

Investigation of Suspected Infection in Critically Ill Patients

Local Guidelines

This section should be referred to in conjunction with local Trust guidelines. In addition the advice of a Consultant Microbiologist should be sought when there is doubt about the appropriate course of action, and in complex cases.

Clinical indicators of infection

Whenever possible, antibiotics should be avoided unless there is good evidence of clinically significant bacterial or fungal infection. Antibiotics are rarely indicated for the treatment of microbial colonisation, which commonly affects the respiratory and urinary tracts of critically ill patients. Another pitfall is the systemic inflammatory response to non-infective conditions such as major trauma and surgery, which may manifest many of the clinical features of infection.

In addition to universal signs of infection e.g. purulent sputum, erythema and discharge from a wound, other clinical indicators include:

- Pyrexia or hypothermia (temperature $> 38^{\circ}\text{C}$ or $< 35^{\circ}\text{C}$).
- Leucocytosis. A raised white cell count ($> 11,000/\text{ml}$) may indicate bacterial infection if associated with a high neutrophil count and increased immature forms. However, mild increases ($11\text{-}15,000/\text{ml}$) can be caused by any form of acute stress. In very severe sepsis, leucopaenia may occur ($\text{WCC} < 4,000/\text{ml}$)
- C-reactive protein (CRP). CRP levels are elevated as a result of trauma, infection or inflammation, and the range of concentrations found in ICU patients is wide.

There are several studies looking at the clinical utility of these parameters in the ICU setting¹⁻⁵. Data are often conflicting but, in general, such markers are non-specific and have to be interpreted in conjunction with the overall clinical picture. They should be used as supporting evidence to precipitate investigations for the presence of infection. They should not be used in isolation to justify the commencement of antibiotics. CRP measurement may also be used to monitor response to therapy and to predict clinical outcome^{6,7,8}.

- Procalcitonin (PCT). Serum PCT, a precursor of calcitonin, is a 116 amino-acid protein which can be used as a marker of sepsis⁹. PCT levels are elevated in severe bacterial and fungal infections, but not in viral infections or auto-immune processes.

PCT levels have been used to differentiate between severe systemic sepsis and other causes of SIRS¹⁰. It may also be a more reliable marker of sepsis and predictor of outcome than CRP¹¹⁻¹⁴. However, this is not a universal finding in the ICU setting^{15,16}. In addition, no studies to date have demonstrated that procalcitonin monitoring is cost-effective or improves patient care and clinical outcomes. Although a recent study¹⁷ suggests that procalcitonin monitoring can reduce antibiotic prescribing rates for patients presenting with lower respiratory tract infections, further studies are needed to ascertain its role in intensive care management.

- Hypotension. Septic shock is usually associated with vasodilatation and high cardiac output.
- Coagulopathy. Severe sepsis may be associated with Disseminated Intravascular Coagulation (DIC), manifesting as a bleeding tendency with increased prothrombin and partial thromboplastin times, thrombocytopenia, raised D-dimer and low fibrinogen.

However the Systemic Inflammatory Response Syndrome (SIRS) is also characterised by pyrexia, leucocytosis, hypotension and coagulopathy. Non-infective causes include pancreatitis, trauma, major surgery and burns.

Microbiological indicators of infection

Samples should be sent for culture **before** antibiotic treatment is started, in order to maximise the chance of identifying the responsible pathogen, but treatment of life-threatening infection should not be delayed while results are awaited. Choice of diagnostic tests should be guided by clinical suspicion.

Bacteraemia / fungaemia (including catheter-related infections)

Bacteraemia is a common feature of many serious community-acquired infections, such as pneumonia, meningitis, and urinary tract infection. Nosocomial bacteremia/fungaemia is also a common complication in intensive care and is increasing in frequency, mainly because of the extensive use of intravascular catheters¹⁸. Blood cultures are therefore an essential component of the investigation of suspected infection in any sick patient. If catheter-related infection is suspected, submission of simultaneous central line and peripheral blood cultures and the subsequent measurement of time to positivity may be of value¹⁹.

Ventilator-associated pneumonia (VAP)

The techniques available for the optimum diagnosis of VAP have recently been reviewed by²⁰. The diagnosis of VAP is usually based on three components – systemic signs of infection, new or worsening infiltrates on chest X-ray (CXR) and bacteriological evidence of pulmonary parenchymal infection. As outlined above, systemic signs of

infection are unreliable in the ICU setting. CXR findings of infection may be difficult to distinguish from other common pathologies e.g. pulmonary oedema, atelectasis. If microscopy and/or qualitative culture are performed solely on tracheal secretions or expectorated sputum the results obtained may not confirm that parenchymal infection is necessarily present or what its true cause is. In order to enhance diagnostic accuracy, a variety of more sophisticated techniques have been employed. Quantitative cultures of endotracheal secretions (using a cut off of $>10^6$ cfu/ml of respiratory secretions as a marker of infection) have been claimed to improve the differentiation between colonising flora of the upper airways and true causes of infection. Blind aspiration of lower airways secretions via an endobronchial catheter wedged in the tracheobronchial tree may allow the sampling of lower airways secretions without the need for formal bronchoscopy. If bronchoscopy is performed, broncheo-alveolar lavage or a protected specimen brush may be used to obtain diagnostic samples. All of these techniques carry different clinical risks and resource implications and their optimum use in the ICU remains an area of continued debate among intensivists²¹.

Although bronchoscopic techniques have been advocated²⁰, an alternative recommended is use of the Clinical Pulmonary Infection Score²². In immunocompromised and some other patient groups there may be a need to screen for opportunist pathogens e.g. *Pneumocystis jiroveci*, CMV, mycobacteria. Specialist advice should be sought where required.

Community-acquired pneumonia (CAP)

The appropriate diagnostic management of patients admitted to hospital with CAP has been outlined in the British Thoracic Society's own CAP guidelines²³. It is recommended that all patients should have the following general investigations:

- CXR
- Full blood count
- Urea & electrolytes
- Liver Function Tests
- C-reactive protein
- Oxygenation assessment

The following microbiological investigations are recommended:

- Blood cultures prior to commencement of antibiotics
- Sputum culture
- Paired serological samples (acute and convalescent) for viral & atypical serology
- Legionella urinary antigen testing
- Legionella cultures if bronchoscopy is performed
- Pneumococcal and chlamydia antigen testing should also be considered

Urinary tract infection (UTI)

Asymptomatic colonisation of urinary catheters is common in the ICU setting²⁴. Diagnosis of UTI on the basis of microscopy and culture of urine alone is unreliable. Other evidence of urinary tract infection must be present e.g. pyrexia, rigors. Catheter-associated bacteriuria has been defined as 10^5 cfu/ml or greater²⁴. Urine dipsticks (screening for nitrites and leucocytes) have been shown to be cost-effective technique in screening patients for bacteriuria in the ICU²⁵.

Meningitis (including meningococcal septicaemia) & encephalitis

The early management and diagnosis of meningitis and meningococcal septicaemia has recently been outlined by the British Infection Society²⁶. In addition to clinical diagnosis, the following investigations were recommended:

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- Full blood count
- Urea & electrolytes
- Blood glucose
- Blood gases
- Clotting profile
- Blood cultures
- EDTA blood for polymerase chain reaction (PCR)
- Throat swab

In patients with suspected meningitis who have signs of deteriorating conscious level or other organ dysfunction there should be early involvement of the critical care team and a low threshold for interventions to minimise the risk of secondary brain injury (e.g. mechanical ventilation, circulatory support). Early empirical broad spectrum antibiotic and antiviral therapy should be initiated in any cases of suspected meningitis / encephalitis; lumbar puncture (LP) may be appropriate in cases where there is reason to suspect atypical infection, but should only be performed when the patient's condition is adequately stabilised and contraindications (raised intracranial pressure, focal neurology, coagulopathy etc.) have been excluded. A normal CT brain scan does not exclude raised intracranial pressure. A delayed LP performed when the patient's condition has been stabilised may provide additional information that influences further management, for example, raised protein and positive antigen tests.. LP investigations should include;

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- Microscopy
- Culture
- Protein & glucose
- PCR

For those patients with suspected Herpes simplex encephalitis (HSE) European guidelines²⁷ recommend the following:

- CT/MRI
- EEG

- CSF microscopy
- CSF – PCR for Herpes simplex virus (HSV)
- CSF – HSV antibodies

Endocarditis

The optimum diagnosis of infective endocarditis (IE) has been recently outlined by the European Society of Cardiology²⁸. Those patients in whom there is a clinical suspicion of IE should be investigated as follows:

- Echocardiography – initial screening with transthoracic ECHO, progress to transoesophageal ECHO if high suspicion of IE
- Three or more blood culture sets (irrespective of temperature) taken at least one hour apart. If previous antibiotic therapy, these may not become positive at least up to 6-7 days after discontinuation. Ideally 10ml of blood (1-5ml in children) should be collected for each bottle.
- Additional serological investigations e.g. Q fever should be considered as appropriate

Intra-abdominal sepsis

Patients clinically suspected to have intra-abdominal infections should be diagnosed using a combination of microbiological and radiological/ultrasonic techniques. Microbiological investigations include blood cultures and culture of material e.g. pus, tissue obtained either at surgery or by radiologically-guided drainage/aspiration. Specimens obtained from drains may yield colonising flora that may not truly represent the nature of the deep infection.

Infective gastroenteritis

For patients admitted from the community with suspected infective gastroenteritis a stool sample should be sent for common enteric pathogens e.g. *Salmonella* sp, *Shigella* sp, *Campylobacter* sp. It is important to obtain an appropriate food and travel history because this may guide the laboratory in screening for other important pathogens e.g. *Vibrio cholerae*. For those instances where outbreaks of viral gastroenteritis are suspected, electron microscopy and other techniques may be employed to screen for Noroviruses. Some studies have suggested that patients who have resided in hospital for more than three days should only be screened for *Clostridium difficile* toxin because the yield of other pathogens is low²⁹. Further studies have suggested modifications to these protocols to minimise the risk of mis-diagnosis³⁰.

There may be many other patients in whom diagnosis of suspected infection does not fall under the above umbrella. In these instances it is important that the intensive care team discuss the optimum approach to diagnosis with microbiologists and infectious disease specialists as appropriate.

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