

# Sepsis: at-risk patients, clinical manifestations and management

**New knowledge of sepsis has led to improved clinical outcomes.**

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Sepsis is a major clinical challenge, especially to clinicians working in emergency and critical care units. Research over the last decade into a better understanding of the pathophysiology and management of sepsis has resulted in a remarkable increase of new knowledge on the subject. Some findings translate into improved outcomes, while others lack reproducibility in large clinical trials.

Sepsis is a clinical syndrome characterised by systemic inflammation (SIRS) due to infection. Although inflammation is an essential and beneficial host response, sepsis involves a dysregulation of the normal inflammatory process. The result is an uncontrolled release of pro-inflammatory mediators that, coupled with the release of bacterial toxins, induce widespread tissue injury. As this process invariably occurs within the vasculature, most of the damage is to the endothelium. The endothelium is not a passive surface, and is widely involved in maintenance of circulating volume and in coagulation and fibrinolysis.<sup>1-4</sup>

A spectrum of clinical disease follows: when the infection produces multiple systemic symptoms, such as fever and increased respiratory or heart rate, the syndrome is referred to as sepsis; if the systemic response to infection progresses and causes evidence of organ dysfunction distant from the site of infection, patients are classified as having severe sepsis; septic shock is defined as severe organ dysfunction with hypotension or hypoperfusion not responsive to initial fluid resuscitation (Table I).<sup>1-7</sup>

As sepsis progresses to septic shock, the risk of dying increases substantially. Where sepsis is usually reversible with early appropriate therapy, patients with septic shock have a mortality of 40 - 60% despite aggressive therapy.<sup>3,4,7,8</sup>

## *Risk factors for developing sepsis<sup>3,4,8-10</sup>*

The risk for developing sepsis depends mainly on the presence of co-morbid conditions associated with immune defects and/or the use of immunosuppressive therapies. The site of primary infection and the specific infecting microbe plays an additional role while genetic factors may also be important.

Advanced age, lack of splenic function, alcoholism with significant liver disease, chronic renal disease, intravenous drug use, malnutrition, HIV infection, diabetes mellitus and malignancy all predispose to specific infections, frequently with increased severity. Cancer chemotherapy, immunosuppressive therapies after organ transplantations and chronic steroid therapy also increase the risk for sepsis.

Certain sites of primary infection may provide a nidus for bacterial invasion: recent upper or lower respiratory tract infections, prior major trauma, disruption of cutaneous barriers due to lacerations, burns, surgery or decubiti ulcers and the presence of foreign material such as nasal packing, barrier contraceptives, tampons, arteriovenous fistulas, indwelling catheters, prosthetic joints and mechanical ventilation are all associated with an increased risk for sepsis.

Specific organisms that may predispose to more severe infection are often associated with the above risk factors and include *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Circulating bacteria and their products may also directly stimulate inflammatory responses within the vasculature, e.g. meningococcal endotoxin, or inflammatory mediators from the local site of infection, e.g. pneumonia caused by *P. aeruginosa*.

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## *Clinical manifestations of the septic response<sup>3,4</sup>*

Clinical manifestations are nonspecific and usually superimposed on the symptoms and signs of the patient's underlying illness and primary infection. There are striking individual variations in presentation and the rate at which symptoms develop may differ from patient to patient.

Patients usually present with fever or hypothermia. A normal temperature on presentation is uncommon but may occur in neonates, the elderly, alcoholics and the severely immunosuppressed.

Early symptoms and signs may include hyperventilation and sometimes confusion or disorientation. Signs of encephalopathy are more common in the elderly and in individuals with pre-existing neurological disorders. Focal neurological deficits are not usually a feature of sepsis, but existing deficits may become more prominent in the septic patient.

**Table I. Explanation of terms used**

Infection	Presence of a micro-organism in a normally sterile site – differentiate from colonisation
Bacteraemia	Bacteria cultured from blood – poor correlation with severe sepsis, may be transient without any clinical consequences
Systemic inflammatory response syndrome (SIRS)	Systemic inflammation due to infectious and non-infectious triggers. Two or more of the following: <ul style="list-style-type: none"> <li>• Temperature <math>&gt;38^{\circ}\text{C}</math> or <math>&lt;36^{\circ}\text{C}</math></li> <li>• Heart rate <math>&gt; 90</math> beats/min</li> <li>• Respiratory rate <math>&gt;20</math> breaths/min or <math>\text{PaCO}_2 &lt;4</math> kPa</li> <li>• WCC <math>&gt; 12\ 000</math> cells/mm<sup>3</sup> or <math>&lt;4\ 000</math> cells/mm<sup>3</sup> or <math>&gt;10\%</math> immature (band) forms</li> </ul>
Sepsis	If SIRS is associated with infection (proven or suspected)
Hypotension	Systolic blood pressure of $< 90$ mmHg; MAP $<70$ mmHg or a reduction of $>40$ mmHg from baseline (exclude other causes for hypotension)
Tissue hypoperfusion	Manifests as one or more of the following: <ul style="list-style-type: none"> <li>• Septic shock</li> <li>• Serum lactate <math>&gt;2.0</math> mmol/l</li> <li>• Oliguria (<math>&lt;0.5</math> ml/kg per hour)</li> </ul>
Severe sepsis	Sepsis associated with dysfunction of organ(s) distant from the site of infection – hypotension or hypoperfusion, if present, must be reversible with adequate fluid resuscitation
Septic shock	Sepsis-induced hypotension not responding to adequate fluid resuscitation and requiring vasopressor therapy
Refractory sepsis	Septic shock for $>1$ hour, not responding to vasopressor therapy

On occasion, skin lesions that suggest a specific pathogenic aetiology may be present at the sites of haematogenous seeding of organisms and/or toxins to the skin (Table II).

Nausea, vomiting, diarrhoea and ileus are usually nonspecific manifestations of the septic response, but may suggest acute gastroenteritis as primary infection.

### Laboratory findings<sup>3,4</sup>

Early abnormalities include leucocytosis or leucopenia, thrombocytopenia (up to 30% of patients), and proteinuria. Neutrophils may contain toxic granulations or cytoplasmic vacuoles.

With progression of the septic response thrombocytopenia becomes more

severe ( $<50\ 000$ ) and if accompanied by prolongation of the thrombin time, decreased fibrinogen and increased D-dimers are highly suggestive of DIC. Active haemolysis with fragments on the blood smear strengthens the diagnosis of DIC.

Abnormal liver enzymes are a common early manifestation of sepsis and may include cholestatic jaundice with elevated serum conjugated bilirubin and alkaline phosphatase. Prolonged severe hypotension may cause marked elevation of transaminases due to ischaemic hepatocyte necrosis.

During the septic response tissues cannot extract oxygen from the blood as normal, resulting in anaerobic metabolism. Blood lactate levels rise early and eventually lead

to metabolic acidosis. Hyperglycaemia is often present, mostly in diabetics, and may trigger diabetic ketoacidosis.

Hyperventilation during early sepsis may lead to respiratory alkalosis, but this is soon replaced by metabolic acidosis (with increased anion gap) due to respiratory fatigue and hyperlactataemia.

The acute phase response results in increased production of C-reactive protein, ferritin, fibrinogen and complement components.

Chest radiograph findings vary from normal to pneumonic consolidation to fluid overload and the diffuse infiltrates of acute respiratory distress syndrome (ARDS), depending on the underlying disease process. ECG usually shows a

**Table II. Skin lesions in severely ill patients associated with specific aetiological agents**

Skin lesion	Clinical associations	Pathogen
Petichiae and/or purpura	Meningitis	<i>Neisseria meningitides</i>
	Tick bite	Tick bite fever, Crimean-Congo haemorrhagic fever
	Dog bite	<i>Capnocytophaga canimorsus</i>
Ecthyma gangrenosum (bullous with central haemorrhage/necrosis)	Neutropenia	<i>Pseudomonas aeruginosa</i>
Generalised erythroderma	Toxic shock syndrome	<i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i>

sinus tachycardia and sometimes some nonspecific ST-T wave abnormalities.

### Complications<sup>3,4,6,7</sup>

Early in the course of sepsis, increasing alveolar capillary permeability causes increased pulmonary water content, which interferes with oxygen exchange and results in ventilation perfusion mismatching and a fall in PO<sub>2</sub>. Progressive diffuse pulmonary infiltrates and arterial hypoxaemia (PaO<sub>2</sub>/FIO<sub>2</sub> <200) indicate the development of ARDS. Failure (fatigue) of respiratory muscles further exacerbates hypoxaemia and hypercapnia. ARDS must be differentiated from fluid overload, cardiac failure, viral pneumonitis and pneumocystis pneumonia.

Sepsis-induced hypotension develops from general microcirculatory maldistribution of blood flow and blood volume, and from hypovolaemia due to capillary leakage of intravascular fluid. Dehydration secondary to insensible fluid losses, diarrhoea, vomiting and polyuria also contribute.

During early septic shock systemic vascular resistance is usually elevated and cardiac output decreased. After fluid repletion, cardiac output typically increases, but systemic vascular resistance falls. Increased or normal cardiac output and decreased systemic vascular resistance is the hallmark of septic shock. Other conditions that may cause this combination include anaphylaxis, liver cirrhosis, and an overdose of narcotics.

Depressed myocardial function (low ejection fraction) develops within 24 hours in most patients with severe sepsis. Cardiac output is, however, maintained because ventricular dilatation permits a normal stroke volume. Although myocardial dysfunction may contribute to hypotension, refractory hypotension is usually due to the low systemic vascular resistance.

Decreased urinary output is often present, but some patients may be inappropriately polyuric. Renal failure is usually due to acute tubular necrosis (ATN), induced by hypotension or capillary injury. ATN may be aggravated by giving hypovolaemic patients aminoglycoside antibiotics.

### Diagnosis<sup>3,4,6,11</sup>

There is no specific diagnostic test for the septic response. The classic septic parameters are sensitive clinical findings for infection and include fever or hypothermia, tachypnoea, tachycardia and leukocytosis or leukopenia. An acutely altered mental state, thrombocytopenia, raised serum lactate and hypotension

**Table III. Non-infectious aetiologies of SIRS**

Pancreatitis
Burns
Trauma
Myocardial infarction
Pulmonary embolism
Dissecting aortic aneurism
Cardiac tamponade
Adrenal insufficiency
Anaphylaxis
Drug overdose

further increase the clinical suspicion for sepsis. The septic response can however be varied and patients with sepsis can present without many of the typical clinical findings. Conversely, patients may present with all the clinical features of systemic inflammation but without an infectious cause (Table III).

A definitive aetiological diagnosis requires isolation of a micro-organism. At least 2 blood culture samples should be obtained from different venepuncture sites. Microbial invasion of the bloodstream is not essential for the development of sepsis, since local infection can also cause a systemic inflammatory response with organ dysfunction. It is therefore crucial to culture material from the primary site of infection or from infected cutaneous lesions wherever possible.

Cultures often remain negative despite a definitive presence of an infection. Negative cultures may be due to recent antimicrobial use, presence of slow growing or fastidious organisms or the absence of microbial invasion of the bloodstream.

### Treatment<sup>1,3,5,6,11</sup>

Successful management of suspected sepsis requires urgent measures to treat the local site of infection, to provide haemodynamic and respiratory support and to eliminate the offending micro-organism. The patient's underlying disease must also be managed aggressively. Rapid assessment and diagnosis is essential to facilitate the initiation of these measures within the first 6 hours after presentation.

Antimicrobial agents should be started immediately after samples from blood, urine and other clinically relevant sites have been taken for culture. Studies have shown that starting appropriate antimicrobial chemotherapy within 1 hour after presentation with septic shock is associated with improved survival

rates. Knowledge of the likely pathogen at specific sites of local infection and of the most recent data on susceptibility patterns of bacterial isolates from the hospital and the community is essential in making an appropriate antibiotic choice. As a rule initial empiric antibiotic cover must be effective against both Gram-negative and Gram-positive bacteria. Maximum recommended antibiotic doses must be given intravenously. Duration of therapy is usually 7 - 10 days, but is influenced by the response to treatment, the site of infection, the adequacy of surgical drainage, underlying co-morbid disease and the susceptibility of the bacterial isolate.

Removal or drainage of a local source of infection is essential. The risks and benefits of the specific method of source control must be considered carefully. Invasive devices must be removed where possible and sent for culture. Where the source of infection is not clear, occult infection should be sought.

Adequate organ perfusion is essential for proper oxygen and substrate delivery to the tissues. Effective intravascular depletion is common in patients with sepsis and initial management of hypotension should include administration of 1 - 2 litres of Ringer's lactate over 1 - 2 hours guarding against fluid overload by keeping the CVP between 8 and 12 cmH<sub>2</sub>O. Normal saline is not recommended for initial resuscitation due to the increased risk of developing hyperchloraemic metabolic acidosis. Aim for a urine output rate of ≥0.5 ml/kg per hour and try to keep the MAP ≥65 mmHg (systolic blood pressure above 90 mmHg). Adequate fluid volume replacement does not necessarily equate to proper microcirculatory tissue perfusion. Serial lactate measurements are very helpful to assess organ perfusion and levels of <2 reflect adequate perfusion. Circulatory adequacy should also be assessed by clinical parameters (mentation, urine output, skin perfusion). If unable to obtain these goals with fluid therapy inotropic and vasopressor therapy is indicated.

A low haemoglobin concentration (<7 g/dl) will impair oxygenation. Blood transfusion is indicated to keep the haemoglobin between 7 and 9 g/dl.

Mechanical ventilation is indicated for progressive hypoxaemia, hypercapnoea, neurological deterioration or respiratory muscle failure. Sustained tachypnea (>30 breaths/min) is frequently a sign of impending respiratory collapse and early ventilation will ensure adequate oxygenation, divert blood from the muscles of respiration, reduce the cardiac afterload and prevent aspiration.

DIC, if complicated by severe bleeding, should be treated with fresh frozen plasma and platelets. Bicarbonate may sometimes be used in severe refractory metabolic acidosis. However, successful treatment of the infection is essential to reverse both DIC and acidosis. Patients with acute renal failure may benefit from either haemofiltration or haemodialysis.

Important preventive measures to assist recovery include prevention of skin breakdown (skin care), deep venous thrombosis (heparin), nosocomial infections (infection control) and stress ulcers ( $H_2$  blockers or PPIs).

## There are striking individual variations in presentation and the rate at which symptoms develop may differ from patient to patient.

### Other measures<sup>11-15</sup>

Despite aggressive management many patients with severe sepsis and septic shock still die. Treatment modalities that may prevent these deaths have been investigated in depth and include early goal-directed therapy (EGDT), tight glucose control, physiological steroid replacement and recombinant activated protein C.

EGDT is an algorithm for the acute management of sepsis published by Rivers in 2001. It is used for the first 6 hours after a patient presents to the emergency unit. Following the algorithm resulted in a 16% reduction in 28-day mortality compared with controls. The main clinical goals of EGDT are early recognition of disease, and improving of indices of organ perfusion, including blood pressure (MAP  $\geq 65$  mmHg), serum lactate concentration

(<2 mmol/l) and central venous oxygen saturation ( $\geq 70\%$ ). Early appropriate antibiotics and control of the source of infection are other important factors. EGDT is strongly recommended, but the findings still need to be validated in large prospective trials.

Initial data showing improved outcomes with tight glycaemic control (4.4 - 6.1 mmol/l) could not be reproduced in follow-up studies. Insulin infusions require intensive protocol-driven control measures and are often complicated by hypoglycaemia. Although adequate glycaemic control (aim for  $\leq 8.3$  mmol/l) is still part of standard care, most ICU specialists have abandoned the practice of tight glycaemic control.

Adrenal insufficiency should be considered in septic patients with refractory hypotension, fulminant *Neisseria meningitidis* bacteraemia, prior glucocorticoid use, disseminated tuberculosis and AIDS. The CORTICUS trial on low-dose hydrocortisone was also not able to reproduce results of earlier trials with improved outcomes. It is, however, acceptable to give hydrocortisone 50 mg IVI 6-hourly as a therapeutic trial to a subset of patients with septic shock not responding to adequate fluid and vasopressor therapy. If improvement follows in the next 24 - 48 hours, continue, tapering the dose over 5 - 7 days.

The use of activated protein C has been the subject of controversy ever since the publication of the PROWESS trial results in 2001. The study was terminated prematurely on the grounds of efficacy. Other studies have however failed to show benefit and the current international guideline on the management of severe sepsis does not recommend its routine use.

### References

1. Surviving Sepsis Campaign. About sepsis. [http://www.survivingsepsis.org/about\\_sepsis](http://www.survivingsepsis.org/about_sepsis) (accessed 20 March 2010).

- Hotchkiss R, Karl I. The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348: 138-150.
- Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Churchill Livingstone, 2010: 987-1010.
- Kasper DL, Braunwald E, Fauci AS, et al., eds. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008.
- Members of the American College of Chest Physicians/Society of Crit Care Med Consensus Conference Committee: American College of Chest Physicians/Society of Crit Care Med Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864-874.
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296-327.
- Becker JU, Theodosis C, Shevin TJ, Wira CR, Grace NE. Surviving sepsis in low-income and middle-income countries: new directions for care and research. *Lancet Infect Dis* 2009; 9: 577-582.
- Vincent JL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; 34: 344-353.
- Pettit D, Thievent B, Wenzel RP, et al. Importance of pre-existing co-morbidities for prognosis of septicemia in critically ill patients. *Int Care Med* 1993; 19: 265-272.
- Esper AM, Moss M, Lewis CA, et al. The role of infection and co-morbidity: factors that influence disparities in sepsis. *Crit Care Med* 2006; 34: 2576-2582.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345(19): 1368-1377.
- Anname D, Seville V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288(7): 862-871.
- Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358: 111-124.
- Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345(19): 1359-1367.
- Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 283-297.

### In a nutshell

- Some findings translate into improved outcomes, while others lack reproducibility in large clinical trials.
- Sepsis involves a dysregulation of the normal inflammatory process.
- When the infection produces multiple systemic symptoms, such as fever and increased respiratory or heart rate, the syndrome is referred to as sepsis.
- If the systemic response to infection progresses and causes evidence of organ dysfunction distant from the site of infection, patients are classified as having severe sepsis.
- Septic shock is defined as severe organ dysfunction with hypotension or hypoperfusion not responsive to initial fluid resuscitation.
- Where sepsis is usually reversible with early appropriate therapy, patients with septic shock have a mortality of 40 - 60% despite aggressive therapy.
- The risk for developing sepsis depends mainly on the presence of co-morbid conditions associated with immune defects and/or the use of immunosuppressive therapies.
- Early in the course of sepsis, increasing alveolar capillary permeability causes increased pulmonary water content, which interferes with oxygen exchange and results in ventilation perfusion mismatching and a fall in  $PO_2$ .
- There is no specific diagnostic test for the septic response.
- Successful management of suspected sepsis requires urgent measures to treat the local site of infection, to provide haemodynamic and respiratory support and to eliminate the offending micro-organism.