PRIMEVIEW

SEPSIS AND SEPTIC SHOCK

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For the Primer, visit doi:10.1038/nrdp.2016.45

Sepsis has historically been difficult to define clinically. The condition is characterized by a dysregulated systemic inflammatory and immune response to infection that produces organ injury. Septic shock is characterized by persistent hypotension and substantially increases the risk of death.

EPIDEMIOLOGY

Estimating the burden of sepsis is complicated by the heterogeneous presentation of patients, controversy in clinical definitions, varying levels of awareness of sepsis as well as different coding systems for sepsis in hospital databases. An estimate in high-income countries suggests that 31.5 million cases of sepsis occur annually, with potentially 5.3 million deaths. Data are scant on incidence and mortality in low-income and middle-income countries.

DIAGNOSIS

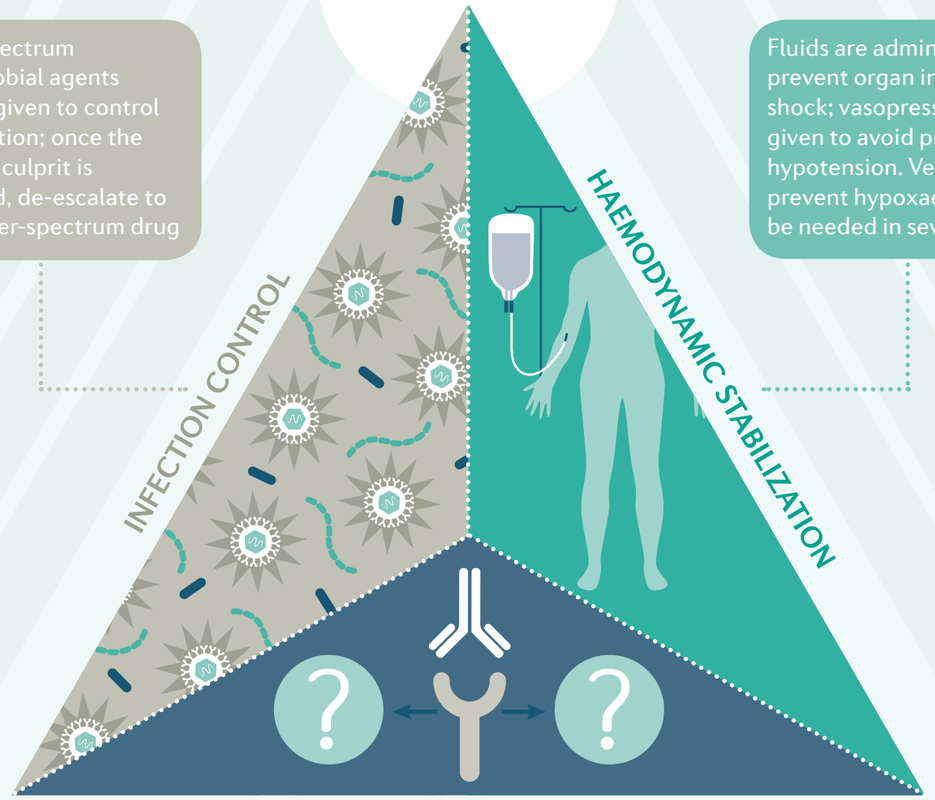
The symptoms of sepsis are variable and include mental alterations and difficulty breathing. Although infection is the precipitating event in sepsis, a causative pathogen is not identified in every patient. Rapid bedside assessment of early organ dysfunction is crucial to facilitate the diagnosis of sepsis. Septic shock is characterized by severe hypotension (which requires vasopressor therapy to maintain a mean arterial blood pressure of >65 mmHg) that is associated with an increased plasma lactate level of >2 mmol per l.

MANAGEMENT

Treatment of sepsis needs to be early and aggressive, and has three main components

Broad-spectrum antimicrobial agents must be given to control the infection; once the infective culprit is identified, de-escalate to a narrower-spectrum drug

Fluids are administered to prevent organ injury and shock; vasopressors are given to avoid prolonged hypotension. Ventilation to prevent hypoxaemia might be needed in severe cases.



MODULATION OF THE SEPTIC RESPONSE

Many biological agents to modify the early septic response have been assessed; these include antibodies that target various components of the signalling cascades in sepsis. However, none has proven effective to date, although several are still in trials.

PREVENTION

Given that hospitalized patients are at high risk of developing sepsis, clean care and minimization of invasive procedures are effective preventive strategies. Hospitals should implement early warning systems that evaluate haemodynamics, urine output, body temperature and mental function in critically ill patients to prevent sepsis and its progression to septic shock and multiple organ failure.

However, a considerable number of patients develop sepsis outside of the hospital setting. In this regard, vaccination to reduce the burden of infectious disease can reduce the risk of sepsis.

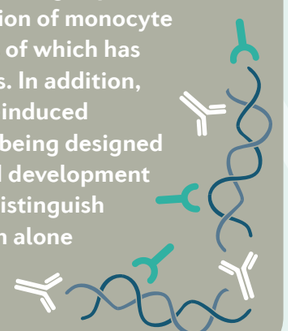
MECHANISMS

Sepsis is a complex process that is not fully understood, although two broad phases have been described: an inflammatory burst and immune suppression. The inflammatory burst involves simultaneous recognition of infection-derived microbial products and endogenous danger signals that trigger multiple converging signalling cascades, leading to the expression of genes encoding various inflammatory chemokines and cytokines. Complement activation leads to vasodilation, tissue damage and multiple organ failure. If patients survive this phase, they can go on to exhibit chronic suppression of both the innate and the adaptive immune systems in spite of ongoing inflammation. This phase of sepsis is characterized by profound leukocyte apoptosis.

! Endothelial barrier dysfunction occurs early in sepsis and septic shock in particular, leading to hypotension and oedema

OUTLOOK

Defining the immunological state of the patient with sepsis or septic shock is of particular interest to better understand the syndrome, as well as to design and assess immunotherapies. Indeed, immunophenotyping of patients with sepsis is being explored and includes quantification of monocyte HLA-DR expression, loss of which has been implicated in sepsis. In addition, drugs to reverse sep–sis-induced immunosuppression are being designed and assessed. Continued development of biomarkers that can distinguish sepsis from inflammation alone also remains an area of active investigation.



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Article number: 16046; doi:10.1038/nrdp.2016.46; published online 30 June 2016