoagulant activity such as antithrombin, protein C and protein S is attenuated in septic patients (7). Also, TF pathway inhibitor (TFPI) that may play a positive role during an early stage of sepsis by downregulation of endothelial cells adhesiveness is decreased. In addition, PAI-1 released in higher amounts during an initial stage of sepsis attenuates fibrinolysis leading to further enhancement of sepsis-associated procoagulation status.

The aforementioned pathophysiological changes in the coagulation and fibrinolysis, together with presence of other risk factors such as hypotension reduced tissue perfusion, decreased blood flow, mechanical ventilation, insertion of central venous catheters, use of vasopressors etc., create an important prerequisite for TE disease development in critically ill septic patients. High incidence of TE disease in patients with severe sepsis and septic shock has been also reflected in the recommendations listed in the Surviving Sepsis Campaign Guidelines (8). According to the guidelines, severe sepsis and septic shock should be managed either with a low dose of unfractionated heparin or low-molecular-weight heparin (LMWH) given subcutaneously. This recommendation received a very strong rating as 1A evidence. Furthermore, patients with a high risk of TE disease should have pharmacological as well as mechanical prophylaxis. The guidelines of the 7th ACCP Conference also suggest antithrombotic prophylaxis in a majority of intensive care unit (ICU) patients (1A evidence) (9).

Failure of pharmacological prophylaxis of TE disease is not uncommon, especially in patients with severe sepsis and septic shock. The effectiveness of TE disease prophylaxis can be diminished by decrease of peripheral perfusion, subcutaneous edema and use of catecholamines. In accordance with this a reduced factor Xa activity, which is used for LMWH treatment and

Correspondence to:
Michal Holub, MD, PhD
Department of Infectious Diseases
University Hospital Bulovka
Budínova 2, Praha 8, CZ-180 81, Czech Republic
Tel.: +420 26608 2472, Fax: +420 26608 2717
E-mail: michal.holub@lfl.cuni.cz

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prophylaxis monitoring, was demonstrated in ICU patients (10). There are also some potential risks associated with TE disease prophylaxis: thrombocytopenia (especially heparin-induced), severe bleeding after trauma and surgery as well as increased incidence of haemorrhagic complications in septic patients with renal failure receiving LMWH prophylaxis (LMWH is mainly excreted by the kidney). Thus, careful factor Xa monitoring should be provided in patients with creatinine clearance below 30 ml/min.

Despite the low incidence of TE disease reported by Levine et al. the study design enabled to define TE disease in septic patients, whose acute coronary syndromes could be questionable (i.e. ischemic chest pain and elevation of cardiac enzymes but no ST elevation). High levels of cardiac troponins have been detected in many critically ill adult patients, and a number of studies have suggested a possible association between elevated serum troponins and non-cardiac diseases including severe sepsis and septic shock (11). There are also several pediatric studies showing a similar link between cardiac impairment during sepsis and high serum troponin levels (12). Possible reasons for an increased troponin release during sepsis include high oxygen consumption, bacterial myocarditis as well as reduced oxygen delivery to the cardiac muscle, which may be caused by hypotension, shock and inotropic agents.

A similar concern deals with the criteria of ischemic stroke used by the authors, because the case definition was based only on clinical diagnosis and absence of intracranial haemorrhage ruled out by brain imaging with non-contrast computed tomography scanning. In fact, alteration of mental status can be found in up to 70% patients with sepsis. Post-mortem examinations of many septic patients reveal ischemia, haemorrhage, micro-abscesses and focal necrotizing leukoencephalopathy. Potential mechanisms of sepsis-associated encephalopathy mainly include blood-brain barrier breakdown as well as neuronal damage caused by metabolic and pro-inflammatory mediators. In the study by Sharshar et al. (13), which employed magnetic resonance imaging and post-mortem microscopic examination of the brain of septic patients, no characteristic ischemic lesions were observed. The findings were rather compatible with vasogenic brain edema and blood-brain barrier breakdown.

In conclusion, the thromboembolic complications seriously worsen the outcome of sepsis, and thus draw a lot of attention. Despite a very wide range of reported incidence of TE disease (3.2–33%) in critically ill septic patients, its clinical importance is undoubted. Therefore, TE prevention should be properly managed with pharmacological and if required also with mechanical prophylaxis.

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