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CLINICAL REVIEW

Sepsis, severe sepsis, and septic shock: A review of the literature

Septicémie, septicémie grave et choc septique: étude bibliographique

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Sepsis represents a continuum of illness due to systemic inflammation caused by an infection that requires prompt recognition and treatment. While sepsis is a significant cause of death worldwide, its mortality is believed to be disproportionately high in low- and middle-income countries (LMICs). Since 1992, its definition has become standardized, and beginning in 2002, an international collaboration has produced a set of consensus guidelines on the optimal management of septic patients. Based on new evidence, significant updates have been made since then. It is known that application of a bundled approach to patient care with the use of specific resuscitation endpoints to guide therapy leads to significant reductions in mortality from sepsis. However, it is also recognized that the implementation of such interventions in LMICs is extremely challenging. Consequently, a body of literature on practical guidelines for sepsis in developing countries has emerged. This article provides a review of the evidence for the best practice of sepsis management, with recommendations for resource-limited settings.

La septicémie représente un éventail de maladies dues à une inflammation systémique provoquée par une infection qui nécessite une identification et un traitement rapide. Si la septicémie est une cause de décès importante dans le monde, la mortalité associée est considérée comme disproportionnellement élevée dans les pays à faible et moyen revenus. Depuis 1992, sa définition s'est standardisée, et à partir de 2002, une collaboration internationale a produit un ensemble de lignes directrices consensuelles sur la prise en charge optimale des patients souffrant de septicémie. Sur la base de nouvelles données factuelles, des mises à jour d'envergure y ont depuis été apportées. On sait que l'application d'une approche globale à la prise en charge des patients, combinée au recours à des critères de réanimation visant à guider la thérapie, permet d'obtenir une réduction significative de la mortalité liée à la septicémie. Il est cependant également reconnu que la mise en œuvre de telles interventions dans les pays à faible et moyen revenu est extrêmement difficile. Par conséquent, un certain nombre de publications sur les directives pratiques relatives à la prise en charge de la septicémie dans les pays en voie de développement sont apparues. Cet article propose un examen des éléments probants sur une meilleure pratique de la gestion de la septicémie, ainsi que des recommandations pour les milieux à ressources limitées.

African relevance

- Sepsis has an especially high mortality in Africa.
- Rapid recognition of sepsis and a protocoled approach to management save lives.
- Tailored recommendations for resource-limited settings offer a practical approach to sepsis care.

Introduction

In 1992, "sepsis" was formally defined as the presence of both suspected infection and two of the four criteria of the systemic inflammatory response syndrome (SIRS) (Tables 1 and 2).[1,2] Since then, additional terminology has emerged. Sepsis complicated by organ dysfunction is referred to as "severe sepsis," while sepsis complicated by hypotension refractory to adequate volume resuscitation in the absence of an alternate cause has been termed "septic shock".[1] The clinical significance of the sepsis spectrum of illness cannot be understated. In the US alone, the incidence of severe sepsis is over 700,000 annually with an estimated 30% mortality.[3] This is estimated to represent over 450,000 emergency centre (EC) visits per year.[4] While some research has been devoted to the study of sepsis in developing countries, its epidemiology in these countries remains poorly described.[5,6] Despite this, the morbidity and mortality of sepsis in low- and middle-income countries (LMICs) are believed to be disproportionately high, given environmental degradation, widespread malnutrition, and higher rates of bacterial, parasitic, and HIV infection.[6,7] In an effort to reduce the risk of death from sepsis, the Surviving Sepsis Campaign (SSC) was initiated in 2002 from the collaboration of the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SSCM). In 2004, the SSC

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Table 1 SIRS criteria.[1]

Presence of two or more of the following.	
1. Temperature	• > 38 °C (100.4 °F) or • < 36 °C (96.8 °F)
2. Heart rate	• > 90/min
3. Respiratory rate	• > 20/min or • $PaCO_2$ < 32 mmHg
4. White blood cell count	• > 12,000/μL or • < 4000/μL

Table 2 Diagnostic criteria for sepsis.[1] WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial pressure. Table adapted from Levy et al. (2003).[1]

Infection (documented or suspected) and some of the following.	
Classification	Variables
General	Fever (> 38.3 °C) Hypothermia (core temperature < 36 °C) Heart rate > 90/min or more than two SD above the normal value for age Tachypnea Altered mental status Significant oedema or positive fluid balance Hyperglycaemia
Inflammatory	Leukocytosis Leukopenia Normal WBC count with greater than 10% bands Plasma C-reactive protein > 2 SD above the normal value Plasma procalcitonin > 2 SD above the normal value
Hemodynamic	Hypotension (SBP < 90 mmHg, MAP < 70 mmHg, or an SBP decrease > 40 mmHg in adults or < 2 SD below normal for age)
Organ dysfunction	Creatinine increase Coagulopathy Hypoxaemia Ileus Oliguria Thrombocytopenia Hyperbilirubinemia
Tissue perfusion	Hyperlactatemia Decreased capillary refill or mottling

produced the "Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock," one of the most recognized consensus statements regarding the treatment of sepsis (most recently updated in 2012).[8] In many countries, it is held to be the standard of care.[7] As 50% of hospital admissions occur through the ED, there is a significant opportunity to improve outcomes.[9] This review will discuss the epidemiology, pathophysiology, and diagnostic and therapeutic approach to patients with sepsis, severe sepsis, and septic shock in the ED and other acute care settings. It is important to note that as international guidelines focus on the evaluation and management of patients with severe sepsis and septic shock (SS/SS) as opposed to sepsis without evidence of SS/SS, this article will primarily discuss SS/SS. A particular focus will be on providing care in resource-limited settings with tailored recommendations. Of note, this review pertains specifically to adults and not to children. See Tables 1 and 2 for definitions.

Epidemiology

Despite the documented impact of sepsis in developed countries, literature on its incidence, prevalence, and mortality in developing countries is sparse.[10] What is recognized, however, is that the global burden of sepsis lies in LMICs. As a surrogate marker for sepsis, over 90% of worldwide deaths due to pneumonia, meningitis, and other infections occur in less developed nations.[6,11] Globally, an estimated 70% of the 9 million annual neonatal and infant deaths are attributable to sepsis, and more than half of these occur in Asia and Sub-Saharan Africa.[11,12]

Pathophysiology

During infection, offending microbes interact with the host immune system producing a downstream inflammatory cascade involving cytokines and other mediators, which in turn triggers a systemic response. The resultant effects include vasodilation, increased vascular permeability, myocardial depression, and impairment of the coagulation cascade, resulting in global imbalance of systemic oxygen supply and demand, and a procoagulant state. During the late stage of sepsis, immunosuppression predominates, leading to multiorgan dysfunction and further clinical deterioration.[13]

Clinical assessment

During history taking, the focus should be on detecting risk factors for infection (such as immunosuppression), the presence of infection, and if suspected, the most likely sources. Caution should be advised in geriatric patients, as they may not be able to communicate traditional symptoms (e.g., dysuria in occult urinary tract infections). The physical examination should be used to identify possible foci of source control. A critical action at this point is the measurement, documentation, and evaluation of vital signs, including temperature, blood pressure (BP), heart rate (HR), respiratory rate (RR) and oxygen saturation (if below 90% then supplemental oxygen should be immediately applied). Repeated recording of these parameters will be used to gauge clinical improvement or deterioration and trigger specific interventions (see below). Consistently analysing the vital signs for the presence of SIRS criteria in any possible patient with sepsis will aid in the early recognition of critical illness.

Importantly, vital sign derangements may be absent early on and in elderly patients.[14,15] Specific physical exam findings that are predictive of sources of infection include indwelling devices (e.g., intravascular or urinary catheters), rales, abdominal tenderness, and evidence of CNS infection.[16,17] A cardiovascular and volume status assessment, including auscultation, mucous membranes, skin colour and turgor, peripheral pulses, capillary refill and oedema should be undertaken at this stage as well.