Global Alliance for Infections in Surgery

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World Sepsis Day
13 September, 2019

The global burden of sepsis

The management of sepsis from a global perspective

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What is sepsis

Sepsis represents the host's systemic inflammatory response to intra-abdominal infections. Sepsis is a dynamic process that can evolve into conditions of varying severity. The inflammatory response in patients with sepsis depends on the causative pathogen and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels. If left untreated, it may lead to the functional impairment of one or more vital organs or systems. It was previously defined that severity of illness and the inherent mortality risk escalate from sepsis, through severe sepsis and septic shock up multi-organ failure. However, differences the in spectrum of etiology and patient factors, including age and co-morbidities, makes the course of sepsis different from patient to patient. HIV patients, common in Sub-Saharan Africa, have an increased risk to develop sepsis due to the HIV infection itself that affects several components of the immune system involved in sepsis pathogenesis. HIV causes increased susceptibility to invasive infections and affects sepsis pathogenesis caused by pre-existing activation and exhaustion of the immune system and even if HIV-infected patients on antiretroviral therapy can now safely undergo major abdominal surgery with encouraging results, they are still relatively poorer than those of HIV-negative subjects.

Several studies demonstrated that sepsis-related mortality reduced steadily over the years. A meta-analysis reported a reduction of sepsis 28-day mortality rates from 46.9% during the period 1991–1995 to 29% during 2006–2009. In the US, mortality due to severe sepsis decreased by 51% from 1988 to 2012. In Australia and New Zealand an overall decrease of 16.7% in hospital sepsis mortality was reported between 2000 and 2012 (from 35% to 18.4%). However, high mortality rates are still reported in low and middle-income countries (LMIC).

Despite decades of sepsis research, no specific therapies for sepsis have emerged. Without specific therapies, management is based on control of the infection and organ support.

Early antibiotics, source control and fluid resuscitation support of vital organ function are the cornerstones for the treatment of patients with sepsis.

Sepsis-3 definitions

Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has recently been published, and updated previous classifications. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. Septic shock should be defined as a subset of sepsis and should be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. The definition of severe sepsis is now superfluous. The new definition of sepsis suggests that patients with at least 2 of these 3 clinical variables: Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mmHg or less, and respiratory rate 22/min or greater (quick SOFA - qSOFA) may be prone to a poor outcome typical of sepsis and patients with positive qSOFA should be clinically characterized as septic by SOFA score.

Some concerns about the new definition of sepsis have been reported.

Since the first classification in 1991, the definitions of sepsis, severe sepsis, and septic shock, though imprecise, have provided to clinicians a useful framework for clinical management, stressing the need for early recognition. The new definition of sepsis requiring the presence of organ failure has lost its predictive potential and may hinder the awareness of the importance of early recognition and treatment of sepsis, de-emphasizing intervention at earlier stages when it is most treatable and leading to a higher risk of delayed diagnosis.

The Sepsis-3 definitions recommend using an increase in the SOFA score of 2 or more points to represent organ dysfunction. The SOFA score is intended to be used in ICU and, to a lesser extent the ED. Outside the ICU, SOFA was found only as good as the previous SIRS criteria (AUROC=0.79 vs. AUROC= 0.76). Moreover, it is a valuable predictor of unfavourable outcome. The SOFA score was proposed in 1996 by the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine to objectively describe the degree of organ dysfunction over time and to evaluate morbidity in patients in the ICU with sepsis. It was demonstrated to be a good indicator of prognosis in critically ill patients during the first few days of ICU admission. The use of the SOFA score in research is commonly performed and constitutes a routine component of data collection for clinical trials in ICUs. However, the SOFA score is not universally accessible, especially for PaO2, which would require an arterial blood gas measurement. Sepsis-3 definition introduces Quick SOFA (qSOFA) as a tool for identifying patients at risk of sepsis with a higher risk of hospital death both inside and outside critical care units.

An important limitation of the new definitions is the poor sensitivity of the qSOFA scoring system. This leads to a high number of false negatives and, subsequently, to a delayed diagnosis in many patients, which likely excludes its use as a screening tool for early sepsis, the stage in which treatment is most effective. Sepsis requires urgent recognition because delayed treatment increases mortality. To optimize the timing of therapy, a screening test should be as sensitive as possible. Thus, it is preferable to have a more sensitive test with lower false negative results in order to not miss cases of serious sepsis.

Clinicians should keep in mind the difference between a screening tool and a risk-stratification tool. A screening tool aims to identify patients with a particular disease from a larger pool of patients. Once these patients are identified, a risk-stratification tool can be applied to determine their likelihood of meeting a particular outcome.

Finally, although some patients with ongoing sepsis may not have elevated lactate levels at presentation or during their clinical course, lactate measurement is advised as an important component of the initial evaluation of patients with sepsis. Elevated lactate levels (even if > 4 mmol/l) are no longer part of organ dysfunction criteria to define sepsis. According to the new definition of sepsis, high lactate levels should be used only as one of the criteria to define septic shock.

In the new definition of septic shock hyperlactatemia is a required component for septic shock, differently from Sepsis-1 and Sepsis-2 definitions in which just the presence of refractory hypotension to fluid loading was considered shock. Therefore, when lactate measurements are not available, the diagnosis of septic shock can be more challenging and patients with potential shock will be considered as having only sepsis.

The new definitions are based on a retrospective evaluation of large hospital databases from two countries (the United States and Germany). The majority of sources of infection were hospital patients in referral centres with respiratory and postoperative infections. The target reader is an intensive care unit (ICU) physician.

Although these definitions are of help for research purposes, they may not be representative of the wider clinical community Major international differences exist in the prevalence of infections, types of infecting microorganisms, and mortality rates. EPIC II demonstrated significant differences in Eastern Europe as compared to Western Europe, in Australasia as compared to Asia, and in Latin America as compared to North America.

Early recognition of sepsis is a general principle of sepsis management and is very important in LMICs where the priorities for improving the quality of care for critically ill patients are different. Documenting the burden of critical illness in low-resource settings is challenging. In these settings, a triage system that quickly recognizes critically ill patients and transfers them immediately to an acute care unit is a vital component of the emergency services. The most important challenges in the management of sepsis in these areas are triage and pre-hospital diagnosis. It should be done by very sensitive and non-invasive methods outside the hospital setting.

As a consequence, any process of improving quality of sepsis care globally should focus on simple diagnostic criteria based on physical examination findings that can recognize patients needing critical care. In these settings, a feasible, low-cost method of rapidly identifying patients requiring critical care is crucial. Early warning system scores utilize physiological, easy-to-measure parameters, assessing physiological parameters such as systolic blood pressure, pulse rate, respiratory rate, temperature, oxygen saturations and level of consciousness. They are simple, non-invasive and easy-to-repeat measurement bedside tools. Large multi-centre trials will be needed to explore if these findings can be shared all over the world.

The management of sepsis

The data from WISS study showed that mortality in patients with intra-abdominal infections was significantly affected by sepsis – mortality by sepsis status was: no sepsis 1.2%, sepsis only 4.4%, severe sepsis 27.8% and septic shock 67.8%.

Identifying patients with ongoing sepsis early and correcting the underlying microvascular dysfunction may improve patient outcomes. If not corrected, microvascular dysfunction can lead to global tissue hypoxia, direct tissue damage, and ultimately, organ failure.

Fluid therapy to improve microvascular blood flow and increase cardiac output is an essential part of the treatment of patients with sepsis. Crystalloid solutions should be the first choice, because they are well tolerated and cheap. They should be infused rapidly to induce a quick response but not so fast that an artificial stress response develops. They should be interrupted when no improvement of tissue perfusion occurs in response to volume loading. Basal lung crepitations may indicate fluid overload or impaired cardiac function. Recently, measuring IVC diameter by ultrasound was suggested as a novel outcome measure to guide this resuscitative approach.

The Surviving Sepsis Campaign (SSC) is a joint collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine committed to reducing mortality from severe sepsis and septic shock worldwide in 2002. SSC guidelines have been regarded as the standard of care in patients with severe sepsis and septic shock in many hospitals worldwide. However, the possibility to implement the SSC guidelines has been questioned in LMICs where simple and low-cost standardised laboratory testing should be emphasised to allow accurate diagnosis, prognosis, and monitoring of treatment response. A study conducted as an anonymous questionnaire-based, cross-sectional survey among anaesthesia providers, suggested that SSC guidelines cannot be implemented in Africa, particularly in Sub-Sahara Africa, due to a shortage of required hospital facilities, equipment, drugs and disposable materials.

In 2016 Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock were updated. Previous iterations of these guidelines aimed to treat the early hypovolemic phase of sepsis by providing appropriate high volume resuscitation targeting: central venous pressure 8 to 12 mm Hg, mean arterial pressure (MAP) >65 mm Hg, urine output >0.5 mL/kg/hr, central venous (superior vena cava) or mixed venous oxygen saturation >70% or >65%, respectively. Since the first draft of guidelines the basic concept of the initial resuscitation has been early-goal-directed-therapy (EGDT) described by Rivers in 2001, who reported that patients with severe sepsis and septic shock presenting to the emergency department had a lower mortality rate, if they received a specific 6 h resuscitation bundle of EGDT. Three randomized controlled trials (ProCESS, ARISE, and ProMISe trials) results have questioned River's resuscitation protocol results demonstrating that use of early goal-directed therapy for patients presenting to the emergency department with early septic shock did not reduce mortality compared with usual care.

These data indicate that an early identification and prompt administration of intravenous fluids are mandatory. However, initial resuscitation should no longer be based on a predetermined protocol but on clinical endpoints.

Hypotension is the most common indicator of inadequate perfusion. The SSC advocated a MAP goal of 65 mm Hg during the first 6 hours of treatment. It was confirmed by a randomized controlled trial "Sepsis and Mean Arterial Pressure" (SEPSISPAM) examining high versus low MAP goals in patients with septic shock. It demonstrated that targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. Particularly in patients with abdominal sepsis, requiring urgent surgical intervention, overly aggressive fluid resuscitation may increase intra-abdominal pressure and worsen the inflammatory response, which is associated with a high risk of complications. In patients with septic shock fluid infusion during resuscitation, bowel oedema and forced closure of the abdominal wall can cause intra-abdominal hypertension and abdominal compartment syndrome that can consequently modify pulmonary, cardiovascular, renal, splanchnic, and central nervous system physiology causing significant morbidity and mortality.

Clinical endpoints in monitoring fluid volume infusions should include mean arterial pressure, skin colour and capillary refill, mental status, or urinary output. Central venous access, where available, may be helpful for monitoring of central venous pressure. Simpler non-invasive devices such as tissue perfusion monitors may be more practical but are not yet widely used. Repeated measurements of IVC diameter by ultrasound can be a simple and useful method for defining fluid requirements.

Vasopressor agents should be administered to restore organ perfusion if fluid resuscitation fails optimizing blood flow and if hypotension persists following fluid loading. These agents should be globally available. Vasopressor and inotropic agents have increasingly become a therapeutic cornerstone for the management of sepsis. They have excitatory and inhibitory actions on the heart and vascular smooth muscle, as well as important metabolic, central nervous system, and presynaptic autonomic nervous system effects. The optimal timing of vasopressors relative to fluid infusion has been debated. A large multi-center retrospective analysis of 2,849 patients with septic shock, investigators found that mortality was lowest when vasopressors were delayed by 1 hour and infused from hours 1 to 6 following onset of shock. Norepinephrine is now the first-line vasopressor agent used to correct hypotension in the event of septic shock. Norepinephrine is more efficacious than dopamine and may be more effective for reversing hypotension in patients with septic shock. Dopamine may cause more tachycardia and may be more arrhythmogenic than norepinephrine, and as an alternative vasopressor agent to norepinephrine, it should be used only in patients with low risk of tachyarrhythmias and absolute or relative bradycardia.

Dobutamine is an inotropic agent used to treat septic shock patients increasing cardiac output, stroke index, and oxygen delivery (DO2). It has been suggested to be administered to pre-existing vasopressor therapy in the presence of myocardial dysfunction, defined as elevated cardiac filling pressures and low cardiac output. However, dobutamine increases DO2 to supranormal values and in critically ill patients it has raised serious questions regarding its safety in the treatment of septic shock. Because dobutamine provides direct stimulation of the β-1 adrenergic receptors, it is recognized as more problematic with regard to tachycardia and arrhythmia.

In LMICs it may be acceptable to use adrenaline infusions as the inotrope of choice, given it is readily available, cheap and has been shown to be equivalent to noradrenaline in septic shock.

Increased global availability of vasopressors together with a better understanding of their indications, pharmacodynamics and important adverse effects are mandatory to fight sepsis worldwide. Sepsis is a burden for global health. Its global nature calls for a global response, both in the geographic sense and across the whole range of sectors involved. There is urgent need to implement global strategies to monitor sepsis morbidity and mortality from a global perspective.

On Friday, May 26th, 2017, the World Health Assembly and the World Health Organization made sepsis a global health priority, by adopting a resolution to improve, prevent, diagnose, and manage sepsis adopting sepsis as a global priority.

The Global Alliance for Infections in Surgery joins the global declaration and its goals.

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