Immunology and management of sepsis

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Readers are invited to use this article as a self-assessment exercise and to update their knowledge.

ILLUSTRATIVE CASE HISTORIES

Case 1
A 27-year-old male schoolteacher presented at 11 PM as an emergency to the casualty department. According to the history taken from his wife, he had been completely well that morning but had returned home early from work thinking that he had influenza. He had complained of aches in his muscles and feeling shivery. He had gone to bed and at 8 PM he had told his wife that he was feeling a little better. At 10 PM she found him rambling and incoherent and called a doctor. On examination he was pyrexial (39.5°C, pulse 125 beats/min, BP 90/60) and there was a faint macular rash on the extremities that blanched on pressure. His conscious level was reduced but there was no neck stiffness and there were no focal neurologic signs. Meningococcal infection was suspected and 4 million units of penicillin were administered intravenously. Investigations revealed the following: Hb 13.4 g/dL, WBC 3.2 x 10^9/L, platelets 54 x 10^12/L, Na 143 mmol/L, K 3.6 mmol/L, urea 9.0 mmol/L, HCO₃⁻ 21 mmol/L. Chest radiography and cranial computed tomography (CT) were normal, and a lumbar puncture performed after the CT scan was also normal, with no inflammatory cells and negative Gram stain. Cerebrospinal fluid culture was sterile but blood cultures taken on admission subsequently grew Neisseria meningitidis type B.

The patient was admitted to intensive care and over the next 8 h his condition steadily deteriorated, with the development of severe hypotension requiring inotropic/pressor support, oliguria, a widespread purpuric rash, evidence of disseminated intravascular coagulation and progressive hypoxemia such that he required elective intubation and ventilation. His condition then began to stabilize but he required ventilation for a total of 14 days, and temporary hemodialysis for acute renal failure, and suffered ischemic necrosis of two fingers on his left hand and several toes. He eventually left hospital 6 weeks after the initial admission and was able to return to work 3 months later.

Case 2
A 54-year-old female presented with fever and breathlessness and was found to have tuberculous pericarditis. She was treated with antituberculous therapy plus 60 mg of prednisolone daily. Despite this, she developed progressive cardiac failure, and 3 weeks later underwent an uncomplicated pericardectomy. Two days after leaving intensive care she became hypotensive on the general ward. She was transferred back to intensive care and examination revealed the following: temperature 37.2°C, pulse 100 beats/min, BP 60/40, respirations 32/min. Her sternotomy wound was clean and not inflamed, there was dullness and there were coarse crackles at the left base, on cardiovascular examination there was a soft pericardial rub, and she was disorientated but with no focal neurologic signs. Arterial blood gases on air were as follows: pH 7.48, PCO₂ 2.7 kPa, PO₂ 9.8 kPa, HCO₃⁻ 19 mmol/L, base excess -6. Chest X-ray showed some atelectasis and a small pleural effusion at the left base. Cardiac tamponade or pulmonary embolism were thought the most likely diagnoses, and urgent echocardiography and right heart catheterization were performed. Echocardiogram showed no tamponade and her right heart catheter revealed the following: central venous pressure (CVP) +1 cm, cardiac output (CO) 8 L/min, systemic vascular resistance (SVR) 400 dyne/s per cm⁵ (normal 800–1200). The low SVR raised the possibility of underlying sepsis and the patient was treated with...
intravenous fluids, oxygen, pressor agents and intravenous cefotaxime plus fluclouxacillin. Blood and urine both grew Escherichia coli resistant to ampicillin and sensitive to cefotaxime. The patient made a rapid and complete recovery.

COMMENTS ON CASE REPORTS

These two cases were chosen to highlight different aspects of the clinical presentation of sepsis. In the first case a completely well individual was struck down by infection with a highly virulent organism. There was no doubt over the diagnosis at presentation but despite prompt antimicrobial therapy and supportive intensive care the patient's condition progressed within hours, with the development of multi-organ failure from which he was lucky to survive. In the second case the infection was acquired in hospital while the patient was being treated for another condition. This patient was immunocompromised from corticosteroid therapy and had undergone urinary catheterization after cardiothoracic surgery, both of which are risk factors for infection. Prompt recognition and therapy prevented progression to multi-organ failure. The presentation was obscure and highlights the fact that sepsis should always be considered in the differential diagnosis of hypotension even, as in this case, if the patient is apyrexial.

MULTIPLE-CHOICE QUESTIONS

Clinical and immunologic aspects of sepsis

In each of the numbered questions at least one, and up to four, of the individual entries are correct. (The answers are at the end of this article).

1. Etiology and epidemiology of sepsis
   a) Sepsis refers to bloodstream infection by pathogenic organisms True/False
   b) Gram-positive bacteria are the commonest underlying infection True/False
   c) Most cases are due to community-acquired infection True/False
   d) The mortality from septic shock has improved steadily over the past 20 years True/False
   e) Patients may display the signs of sepsis without any infection True/False

2. The following clinical features suggest underlying sepsis
   a) Diarrhea True/False
   b) Confusion True/False
   c) Hypothermia True/False
   d) Ecthyma gangrenosum is suggestive of Staphylococcus aureus bacteremia True/False
   e) Respiratory alkalosis True/False

3. Pathophysiologic changes in sepsis
   a) Pulmonary vascular resistance is typically reduced True/False
   b) Cardiac index may be elevated or suppressed True/False
   c) Ketonacidosis is a common complication True/False
   d) Hypoglycemia may occur True/False
   e) Tissue oxygen extraction is increased True/False

4. In the pathogenesis of sepsis
   a) Activation of tissue factor promotes a procoagulant state True/False
   b) Interleukin-10 may protect against sepsis True/False
   c) Neutropenia predisposes to septic shock True/False
   d) Decreased nitric oxide production leads to vasodilatation True/False
   e) Bacterial translocation from the gut may occur True/False

5. The following are true of endotoxin (lipopolysaccharide, LPS)
   a) Endotoxin is an integral component of the Gram-positive bacterial cell wall True/False
   b) Lipid A is the bioactive subunit of endotoxin responsible for triggering sepsis True/False
   c) In experimental animals antibodies directed against the outer polysaccharide moiety of endotoxin protect against challenge with heterologous Gram-negative bacteria True/False
   d) CD14 mediates endothelial responses to endotoxin True/False
   e) Lipopolysaccharide-binding protein (LBP) neutralizes endotoxin True/False

6. Tumor necrosis factor (TNFα)
   a) Causes myocardial depression True/False
   b) Decreases neutrophil adherence to endothelium True/False
   c) Can be augmented in its effects by circulating forms of the TNFα receptor True/False
   d) Can be detected in the circulation of humans after intravenous challenge with endotoxin True/False
   e) Induces an anabolic state True/False
7. Staphylococcal toxic shock syndrome
a) Is almost always seen in menstruating women  True/False
b) Requires bloodstream invasion and dissemination of staphylococci True/False
c) Toxic shock syndrome toxin-1 is a superantigen True/False
d) Palmar desquamation typically occurs True/False
e) Has a higher mortality than Gram-negative septic shock True/False

8. In the therapy of sepsis
a) Antibiotics may liberate free endotoxin from Gram-negative bacteria True/False
b) Early antibiotic therapy reduces the mortality of meningococcal sepsis True/False
c) Corticosteroids are indicated in severe sepsis with shock True/False
d) Noradrenaline improves renal blood flow True/False
e) Dobutamine is often used to increase the cardiac index True/False

COMMENTS ON MULTIPLE-CHOICE QUESTIONS

Question 1
There has been much debate over the terminology of sepsis during the past decade. Currently accepted terminology and definitions were agreed at a consensus conference of the Society for Critical Care Medicine and the American College of Chest Physicians [1] and are as listed in Table 1. Thus bacteremia and sepsis are not the same thing, and patients may develop a severe systemic response to a localized infection, namely the systemic inflammatory response syndrome (SIRS).

Furthermore, a number of non-infectious inflammatory insults such as pancreatitis, trauma and burns can cause SIRS independently of infection. The exact prevalence of severe sepsis is not known and will vary between different patient populations. In recent epidemiologic studies the attack rate for SIRS has been measured at 13.6/1000 hospital admissions [2]. SIRS appears to be responsible for about 10% of admissions to intensive care [3] but may develop in up to 68% of patients whilst in the intensive care unit (ICU) [4]. Mortality rates vary from 10–20% for Gram-negative bacteremia, to 30–50% in severe sepsis, to over 70% in refractory septic shock with multi-organ failure.

Early epidemiologic studies identified a predominance of Gram-negative bacterial infections in patients with shock. However, over the past 10 years there has been a shift in the microbiology of hospital infections towards gram-positive bacteria and in most studies Gram-positive bacteria, are now responsible for at least 50% of cases of sepsis [5,6]. Risk factors for sepsis include hospitalization, immunosuppression, trauma and surgical procedures, and it is not surprising that the majority of cases are nosocomially acquired [7]. Although prompt recognition and treatment of early sepsis may prevent disease progression, once refractory shock is established the mortality is at least 50% and has not been reduced by current therapies.

Question 2
The symptoms of sepsis are non-specific and the diagnosis is frequently not made until hypotension develops. Diarrhea and/or vomiting are frequently seen early in patients with sepsis, and are often dismissed as being due to gastroenteritis. Mental confusion may occur as a result of hypoxia or acidosis, or as part of a ‘septic encephalopathy’. In sepsis, increased lactic acid production leads to increased respiratory drive. Thus, in the early stages the patient is often breathless but with normal lungs and a respiratory alkalosis on arterial blood gases. As the disease progresses, these compensatory changes fail and metabolic acidosis with increased serum lactate dominates the picture. It is important to remember that patients with severe sepsis may be hypothermic and that this carries a higher

| Table 1 Terminology and definitions associated with sepsis |
|-----------------|-----------------|
| Condition       | Clinical features |
| Bacteremia      | Presence of viable bacteria in the bloodstream |
| Systemic inflammatory response syndrome (SIRS) | Systemic inflammatory response to a variety of insults |
|roller>38°C or <36°C  |
| Resp rate >20/min or reduced PaCO2 |
| WBC >12 or <4 or >10% 'bands' |
| Sepsis          | Identical to SIRS but as the result of infection |
| Severe sepsis   | Sepsis associated with organ dysfunction, hypoperfusion or hypotension |
| Corticosteroids are indicated in severe sepsis with shock True/False |
| Noradrenaline improves renal blood flow True/False |
| Dobutamine is often used to increase the cardiac index True/False |
| Septic shock    | Sepsis plus hypotension despite adequate fluid resuscitation and dependence on pressor agents to maintain BP |

Adapted from Bone et al. [1].
mortality. Ecthyma gangrenosum is a characteristic skin lesion with a black necrotic center seen in neutropenic sepsis and is most commonly due to Gram-negative bacteria, particularly *Pseudomonas aeruginosa*.

**Question 3**
The key physiologic change in sepsis is a fall in systemic vascular resistance with microvascular shunting across capillary beds. There is an associated increase in cardiac index to compensate for the lowered systemic resistance but in severe sepsis the effects of cytokines and acidosis may lead to impaired myocardial function and so the cardiac index may actually be reduced. Reduced arterial oxygenation and capillary shunting produces tissue hypoxia and anaerobic respiration, adding to lactic acidosis. Despite the need of the tissues for oxygen, capillary bed shunting means that tissue oxygen delivery (and therefore oxygen extraction) is reduced, further exacerbating the tissue hypoxia. Although systemic vascular resistance is low, the response of the pulmonary vascular bed to hypoxia is to constrict, leading to elevated pulmonary vascular resistance.

**Question 4**
Severe sepsis and multi-organ failure is the end result of a complex interaction of pro-inflammatory and anti-inflammatory processes triggered by bacterial products such as endotoxin (lipopolysaccharide, LPS). Following activation of responsive cells (predominantly macrophages, neutrophils and endothelial cells), numerous inflammatory mediators are released, including cytokines (e.g. TNFα, IL-1), activated complement factors, kinins, arachidonate metabolites and platelet-activating factor. On the vascular endothelium, the end result of these stimuli is the activation of procoagulant activity, which is one factor contributing to the development of disseminated intravascular coagulation. Endothelial activation and damage also leads to increased neutrophil transmigration into tissues and widespread ‘capillary leak’. The migration of activated neutrophils into healthy tissues is a key factor in the pathogenesis of organ failure [6,8–11], and although bacteremia is a common consequence of neutropenia, full-blown septic shock is encountered relatively less often in neutropenic patients. Anti-inflammatory (or counter-regulatory) mediators released in sepsis include IL-4, IL-10, IL-13, platelet-derived growth factor-β, IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptors (sTNFR) [9,12]. IL-10 inhibits the release of both TNFα and IL-1 and is being investigated as a possible therapy for severe sepsis. Nitric oxide (NO) is an endogenous vasodilator synthesized in many cell types, including vascular smooth muscle and endothelium. NO production is increased in sepsis and appears to be responsible, at least in part, for the widespread vasodilatation that is so characteristic in sepsis. Inhibiting NO in sepsis increases SVR and blood pressure but at the expense of impairing tissue oxygenation and cardiac output. Breakdown of gastrointestinal integrity is common in severe illness, including sepsis, and may allow bacteria or bacterial products to enter the systemic circulation thus bypassing the liver (bacterial translocation). In experimental models this may precipitate or exacerbate sepsis but the clinical importance of this in humans is not known.

**Question 5**
LPS is one of the best recognized causes of sepsis. LPS is found as an integral component of the outer leaflet of the cell wall of all Gram-negative bacteria. Lipid A is a unique di-glucosamine-based phospholipid that is highly conserved across Gram-negative bacteria. Lipid A is covalently linked to a relatively conserved core oligosaccharide and then to a repeated polysaccharide chain (O antigen) that varies widely between bacterial strains. In experimental models synthetic lipid A is capable of inducing septic shock. Antibodies directed against the inner core of LPS may protect against challenge with heterologous bacterial strains, but antibodies to the outer O antigen only protect against that individual strain. Considerable progress has been made in understanding the basis of cellular activation by LPS. LPS first interacts with a serum protein, lipopolysaccharide-binding protein (LBP) [13]. LBP acts as ‘shuttle’ presenting LPS to CD14, a glycosylphosphoinositol-linked protein on the surface of neutrophils and macrophages. Endothelial cells do not express CD14 but soluble CD14 is found in the circulation and appears to be able to mediate endothelial responses to LPS [14]. The currently favored hypothesis is that CD14 is not itself a signaling receptor but mediates the interaction between LPS and an as yet unidentified signaling molecule [15,16]. The elucidation of these events will hopefully lead to specific anti-endotoxin therapeutic strategies in the near future [17].

**Question 6**
TNFα is one of the central inflammatory cytokines in the host response to infection and in the pathogenesis of sepsis [18,19]. TNFα is released in vitro by macrophages and neutrophils in response to LPS or products from Gram-positive bacteria. In human volunteers TNFα appears in the circulation 2 to 4 h after endotoxin challenge [20], and TNFα can induce all of the features of septic shock in experimental animals. TNFα has pleotropic inflammatory actions, including enhancing neutrophil adherence to endothelium by upregulation of both neutrophil and endothelial
adherence molecules. After cellular activation TNFα receptors are proteolytically cleaved from the cell surface and appear in the circulation. These soluble TNFα receptors (sTNFR) bind to and neutralize free TNFα, thus acting as an endogenous TNFα regulatory mechanism. Chimeric forms of the sTNFR bound to the Fc portion of human IgG effectively neutralize cachectin) and also inhibits myocardial contractility [21].

**Question 7**
Staphylococcal toxic shock syndrome is characterized by fever, diarrhea, hypotension, a macular rash which later desquamates on the palms and soles, and organ failure in the context of infection with a toxin-producing strain of *Staphylococcus aureus*. The staphylococcal infection may be generalized, but more commonly is focal, usually a wound infection or vaginal colonization at the time of menstruation. About 50% of cases are menstrually associated, with the remainder evenly divided between males and females. Toxic shock syndrome toxin-1 (TSST-1) is thought to act as a superantigen [22]. Superantigens are able to directly activate T-cells by binding to both the MHC II molecule on antigen-presenting cells and the Vβ subunit of the T-cell receptor. Thus, all T-cells with a compatible Vβ subunit can be activated, and this can be up to 20% of the T-cell population, resulting in widespread immune stimulation [23]. Superantigenic toxins have also been isolated from other staphylococci and some strains of streptococci. The mortality of toxic shock is less than 10%, in contrast to the 30–50% mortality of Gram-negative septic shock.

**Question 8**
Treatment of Gram-negative bacteria with certain antibiotics leads to release of free LPS, and in some experimental animals this may exacerbate or even trigger severe sepsis [24]. In childhood meningitis there is evidence that postantibiotic release of LPS may increase inflammatory indices in the cerebrospinal fluid, but in sepsis it has been difficult to prove that this is a clinically relevant phenomenon. Therefore, until such convincing data are available, antibiotics should be chosen for their efficacy against the likely infecting pathogens rather than on the theoretical consequences of endotoxin release. The cardiac index is impaired in many patients with sepsis and may be improved by dobutamine. Noradrenaline and other pressor agents may be required to increase systemic vascular resistance where vital organ function is threatened by hypo-tension, but may impair renal perfusion and precipitate renal failure. Therefore, a low SVR needs to be interpreted in the context of the clinical picture, and noradrenaline should be used cautiously. Many anti-inflammatory strategies have been investigated in sepsis or are under evaluation [17]. Corticosteroids protect animals from subsequent endotoxin challenge, and after some promising human studies corticosteroids were used in many centers in all septic patients. However, large controlled studies and two meta-analyses have failed to show any benefit from corticosteroids and, indeed, there is a slightly increased mortality as a result of secondary infections [25,26]. Therefore, with the exception of the special case of toxemic typhoid fever, the routine use of corticosteroids in sepsis cannot be supported.

**Answers to the multiple-choice questions**

Q1: a. False; b. True; c. False; d. False; e. True
Q2: a. True; b. True; c. True; d. False; e. True
Q3: a. False; b. True; c. False; d. True; e. False
Q4: a. True; b. True; c. False; d. False; e. True
Q5: a. False; b. True; c. False; d. True; e. False
Q6: a. True; b. False; c. False; d. True; e. False
Q7: a. False; b. False; c. True; d. True; e. False
Q8: a. True; b. True; c. False; d. False; e. True

**Further reading**

**References**


