

Sepsis

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Introduction

Sepsis has become an increasingly important clinical problem in recent years. Paradoxically this has been the result of advances in medical practice and medical technology. The increasing use of invasive equipment, immunosuppressive agents and prosthetic implants have succeeded in prolonging lives but have at the same time created a large population of patients who are also particularly susceptible to infection.

Incidence and definitions

The incidence of septicaemia in the United States has been reported to have increased from 73.6 cases to 175.9 cases per 100,000 population from 1979 to 1987¹. Over half a million new episodes of sepsis and septic shock are reported in the United States each year with an associated crude mortality of 35%². There are marked differences in the incidence of sepsis from hospital to hospital and from country to country because of the lack of a uniform system of definition of disorders related to sepsis.

A system of definition of the spectrum of disorders associated with sepsis has been proposed by Bone³. Table I shows the definitions of these disorders. It should however be stressed that sepsis, sepsis syndrome and septic shock are not discrete entities but delineate increasing severity of the same pathophysiological process. A similar classification of sepsis has also been proposed by the American College of Chest Physicians/Society of Critical Medicine. An initial systemic inflammatory response syndrome (SIRS) as well as three hierarchical stages namely, sepsis, severe sepsis and septic shock have been defined (Table II)⁴.

Pathophysiology of sepsis

The manifestations of septic shock and the development of multi-organ failure (MOF) are due

largely to the pathophysiological effects of cytokines which are released as part of the host immune response⁵. Although the host immune response and the release of cytokines are primarily for the protection against microbes, uncontrolled release of these cytokines can have marked deleterious effects on the body. Sepsis has been described as the immune system gone haywire.

Cytokines are low molecular peptides that act as intercellular signals. Cytokines have a wide range of cellular action and act either in an autocrine or paracrine fashion. The cytokines include the interleukins, interferons, colony stimulating factors, tumour necrosis factor and various growth factors. The cytokines which are important in sepsis include tumour necrosis factor, IL1, IL6, IL8 and platelet-activating factor. Both infection and injury can activate the cytokine cascade as well as the complement coagulation and fibrinolytic systems of the body. This results in shock, disseminated intravascular coagulation and fibrinolysis which are the classical manifestations of sepsis. Shock develops in about 40% of septic patients.

Cellular components of microbes, in particular, the lipopolysaccharide (LPS) of bacterial endotoxin can stimulate phagocytes, endothelial cells and other cells. In macrophages LPS binds to a surface receptor, CD14 and this binding leads to activation of the cell. Activation of the cell results in increased protein tyrosine phosphorylation. One of the targets of this phosphorylation is a protein named p38. Blocking p38 activity results in a marked reduction of IL-1 and TNF. Research into such receptor-dependent mechanisms may reveal novel strategies for the management of sepsis.

Neutrophil activation which results from the action of cytokines is believed to be an important factor in the pathogenetic mechanism⁶. Activated neutrophils tend to form aggregates and become more adherent to

Table I
Definitions of disorders related to Sepsis

Disorder	Definition
Bacteremia	Positive blood cultures (The term septicaemia is imprecise and should be abandoned)
Sepsis	Clinical evidence suggestive of infection plus signs of a systemic response to infection (all of the following): Tachypnea (respiration > 20/min (if patient mechanically ventilated > 10 L/min) Tachycardia (Heart rate > 90/min) Hyperthermia or hypothermia (core or rectal temperature > 38.4°C (101 F) or < 35.6°C (96.1F)
Sepsis syndrome	Clinical diagnosis of sepsis plus evidence of altered organ perfusion (one or more of the following): PaO ₂ < 75 mm Hg on room air in the absence of pulmonary or cardiovascular disease Lactate above upper limit of normal Oliguria (< 30 ml/hr or 0.5 ml/kg/hr) Alteration in mental status Positive blood cultures are not required
Early septic shock	Clinical evidence of sepsis syndrome plus hypotension (systolic BP < 90 mm Hg or 40 mm Hg decrease from baseline systolic BP) that lasts for less than 1 hour and is responsive to conventional therapy (iv fluids or pharmacologic intervention)
Refractory septic shock	Clinical diagnosis of the sepsis syndrome plus hypotension that lasts for > 1 hour despite adequate volume resuscitation and that requires vasopressors or higher doses of dopamine (> 6 µg/kg per hour)

endothelial cells. This is mediated by increased expression of the neutrophil adhesion molecule, CD11/18. Neutrophil activation also results in production of free oxygen radicals. This and other mechanisms lead to endothelial damage, injury to the microvasculature and ischaemia. Ischaemia leads to multi-organ failure. Ischaemia also results in the formation of oxygen radicals when reperfusion occurs which further aggravates the endothelial damage. Increased levels of nitric oxide and nitric oxide products are also found in patients with sepsis and hypotension in sepsis is mediated in part by nitric oxide⁷. Nitric oxide mediated hypotension

does not respond to pressor agents. The resulting haemodynamic abnormalities as well as the injury to the microvasculature is the basis for multi-organ failure.

It is increasingly clear that modulation of the cytokine effects is as important in preventing mortality as eradication of the septic focus and haemodynamic stabilisation. Attempts at immunomodulation include administration of monoclonal antibodies to bacterial endotoxin, anti-tumour necrosis factor, Interleukin-1 receptor antagonist as well as CD11-18 binding peptides.

Table II
American College of Chest Physicians/Society of Critical Care Medicine
consensus conference group definitions of the stages of sepsis

Stage of sepsis	Features
Systemic inflammatory response syndrome (SIRS)	Two or more of the following: (i) Temperature of > 38°C or < 36°C (ii) Heart rate of > 90/min (iii) Respiratory rate of > 20/min (iv) WBC count of > 12 x 10 ⁹ /L or < 4 x 10 ⁹ /L or 10% immature (band) forms
Sepsis	SIRS with a culture-documented infection
Severe sepsis	Sepsis plus organ dysfunction, hypotension, or hypoperfusion (including but not limited to lactic acidosis, oliguria, or acute alteration in mental status)
Septic shock	Hypotension (despite fluid resuscitation) plus hypoperfusion abnormalities

Although animal experiments and some clinical trials have shown they may be useful in reducing the morbidity and mortality of sepsis, it is still too early to make any recommendations on their routine use in clinical practice⁸. Trials on anti-endotoxin monoclonal antibodies have been rather disappointing to date⁹. The use of anti-oxidants like xanthine oxidase inhibitors and pentoxifylline to prevent injury caused by free oxygen radicals has also been proposed¹⁰. The use of nitric oxide synthetase inhibitors has been shown to have some beneficial effects on sepsis-related hypotension¹¹. Nevertheless, more clinical trials have to be done in order to better define the indications for the use of these substances.

Role of the gastrointestinal tract

The role of the gastrointestinal tract in sepsis is increasingly being appreciated¹². The gut is an important source of infection in the severely ill. The resident flora of the gastrointestinal tract of the patient is the primary source of endogenous pathogens causing sepsis. The common pathogens are the aerobic Gram

negative bacilli like *E. coli*, *Klebsiella*, *Enterobacter* and *Pseudomonas aeruginosa*. The anaerobic flora is very rarely implicated in such infections and is believed to be even protective; contributing to the colonisation resistance of the gastrointestinal tract. In critically ill patients who have been in hospital for some time, the gastrointestinal tract may be colonised by the multiply-resistant aerobic Gram negative bacilli found in the hospital environment.

Bacteria from the gastrointestinal tract gain access into the bloodstream via the intestinal wall, a process referred to as translocation. Factors in the gastrointestinal tract that protect against bacterial translocation include gastric acid, mucus, the normal anaerobic flora, avoiding formation of free radicals that may cause epithelial injury, the tight epithelial junctions of the intestinal mucosa and the local immunity of the gut¹³.

Preserving the integrity of the mucosal barrier as well as maintaining a normal bacterial flora thus help to decrease the likelihood of bacterial translocation and

the risk of systemic infection. Enteral feeding is now believed to be an important factor in promoting normal gastrointestinal function¹⁴. Total parenteral nutrition is associated with an increased incidence of sepsis which may be secondary to bacterial translocation. Other factors that also promote normal functioning of the gut include the amino-acid glutamine and xanthine oxidase inhibitors which prevent the formation of free oxygen radicals¹⁵.

Antacids and H₂-antagonists which reduce gastric acidity may cause gastric bacterial overgrowth and oropharyngeal colonisation. It has been shown in some studies that this predisposes to nosocomial pneumonia because of the subsequent aspiration of oropharyngeal or gastric contents which occurs particularly in patients who are on ventilators. In this respect, it has been suggested that sucralfate may be a more suitable mucoprotective agent to use in the critically ill since sucralfate does not affect gastric acidity¹⁶. This situation is however not clearly established and there are some who hold that translocation of bacteria is a more important pathogenetic mechanism in nosocomial pneumonia and therefore the prevention of stress ulcers is of greater importance than prevention of bacterial overgrowth¹⁷.

Patients nursed in the supine position are also more likely to have tracheal, pharyngeal and gastric colonisation as opposed to patients nursed in the semi-recumbent position. Supine patients are also more likely to aspirate gastric contents into the trachea¹⁸.

Selective decontamination of the digestive tract

Since many of the infections are caused by aerobic Gram negative bacilli, one strategy that has been employed as prophylaxis against infection is selective decontamination of the digestive tract (SDD)¹⁹⁻²¹. The purpose of SDD is to eradicate the aerobic bacterial flora and yeasts in the gut and oropharynx by the administration of non-absorbable antimicrobial agents like tobramycin and an oral anti-fungal agent. These antibiotics are applied as a paste to the oropharynx and via a naso-gastric tube. Some regimens also include an initial course of parenteral cefotaxime aimed at eradicating any lower respiratory tract flora (pre-emptive therapy). SDD has been shown to reduce infection among intensive care patients. However, it has thus far

not been possible to show any reduction in mortality. Opponents of SDD point out that this is an expensive measure to undertake on a routine basis. Concern has also been expressed regarding the risk of emergence of bacterial resistance. At present it is not possible to identify patients who are most likely to benefit from SDD. More conclusive evidence and a better understanding of patient selection are required before SDD can be accepted as routine practice in all ICUs.

Principles of management and prevention

In recent years, a better understanding in the pathophysiological processes involved in sepsis has led to innovations in the prevention and treatment of sepsis, some of which have already been mentioned earlier.

Due attention should also be paid to prevention of infection through maintaining normal gut function, reducing risk of bacterial colonisation and translocation. Nursing in the semi-recumbent position, the promotion of enteral feeding, the use of sucralfate and xanthine oxidase inhibitors and selective decontamination of the digestive tract may be some of the measures that would help to achieve this.

Prevention of infection from exogenous sources through high standards of control of hospital infection remains of utmost importance and simple measures like hand washing cannot be substituted for by any of these newer strategies.

The management of sepsis should not only be confined to the use of antimicrobial agents. Haemodynamic stabilisation and immunomodulating agents to neutralise the adverse effects of the cytokine cascade are probably as important as antimicrobial therapy in managing the sepsis. Results of clinical trials undertaken so far show some promise. However, the definitive use of these agents has yet to be firmly established. There are problems of patient selection which remains to be sorted out. Some subsets of patients are more likely to benefit from certain regimens. With a better understanding of the pathogenetic mechanisms involved, it may be possible to select specific strategies for defined groups of patients. Prospects for more effective management of sepsis over the next decade are good.

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QUIZ ON SEPSIS

1. Features of the systemic inflammatory response syndrome (SIRS) include:
 - A. temperature of $> 38^{\circ}\text{C}$
 - B. temperature of $< 36^{\circ}\text{C}$
 - C. hypotension
 - D. acute alteration of the conscious state
 - E. respiratory rate of $> 20/\text{min}$

2. Cytokines that play a major role in the pathophysiology of sepsis include:
 - A. Interleukin-1
 - B. Interleukin-2
 - C. Tumour necrosis factor
 - D. Interleukin-6
 - E. Platelet-activating factor

3. The following statements are true:
 - A. Bacterial endotoxin is a powerful stimulator of macrophages
 - B. Neutrophil activation results in free oxygen radicals production
 - C. Inhibition of nitric oxide production results in hypotension
 - D. The gut is an important source of infection in the critically ill
 - E. Translocation primarily involves the anaerobic flora

4. The following statements are true:
 - A. H₂-antagonists predispose to nosocomial pneumonia
 - B. Enteral feeding promotes gastrointestinal integrity
 - C. Aspiration of gastric contents is more likely to occur in supine patients
 - D. Arginine promotes normal gut function
 - E. A normal bowel flora decreases the risk of systemic infection

5. Selective decontamination of the digestive tract:
 - A. is aimed at eradicating all bacteria from the gut
 - B. involves administration of non-absorbable antibiotics
 - C. involves administration of an antifungal agent
 - D. has been shown to reduce infection rates in the ICU patients
 - E. has been shown to effectively reduce mortality in ICU patients