Septicaemia—the clinical diagnosis

David J. Bihari

Department of Intensive Care, Russell Brock Ward, Guy's Hospital, St Thomas Street, London SE1 9RT, UK

The production and consequences of the components of the state defined as 'clinically significant sepsis', as seen in patients undergoing intensive therapy—fever, shock, respiratory failure and multiple system failure—are complex. The syndrome is not necessarily accompanied by detectable bacteraemia; the effective management cannot wait upon positive blood cultures. Possibilities for more effective intervention include the use of monoclonal antibodies to endotoxin or to tumour necrosis factor, and of prostaglandins to alter the microcirculation. More refined definition of the severe sepsis syndrome will be required before these measures can be fully evaluated.

Introduction

Since ancient times, 'septicaemia' with all its protean manifestations has caused physicians considerable difficulty in both diagnosis and treatment. Little has changed with the introduction of the methods of 'modern medicine'. Indeed, with the more frequent application of aggressive oncological chemotherapy, immunosuppression, the use of invasive medical devices and procedures, together with the increasing survival of high risk cases (the elderly, chronic sick, immunosuppressed), the incidence of sepsis within the hospital population has continued to rise (Balk & Bone, 1989). Nevertheless, despite the classic definitions by Sir William Osier, the exact relationships between 'septicaemia' (the invasion of the blood stream by micro-organisms resulting in a general febrile infection without foci of suppuration), 'pyaemia' (a general disease characterized by recurring chills and intermittent fever and the formation of abscesses in various parts), 'clinically significant sepsis' (a more recent term introduced to describe a putrefactive process with an accompanying systemic immune response leading to localized, and on occasion, generalized tissue injury) and the presence or absence of positive blood cultures have not been clearly defined. This is of some importance since prompt and appropriate treatment with antimicrobial agents requires early recognition of the presence of active infection. Moreover, since it is now fashionable to attempt to manipulate the host's acute inflammatory response in severe sepsis (Bihari & Cerra, 1989), it is no longer acceptable to delay these interventions until the results of blood cultures become available.

These considerations have led directly to the definition of the 'sepsis syndrome' (Table I) in an effort to identify a group of patients with a high risk of developing life-threatening sepsis or septicaemia (Bone et al., 1989). Indeed, Bone and his colleagues provide convincing evidence that these criteria can select such a population although the rate of blood culture positive septicaemia is only 45%. There has been some
Table I. Definition of the sepsis syndrome

1. Clinical evidence of infection
2. Fever or hypothermia
3. Tachypnoea
4. Tachycardia
5. Impaired organ system function or perfusion:
   - altered mentation
   - hypoxaemia
   - elevated plasma lactate
   - oliguria

argument over the validity of this approach, since it is quite clear that a patient can fulfill the criteria of the 'sepsis syndrome' whilst in fact suffering from a drug reaction, tissue necrosis related to surgery or trauma, pancreatitis, myeloproliferative disorders or vasculitis (Raper & Fisher, 1988). This becomes extremely important when one examines the results of controlled clinical trials that purport to examine the effect of some intervention (e.g. steroids) in patients with sepsis, yet are based upon a population of patients of whom the majority were blood culture negative (Bone et al., 1987).

Manifestations of sepsis (Table II)

It is not difficult to make the diagnosis of septicaemia in a new patient presenting in the Accident and Emergency Department with fever, tachycardia, rigors, muscle pains and a readily identifiable source of sepsis.

Table II. Manifestations of sepsis

Common manifestations of sepsis
- fever, rigors and myalgias
- tachycardia, tachypnoea
- cyanosis suggesting hypoxaemia
- proteinuria
- leucocytosis (left shift, toxic granules, Dohle bodies)
- eosinopenia
- hypoferaemia
- irritability, lethargy
- mild abnormalities of liver function tests
- hyperglycaemia (especially in diabetes mellitus)

Less common manifestations of sepsis
- hypothermia, shock, lactic acidosis
- adult respiratory distress syndrome, azotaemia and oliguria
- leucopenia, leukaemoid reaction
- thrombocytopenia, disseminated intravascular coagulation, anaemia
- stupor and coma
- overt upper gastrointestinal bleeding
- cutaneous lesions, fundal lesions
- hypoglycaemia
- acute liver failure
Septicaemia—the clinical diagnosis

However, even in this setting, in which the decision to take blood for culture and initiate treatment with antimicrobial agents is relatively straightforward, errors can occur. The classic mistake is to confuse pulmonary embolism with a chest infection but however the patient and whatever their underlying condition, the presence of fever suggests an infection.

Fever

Given that all pyrexias are of 'unknown origin' at the time of presentation, this one particular physical sign forms the most important indication for the culture of blood. The recent review of septicaemia from the Queens Medical Centre, Nottingham (Ispahani, Pearson & Greenwood, 1987) examined data from 25,066 sets of blood cultures performed over a period of four years, 1980-1983 inclusive. Whilst this retrospective review provided no details of why the clinicians had performed the blood cultures in the first instance, 1782 (71%) yielded a significant growth of microorganisms, and these represented 933 episodes of septicaemia in 887 patients. A further 1540 (6-1%) of blood cultures were considered to be contaminated. The Nottingham investigators noted that in the same period, 165,414 patients were admitted to the four hospitals in the study, giving an overall prevalence of septicaemia of 7.1 episodes per 1000 admissions. This figure is a little lower than that reported from North America, where it is thought that at least one in 100 admissions develop blood culture positive septicaemia at some stage in their hospital stay (Kreger et al., 1980a). Interestingly, the Nottingham study demonstrated that 181 episodes (19%) were associated with a fever of less than 38°C and that the failure to achieve an adequate febrile response ( > 38°C) was associated with a doubling of both the direct and indirect mortality rates (direct mortality 15% and 36%, indirect mortality 7.4% and 15%, respectively).

However, this report did not address the more contentious issue of when and how to treat pyrexia, per se. There is considerable evidence that pyrexia is a beneficial host response, not least from observations made in infected fish and reptiles, who in order to increase their core temperature, seek a warmer environment. Apparently, this behaviour is associated with a greater survival rate compared with poikilotherms denied this advantage (Kluger, Ringler & Anuer, 1975). Against the more efficient functioning of the immune response at higher temperatures, one has to consider the increased metabolic demands engendered simply by a rise in core temperature (a 12% increase in oxygen uptake/°C). This has important consequences for the oxygen transport system of the individual which, very often, is already stressed and, in the elderly, may not be well tolerated. Whether or not it is appropriate to treat a fever of greater than 39.5°C is not clear, and nonsteroidal anti-inflammatory drugs have many other undesirable effects (primarily nephrotoxicity and gastric mucosal toxicity) and so are best avoided. In our Intensive Therapy Unit, it is our practice to use physical means to control the temperature of patients with severe sepsis who develop a pyrexia of greater than 39.5°C in this setting. At the same time, we emphasize that the mainstay of management of the problem is the appropriate treatment of the underlying condition.

Shock

The other manifestations of septicaemia may be divided into two groups—those that are common and those that occur less regularly (Table II). 'Shock'—best defined as an
inadequate delivery of oxygen and other vital substrates to respiring cells—is recognized clinically as an abnormally low blood pressure with some evidence of inadequate tissue perfusion, e.g. fall in urine output, cerebral dysfunction or developing metabolic acidosis. The Nottingham group reported clinical shock in 19-5% of episodes of blood culture positive septicemia with an overall (direct and indirect) mortality rate of 63%. This compared with a mortality rate of only 24% in the non-shocked group and so the presence of hypotension immediately defines a high risk group. It does seem that the prevalence of clinical shock in Gram-negative septicemia is declining from the 40% level reported in the 1970s (Kreger et al., 1980b) and may be related to early recognition and appropriate treatment with antimicrobial agents. What is clear, however, is that the haemodynamic disturbances associated with septicemia are independent of the infecting organism and extremely variable, being more closely related to the age of the patient, presence or absence of pre-existing cardiovascular disease, state of hydration and intensity of the host's response to the invading microorganisms (Table III). The old distinction between 'hot' and 'cold' shock has not stood the test of time and with the widespread introduction of invasive haemodynamic monitoring (pulmonary artery catheterization) with regular measurement of the cardiac output, it has become apparent that clinical signs are not an accurate guide to the prevailing cardiovascular disturbance. In the majority of 'shocked' cases, it is impossible to predict cardiac output and filling pressures from the physical signs alone, and the old dogma that a patient presents early in 'hot' shock (low vascular resistance/high cardiac output) and then deteriorates through 'cold' shock (low cardiac output/high vascular resistance) unto death is now 'hotly' disputed. It seems that many patients who die with severe sepsis maintain a hyperdynamic circulation for as long as they are given support, until just before death (Parker et al., 1987).

The central systemic measurements of a low vascular resistance together with a compensatory high cardiac output appear to reflect a peripheral distribution of flow problem (Bihari, 1987). The septic process—micro-organisms themselves, microbial cell wall products, e.g. endotoxin, and the various host derived mediators (numbering more than 35 in all, but perhaps particularly tumour necrosis factor (TNF) and products of the arachidonic acid cascades)—generates a disturbance in microcirculatory blood flow with inappropriate vasoconstriction in some tissues and dilatation in others. The overall effect is initially dilatation but vasoconstriction can rapidly become the primary problem and is more common in children and the elderly. Tissue hypoxia can occur in the presence of an apparently adequate blood pressure and arterial oxygen tension. Appropriate management depends upon accurate measurements of blood flow and
oxygen delivery to tissues. There is some suggestion that the septic process, even in the absence of clinical shock, so profoundly disturbs the regulation of blood flow to tissues that much of the damage that can occur is related to hypoxia-mediated cell injury. We have been partly instrumental in proposing this hypothesis of hypoxia—related multiple organ failure associated with sepsis in the critically ill (Bihari et al., 1987) and there is increasing evidence accumulating that successful resuscitation of such cases requires close attention to the matching of oxygen delivery (the product of the cardiac output and arterial oxygen content) to the oxygen uptake of the individual (Shoemaker et al., 1982).

Myocardial dysfunction in septicaemia has also been well characterized and dilatation of the left ventricle with a reduction in ejection fraction occurs early in the course of the condition in some patients (Parker et al., 1984). The Frank—Starling relationships between ventricular preload (assessed by measurements of end-diastolic volume and pressure) and stroke work are also disturbed ('flattened') so that increases in preload produce only a blunted increase in stroke work (Ognibene et al., 1988). These changes are reversible, providing the septic process is controlled, and may well reflect the presence of circulating myocardial depressant factors (Cunnion & Parrillo, 1989). A less sophisticated explanation for the observed myocardial systolic and diastolic dysfunction is ischaemia, related to abnormalities in total coronary blood flow and its distribution. Two studies have examined coronary blood flow in patients with severe sepsis and whilst both groups of investigators reported normal values for total coronary flow, these were not related to metabolic demand. The right ventricle is particularly at risk of developing endocardial ischaemic damage since pulmonary artery pressure is often elevated in severe septicaemia (mediator related and reflex hypoxic pulmonary arterial vasoconstriction; the application of high levels of positive pressure during mechanical ventilation) and right ventricular stroke work may be considerably increased. This occurs in the setting of a falling systemic arterial pressure with a reduction in right coronary perfusion pressure and flow (which usually occurs in this low pressure ventricle in both diastole and systole). Whatever the cause, myocardial dysfunction during septicaemia may form an important contribution to the development of hypotension.

**Acute respiratory failure**

Tachypnoea may be an early sign of septicaemia and often occurs in the absence of a pulmonary gas exchange defect. In this setting, the rapid respiratory rate and the consequent respiratory alkalosis appear to arise centrally, presumably through stimulation of the respiratory centre. If a pulmonary capillary leak syndrome does develop, changes in lung compliance may also contribute to this early hyperventilation. Septicaemia is a well recognized cause of an acute lung injury and pulmonary failure can be severe enough to merit the descriptive term 'adult respiratory distress syndrome' (ARDS). Various investigators have carefully defined the incidence of this complication of septicaemia and it is thought to be more commonly associated with Gram-negative sepsis (Kaplan, Sahn & Petty, 1979). Some 16—25% of patients will develop this complication of septicaemia and the occurrence of ARDS increases mortality rates up to and above 80% (Fein et al., 1983). An episode of shock usually precedes the development of pulmonary failure, and thrombocytopenia co-exists in 60% of cases. Obviously, sepsis can complicate the course of ARDS related to some other predis-
posing risk factor, e.g. pulmonary aspiration or lung contusion, and contribute to the development of multiple organ failure, the cause of death in 80% of those patients who fail to survive. In this situation, the evaluation of the presence or absence of sepsis is a difficult business (Norwood & Civetta, 1987) and the ever present risk of septicaemia associated with intravascular devices must be borne in mind. Nosocomial infection in patients with acute respiratory failure greatly increases their mortality rate and the emergence of coagulase negative staphylococci as the most important hospital acquired bloodstream infection has led to an appreciation of its effect on outcome (Martin, Pfaller & Wenzel, 1989).

Other organ systems

Disturbances in coagulation, renal function, brain function and other organ system function occur with monotonous regularity in the presence of septicaemia. These have been reviewed elsewhere (Harris et al., 1987; Bihari, 1989; Bihari & Neild, 1989). Suffice it to say that hepatic dysfunction seems to be a central issue in the ability of the host to mount an adequate but not excessive immune response to the infecting organisms. Numerous studies have demonstrated that hepatic function is a major determinant of outcome (Quale et al., 1988) but a major difficulty resides in attempting to obtain more sensitive tests of hepatic synthetic function.

Conclusion

At the moment, the major thrust in the clinical area of sepsis research surrounds, first, the case definition of septicaemia and severe sepsis in the absence of positive blood cultures, secondly, the role of endotoxaemia in predicting the presence or absence of bacteria and also the outcome of patients with septicaemia or presumed sepsis, and, finally, the use of monoclonal antibodies, e.g. anti-endotoxin antibodies, anti-TNF antibodies, in high risk patients in an attempt to prevent the development of shock and ARDS. Our own particular interest is in the use of vasodilator prostaglandins (specifically prostaclin) to manipulate microcirculatory blood flow in severe septicaemia (Bihari & Tinker, 1989). Further controlled trials of these various interventions are required but before they can proceed case definition must become more accurate with the inclusion of some means of scoring the severity of septicaemia. The latter is essential for prospective stratification within any clinical study and presently, all that is available is the Acute Physiology and Chronic Health Evaluation II scoring system and Stoner's sepsis score. These require further refinement.

Thus, despite the advances in our knowledge of the pathogenesis of the tissue injury associated with severe infection, fatal septicaemia continues to occur unabated and impervious in the main to the introduction of new and broader spectrum antimicrobials. Whilst most clinicians would agree that the best approach to septicaemia is its prevention, the next best step is undoubtedly prompt and appropriate treatment dependent upon early recognition.

References

Septicaemia—the clinical diagnosis


