# SEPSIS OR NOT? IDENTIFICATION OF THE SOURCE OF SEPSIS IN THE INTENSIVE CARE UNIT

**G A Richards**

A frequent difficulty in the intensive care unit is to determine whether sepsis is present and if so, its source. Any insult may initiate a pro-inflammatory response involving a cytokine network which may mimic the features of an infectious process.[1] Postoperatively, for example, patients frequently manifest with pyrexia, tachycardia, tachypnoea and a raised white cell count in response to the release of cytokines such as tumour necrosis factor (TNF) and interleukin-1 (IL1). Low-dose IL1 infusion causes fever, sleeplessness, anorexia, myalgia, arthritis and headache. At doses greater than 100 g/kg a rapid fall in blood pressure occurs. If combined with TNF the coagulation cascade is initiated.[2] Insults as varied as pancreatitis, polytrauma, multiple or incompatible blood transfusions, drug toxicity or thrombo-embolic events may manifest with the systemic inflammatory response syndrome (SIRS) as a consequence of cytokine release.[1]

Antibiotic resistance has become the scourge of modern ICUs. This is in part due to excessive and empiric use of antibiotics without prior confirmation and management of the primary source of sepsis.

Sepsis is defined as the documented presence of infection in association with features of a systemic inflammatory response:[1]

- Temperature > 38° or < 36° (core)
- Heart rate > 90/min
- Respiratory rate > 20/min or partial pressure of carbon dioxide ($PaCO_2$) < 4.31 kPa
- White cell count > 12 x $10^9$/l or > 10% bands.

Severe sepsis incorporates haemodynamic compromise and organ hypoperfusion. Other clinical features of sepsis which we find useful in our ICU are a declining platelet count, retention or lack of mobilisation of fluid, worsening organ function, increasing requirement for inotropes, and worsening glycaemic control.

Fever has various definitions. Some define it as a core temperature of > 38°C and others as two consecutive elevations of > 38.3°C.[3] However, it must be recognised that fever alone is inadequate to indicate the presence of an infection. Conversely, infected patients are often apyrexial, particularly the elderly, those on continuous renal replacement therapy, and those with open abdomens. Axillary temperatures should not be used, and oral temperatures are inadequate in ventilated unco-operative patients. Temperature is best measured electronically by means of intravascular or bladder thermistors, or by oral, rectal or ear probes.[3]

If features of a systemic inflammatory response are present, infection should be presumed until proven otherwise. If the site is not obvious it should be vigorously sought.

The sites that give difficulty are:

- the lungs
- the urinary tract
- wounds (including intra-abdominal sepsis)
- the gallbladder (cholecystitis)
- the intestine (*Clostridium difficile*)
- line sepsis
- the sinuses.

One of the first investigations performed when sepsis is suspected is blood cultures. These should be performed properly. They do not necessarily indicate the site of infection, but the type of organism may provide clues. Sensitivity is related to the volume of blood drawn (10 - 15 ml for each is adequate). Stringent skin sterilisation is necessary, and two sites should be employed. Cultures should be performed following a temperature spike and again 24 hours later. If cultures cannot be obtained from two peripheral sites, draw one peripherally and one from the most recently inserted venous catheter.[3] Positive blood cultures may, however, be difficult to interpret. In a recent study Henke[4] reviewed 121 blood cultures performed for clinical indications: 48 were positive, but of these 20 were thought to be false-positive; 44 had concurrent catheter tip infection, but in only 14 was this the same organism as that in blood culture. In only 19 patients were management changes made as a consequence of the culture.

The chest radiograph is a routine component of investigation. However, it is particularly inexact in determining the presence of pneumonia. A clear chest radiograph essentially excludes the diagnosis, but if it is not clear the differential diagnosis includes adult respiratory distress syndrome (ARDS), cardiogenic pulmonary oedema, pulmonary embolus, pleural effusion, fibroproliferation, haemorrhage, contusion, atelectasis and drug reactions. Whereas it is sometimes necessary to treat an infiltrate as a pneumonia empirically, it is preferable to document the presence of infection. Unfortunately no gold standard for the diagnosis of nosocomial pneumonia, and in particular ventilator-associated pneumonia (VAP), exists. Even positive cultures are confusing and do not clearly distinguish between colonisation and infection. The incidence of hospital-acquired pneumonia is estimated to be between 5 and 10 cases per 1 000 hospital admissions, increasing by as much as 6 - 50-fold in

*Department of Medicine, University of the Witwatersrand, and Multidisciplinary ICU, Johannesburg Hospital, Johannesburg*
**G A Richards**, MB BCh, PhD, FCP (SA), FRCP

ventilated patients.[5] Controversy exists with regard to invasive investigation of VAP. Protected specimen brushing (PSB) and directed bronchiolar alveolar lavage (DBAL) are frequently employed, but are themselves confusing. These tests would only be of value if they limited antibiotic use, allowed diagnosis to be made with a high specificity and sensitivity, and improved outcome. Current data have not proved that any diagnostic technique is better than any other. Very experienced groups report contradictory findings. Fagon *et al.*[6] and Chastre *et al.*[7] report excellent results for PSB but poor results for DBAL. Papazian *et al.*[8] find DBAL to be considerably better then PSB. In contrast to the above, Pugin *et al.*,[9] using a clinical pulmonary infection score consisting of six criteria, (oxygenation, radiography, semi-quantitative culture, temperature, blood leucocytes and tracheal secretions) reported a concordance of 93% between clinical and microbiological data.[9] The issue is further clouded by the study of Kirtland *et al.*,[10] in which no clinical criteria or combination of criteria correlated with the histological diagnosis of pneumonia. The same group later showed that even a histological diagnosis is difficult to make, as no standardised criteria exist.[11]

In terms of outcome benefit, Bregeon *et al.*[12] found no difference in mortality or duration of ventilation between PSB-positive and negative patients who had clinical pneumonia. This suggests that PSB results are irrelevant once there is a clinical diagnosis of pneumonia. In line with this, Timsit *et al.*[13] found that suspicion of pneumonia, not its microbiological confirmation, is the major determinant of outcome.[13] Identification of an organism following invasive investigation will take 48 - 72 hours and initial therapy will still be empiric. Luna *et al.*[14] examined the effects of initial inappropriate therapy and whether subsequent antibiotic change following identification of the organism and its sensitivity would make a difference to outcome. Fifty of 60 BAL-positive patients were treated with antibiotics preceding microbiological results:[16] had received adequate therapy and had 38% mortality; 34 received inadequate therapy and had 91% mortality despite changing to a more appropriate antibiotic once the results became available. Rello *et al.*[15] confirmed the need for initial adequate therapy, but found some opportunity to correct initial errors with data obtained by bronchoscopy. Rumbak and Bass[16] (endotracheal aspirate) and Kirtland *et al.*[10] (blind bronchiolar alveolar lavage), however, confirmed that material obtained by less invasive means is comparable with that obtained by PSB. It is probable that the same antibiotic corrections could have been made with organisms obtained by these methods. Inadequate treatment of infection in ICU patients has recently been confirmed to be an important determinant of hospital mortality.[17] Our unit uses routine surveillance by blind BAL performed twice weekly in all ventilated patients. Colonising organisms so obtained direct therapy if the patient later manifests evidence of infection.

The conclusions to be drawn are that clinical assessment is as good as any other method in determining diagnosis. Invasive tests are non-reproducible, contradictory, and have no impact on outcome. In addition, these tests are expensive and require special skills to perform. Finally, data from these tests are received too late to be of value or could be obtained by simpler means. Currently, in our unit a presumptive diagnosis of hospital-acquired pneumonia is made if there is a new infiltrate on the X-ray accompanied by features of sepsis. Surveillance procedures increase the probability of appropriate therapy.

Sinusitis is a frequently neglected source of infection. In the ICU sinusitis is usually associated with nasotracheal or naso-enteric tubes.[16] Diagnosis is difficult, and relies upon computed tomography (CT) scanning or sinus puncture and aspiration, followed by culture and sensitivity tests. Sinusitis may be sufficiently important to cause systemic signs of sepsis and to be the site of blood-borne sepsis.[18] Nasal intubation should be avoided, but where it has been utilised for longer then 48 hours there should be a high index of suspicion for sinusitis, particularly in the light of a recent study indicating that a vigorous search for and treatment of maxillary sinusitis in nasotracheally intubated patients improves mortality.[19]

One cause of conflict in the ICU is the persistently septic abdomen following rupture of a viscus, surgery or trauma. It is essential to be aware of the fact that the critically ill patient, who is often sedated and on analgesics, seldom has features of an acute abdomen. Planned relook laparotomy after definitive surgery on a contaminated peritoneal cavity has gained most popularity; however, mortality remains high.[20] Demand relook is at least as good as planned,[21] but the decision to re-open should be made by an intensivist experienced in the evaluation of systemic sepsis. If suspicion exists, the abdomen should be re-opened early rather than after delay with CT scans and ultrasound. A negative laparotomy is as valuable to the attending physician as a positive one.

Acute acalculous cholecystitis may develop in critically ill patients, and it appears to be increasing in incidence. Mechanisms involve ischaemia, reperfusion injury, or pro-inflammatory mediators. Diagnosis may be difficult as clinical criteria are nonspecific. Fever, leucocytosis and jaundice are frequently found in the absence of acalculous cholecystitis.[22] Ultrasound is the investigation of choice, gallbladder wall thickening of > 3.5 mm and the presence of pericholecystic fluid being the two most reliable criteria. The presence of sludge, intramural gas or distension (> 5 mm in transverse diameter) are additional helpful signs.[22] The CT scan is as accurate as the ultrasound and the diagnostic criteria are similar.[23]

Other uses for CT scanning are evaluation of the abdomen, particularly if the patient has not previously had a laparotomy. Unsuspected pancreatic pseudocyst or abscess may complicate surgery or trauma and intra-abdominal abscesses may cause occult sepsis. Renal, perinephric, psoas or hepatic abscesses

may be difficult to diagnose by ultrasound alone, particularly in the presence of ileus or previous surgery.

Diarrhoea is a frequent complication in the ICU as a consequence of, among other things, infection, antibiotics, hyperosmolar feeds, insufficient fibre or villous atrophy.[24] Infective diarrhoea should be the first of the differential diagnoses to be excluded because of the danger it confers. Stools should be sent for microscopy, culture and sensitivity (MC&S) and examined for the presence of leucocytes and red cells, the presence of which indicates infection, ischaemia, malignancy or pre-existent inflammatory bowel disease. The supernatant of the stool should be sent for testing for *C. difficile* enterotoxin. This does not depend on culture of the organism, and as a consequence the results can be obtained early, after 2 - 3 hours for the enzyme-linked immunosorbent assay (ELISA) and after 12 hours for the tissue culture assay. If one stool specimen is negative send another. If two specimens are negative empiric therapy is not recommended. If severe illness is present and one is awaiting diagnostic studies, empiric therapy with metronidazole is reasonable.[3]

Urinary tract infections are frequent and most often related to catheterisation. Bacteriuria is particularly frequent, but may represent colonisation only. The catheter should be clamped and a fresh specimen collected. Pyuria may indicate the presence of sepsis, but is not particularly helpful when it is only moderate as catheters and instrumentation may themselves cause pyuria.

Wound sepsis may occasionally be occult. Careful inspection of the wound for erythema, purulence or tenderness is necessary. If suspicion exists the wound should be opened and Gram staining and cultures performed on expressed pus.

Line sepsis is an important and often overlooked source of infection, and is covered extensively elsewhere in this journal.

Gallium scanning is occasionally used to identify a source of infection. However, it is not particularly helpful. In patients with ARDS it is 67% sensitive and 93% specific for extrapulmonary infection. In terms of identifying pneumonia in ARDS there is a 17% sensitivity and 100% specificity.[25]

Non-infectious causes of fever are frequent. Drugs can cause fever either directly (β-lactams, phenytoin) or by causing thrombophlebitis (erythromycin, potassium chloride, amphotericin). Reactions to drugs do not necessarily occur immediately after their administration; in one series the mean lag time before onset of fever was 21 days.[26] Rash and eosinophils are uncommon and the fever may take as long as 7 days to settle.[3] The neurolept malignant syndrome and malignant hyperpyrexia are occasionally seen. The commonest cause of the former is haloperidol, where centrally initiated muscle rigidity causes fever.

Malignant hyperpyrexia is most frequently associated with the operating room and is associated with succinylcholine and halothane. This condition results in intense muscle contraction related to the dysregulation of calcium release from the endoplasmic reticulum.

Acute myocardial infarction and Dressler's syndrome may cause fever. Thyrotoxicosis, acute adrenal insufficiency, subarachnoid haemorrhage, gout, fat embolus, deep-vein thrombosis and Stevens-Johnson syndrome are also culprits.

Diagnosis of sepsis in the ICU may well be difficult, but careful examination and directed investigation can usually determine the source of the infection. This represents a challenge to the intensivist, as inaccurate diagnosis can increase hospital stay, morbidity and mortality, and bring about development of antibiotic resistance. Conversely, over-investigation increases cost.

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