Pyrexia

Clinical problems

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Module Authors (Update 2011)

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LEARNING OBJECTIVES
After studying this module on Pyrexia, you should be able to:

1. Assess fever in the ICU and initiate an appropriate evaluation
2. Determine common causes of fever in the critically ill patient
3. Manage special forms of fever
4. Decide how and when to treat fever

FACULTY DISCLOSURES
The authors of this module have not reported any disclosures.

DURATION
7 hours

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# INTRODUCTION

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**INTRODUCTION**

Thirty per cent of patients will become febrile, while up to 90% of patients with sepsis will experience fever, during a stay in the intensive care unit (ICU). Fever in critically ill patients may be of infective, non-infective, or mixed origin. The confirmation of the source of fever is often difficult which leads to a diagnostic dilemma and a difficult decision (to treat or not to treat) often resulting in a variability of treatment response from the medical and nursing staff.

The Society of Critical Care Medicine practice parameters define fever in the ICU as a (core) temperature above 38.3 °C. The condition is caused by an imbalance between heat production and heat loss. In the clinical context, excessive heat generation is much more common than defective heat loss. The resulting disturbance may be transient and/or trivial or it may portend serious illness.

This module focuses on the differential diagnosis of fever rather than on the antimicrobial treatment of infection.

For current information on fever:
- Website of the Centers for Disease Control and Prevention (CDC) where current information on infection statistics and other relevant information is given. http://www.cdc.gov/
- Website of the journal Emerging Infectious Diseases, published by the CDC http://www.cdc.gov/eid
- Website of the Infectious Diseases Society of America, and the Emerging Infections Network http://www.idsociety.org/
- Website of the European Society of Clinical Microbiology and Infectious Diseases http://www.escmid.org
- Sepsis Resource Center and critical care pages http://www.medscape.com


Marik PE. Fever in the ICU. Chest 2000; 117(3): 855–869. PMID 10713016


**1/ ASSESSING AND MEASURING FEVER IN ICU**

Fever in an ICU patient is always a concern. The first and immediate priority is to determine its clinical significance.

**Assessment of fever of recent onset**

Fever has many causes depending on age, underlying illness, and the environment of the patient. Fever in a healthy adult commonly is considered as a result of viral infections such as influenza but in the hospital environment is considered of non-viral origin. In the critically ill, mechanically ventilated patient, for instance, the most common causes are a bacterial or fungal infection, unless proven otherwise. Non-infective causes of fever include thromboembolism, trauma, and others. The distinction between these various causes is important because of the difference in treatment and prognosis. In both medical and surgical critically ill patients, fever is caused by infective and non-infective conditions in roughly equal proportions. The latter tend to be confirmed once infective causes are ruled out; non-infective causes may include cerebral conditions affecting thermoregulation. Fever above 38.9 °C is more likely to be due to infective than non-infective causes, and vice versa. The higher the fever, the more likely it is to be of infective origin, but a temperature above 41.1 °C can be of neurological origin.

The presence of risk factors for nosocomial microbial infection in the critically ill patient render non-infective causes less likely. In fact, nosocomial infection complicates the hospital course of approximately 30% of critically ill patients, and fever of recent onset in the ICU is caused by nosocomial infection in more than half of cases.

Risk factors for microbial infection include:
- Advanced age
- Severe underlying disease
- Neutropenia
- Immunosuppression
- Intravascular catheters
- Intubation and mechanical ventilation
- Prolonged ICU stay
- Prostheses
- Foreign bodies
- Prior surgery
- Bladder catheters and wound drains
- Nasogastric tubes
- Neurological disease with impaired consciousness.

Stress ulcer prophylaxis is considered a risk factor for nosocomial infections associated with gastric colonisation by enteric organisms. In a large, hospital-based pharmaco-epidemiologic cohort, acid-suppressive medication use was associated with 30% increased odds of hospital-acquired pneumonia while in subset analyses, statistically significant risk was demonstrated only for proton-pump inhibitor use.
More importantly, the presence of invasive devices predispose to infection. Intravascular catheters are associated with catheter-related blood stream infections. Endotracheal intubation and mechanical ventilation are risk factors for ventilator-associated pneumonia and the presence of a nasogastric or nasotracheal tube is a risk factor for sinusitis.

Yeast and fungal infections are common in patients with severe underlying disease, in neutropenia, diabetes mellitus, renal failure, diabetes and after multiple courses of antibiotics. Furthermore, gastrointestinal surgery, open wounds, and a prolonged ICU stay, are risk factors for deep fungal infections. Risk factors for nosocomial infections in the critically ill are studied in:


Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. JAMA 2009; 301(20): 2120–2128. PMID 19470989


Appropriate investigations of a patient with fever should not involve an undirected battery of imaging, laboratory and microbiological tests but should be selected on the basis of a thorough clinical evaluation and targeted toward suspected sources of infection. Expeditious diagnosis is key to early effective therapy. In the diagnostic investigation of fever, the following sequence represents reasonable practice:


**Clinical appraisal**

Clinical assessment starts with a full history and complete physical examination. Assessment of fever of recent onset in the critically ill raises a number of questions:
• When did the fever start and did it relate to any clinical events e.g. to drainage of an infected collection or after removal of a central venous catheter (CVC), when catheter-related infection is suspected?
• Is there a clinically recognisable focus of infection?
• What are the likely micro-organisms involved?
• How high is the temperature?
• Are there risk factors for microbial infection?
• Are there possible non-infective causes?

Q. In the context of fever of recent onset, what are the important items in the clinical history and why?

A. In the case of nosocomial infection, important history might include prior haematological disease e.g. acquired immunodeficiency syndrome (AIDS), since chronic infective disease may flare up in the presence of a decreased immunocompetence. Other items from the history are the duration of tracheal or nasal intubation, mechanical ventilation and indwelling central venous catheters. You will want to know how long these different foreign bodies have been in place as a pointer to the likelihood of infection.

The physical signs of nosocomial infections can be subtle particularly in the patient with neutropenia or other causes of immune-suppression. In mechanically ventilated patients, the physical signs of ventilator-associated pneumonia may be manifest primarily by purulent sputum on tracheal suction. A decrease in oxygenation may suggest pneumonia or pulmonary embolism. Catheter-related infection may be accompanied by redness and discharge from the insertion site but occurs in the absence of such signs. In surgical patients, wound dressings should be removed to inspect wounds if they have not been seen by clinical staff during a scheduled dressing on that day. Wounds may need to be opened in case of suspected infection. Drain fluids should be examined for turbidity. *Clostridium difficile* infection and pseudomembranous colitis should be considered in any patient with fever and diarrhoea.

Q. Is fundoscopy or other specific physical examination procedure useful in the ‘septic work-up’ (see below) and why?

A. Fundoscopic and skin examination may point to evidence of (septic) emboli. Candidaemia may be more likely if there is widespread Candida infection and endophthalmitis. There may be evidence of decubitus ulcers and/or skin fold infection. The appearance of a new murmur may suggest endocarditis.

The ‘septic work-up’ or diagnostic approach to new onset fever in the critically ill can be summarised as follows:
Fever – notable features and measurement

Prior to assessment, you will wish to confirm the presence of fever and determine its severity. Response to fever varies with age. Elderly patients are unable to regulate their body temperature to the same degree as young adults, making them susceptible to extremes of temperature – older patients with serious infections have a substantial prevalence of apyrexia (20% to 30%) and a lower febrile response than younger patients. A lack of fever may contribute to lower resistance to infection, delayed recovery, and suboptimal outcome while lower febrile responses to infection are associated with a higher mortality rate and poorer prognosis. In children between the ages of six months and six years, febrile convulsions may occur.

Core temperature measurement is, of course, the gold standard and several methods may be used in the ICU, involving the placement of a thermistor or similar device in the pulmonary (or femoral) artery, the bladder or the oesophagus. In practice, however, surrogate site (rectal, oral or axillary) temperature measurement is often used (Table below).
Measurement of fever using different techniques at different body sites

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<th>Site</th>
<th>Method</th>
<th>Comments</th>
</tr>
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<td>Pulmonary artery</td>
<td>Mixed venous blood</td>
<td>Core temperature but pulmonary artery catheter required</td>
</tr>
<tr>
<td>Bladder measurement</td>
<td>Thermometer</td>
<td>Core temperature but ‘Foley’ catheter required</td>
</tr>
<tr>
<td>Infrared ear</td>
<td>Thermometer</td>
<td>Values a few tenths below values in the pulmonary artery catheter and brain</td>
</tr>
<tr>
<td>Rectal temperature</td>
<td>Mercury thermometer or electrical probe</td>
<td>A few tenths higher than (and lags behind) core temperature. Unpleasant and intrusive for patients</td>
</tr>
<tr>
<td>Oral measurement</td>
<td>Thermometer</td>
<td>Influenced by warmed gases delivered by respiratory devices, by eating and drinking</td>
</tr>
<tr>
<td>Axillary measurement</td>
<td>Thermometer</td>
<td>Underestimates core temperature, lacks reproducibility</td>
</tr>
</tbody>
</table>

Whether shell or ‘non-core’ temperature can be considered a practical equivalent to core temperature is controversial. Rectal temperature (although sometimes classified as a ‘core’ temperature) may lag behind rapid changes in actual core temperature and therefore is not regarded as a ‘real-time’ measurement of core temperature. Axillary and oral methods are less reliable in reflecting core temperature. Cold liquids, among others, may confound oral temperatures. Infrared tympanic membrane temperature measurement devices have gained some popularity but in the study below, oral thermometry was found to be more accurate when a pulmonary artery core measurement was not available. In addition, in patients with head injury or cerebral bleeding/stroke, brain and thus tympanic temperature may exceed core temperature, but the clinical significance is unknown.

Review the practice in your department concerning temperature measurement. When exploring the pros and cons, how do you rate the practice in your ICU?


An 86-year-old lady with multiple trauma receiving mechanical ventilation for two weeks develops fever (green line, °C), without tachycardia (blue line, b/min). The recording is from the bedside computer monitor, visualising continuous measurements (vertical lines are days). There is a diurnal pattern. The diagnosis made was ventilator-associated pneumonia attributable to *Pseudomonas aeruginosa*. The blue arrow indicates the day of starting piperacillin and tobramycin, and the 'lytic' resolution of the fever is illustrated.

Laboratory appraisal

The clinical assessment is supplemented by selected laboratory measurements. The commonest of these is the leukocyte and differential counts as signs of infection include leukocytosis and a 'left shift'. Investigators have searched for specific ‘sepsis’ markers including circulating C-reactive protein, procalcitonin and the cytokine, interleukin-6. Although the exact predictive values remain uncertain, some of these plasma factors can help to forecast the likelihood of microbial infection in a patient with fever, before the results of Gram stains, and particularly microbiological cultures, are available. On day six after trauma or surgery, development of fever and persistently high circulating IL-6 and C-reactive protein levels may be predictive for nosocomial infection. Similarly, the detection of endotoxaemia by means of rapid assay techniques may be of some predictive value in Gram-negative infection/bacteraemia and its associated morbidity.

The following papers address the (limited) value of surrogate indicators of microbial infection.


Imaging

Bedside chest radiography is routinely used to detect new pulmonary infiltrates in the ICU. In this condition and in sinusitis, CT scan is associated with fewer false negative results than plain radiography. The benefits of CT, however, only rarely outweigh the inconvenience and risk of transferring the patient to the radiology department (see later sections for further discussion).

Other imaging techniques include ultrasonography. Transoesophageal echocardiography can be of help for detecting pulmonary emboli and valvular lesions in endocarditis. Nuclear techniques can supplement other imaging studies, including CT and ultrasound, but are rarely used in critically ill patients with fever of unknown origin. Nuclear techniques that may be helpful to supplement imaging in the critically ill are discussed in:


PACT module on Clinical imaging

Culture techniques

Specimens from sites of suspected infection, together with blood samples when indicated, should be obtained as a matter of course for Gram stain, culture and sensitivity determinations. Taking cultures should precede the use of empirical antibiotics unless undue delays are anticipated. Aspiration of pleural fluid or ascites may indicate potential sites of infection. Aspiration of localised fluid collections or abscesses can be guided by ultrasonography or CT scans.

THINK: What are the indications for these types of radiological investigations and who is the best person to approach for advice in your institution?
Blood should be obtained percutaneously via venipuncture (or via ‘clean-stick’, newly introduced arterial or central venous catheters), and 10 ml placed in each of two bottles for aerobic/anaerobic cultures. At least two to three sets, 10 min apart, should be taken, after proper skin preparation.


**Microbiology**

The commonly identified micro-organisms causing infections in the ICU include Gram-negative bacilli (mainly *Enterobacteriaceae*, *Klebsiella*, *Pseudomonas*, *Acinetobacter* and Serratia spp.), Gram-positive bacteria such as coagulase-negative staphylococci and *S. aureus* and *Candida albicans*.

Blood culture results with *S. epidermidis* are considered clinically ‘significant’, if present in more than one bottle and are rapidly growing in culture. *Candida* spp. may cause catheter-related blood stream infections, wound infections, and peritonitis. Culture of *Candida* spp. may, of course, represent colonisation as opposed to infection, but there are no commonly accepted criteria to separate these conditions. Candiduria exceeding $10^5$ colony forming units/mL in two urine specimens taken before and after change of a bladder catheter in a patient with clinical signs of sepsis may point to *Candida* as the aetiology. A high Candida colony count in urine, recovery from two or more otherwise sterile sites (excluding urine and sputum) may point to Candida sepsis in the febrile ICU patient with leukocytosis (>12.0 x 10⁹/L). Candidaemia (e.g. after change of intravascular catheters) is indicative of infection. Candida endophthalmitis, oesophagitis, suppurative thrombophlebitis or wound infections/peritonitis (‘open abdomen’) may be the source of deep Candida infections. Further relevant details are to be found in the following reference.


Viral infections causing pneumonia, even in critically ill, immunocompromised (or immunocompetent) patients, are rare. Herpes virus, cytomegalo, adeno- or respiratory syncytial viruses or *Chlamydia* spp. are considered the most frequent causes.


**THINK** about the common clinical contexts relevant to these specific organisms. When do you think viral reactivation is harmful and when not?

**Q. Why is viral reactivation important in clinical management?**

A. In order to make an informed decision as to appropriate ‘best guess’ antibiotic treatment.

**Note** Rare fungal infections developing in the critically ill may include *Aspergillus fumigatus* lung infections after near drowning or in the neutropenic/organ transplant patient with underlying haematologic malignancy or immunosuppression. A rare cause of bilateral sinusitis may be infection with Rhizopus (mucormycosis), particularly in diabetics, as illustrated in the references below.


For further insight into the evolution of microbiology of nosocomial bacteraemia in the ICU, see:

For opportunistic infections in surgical patients:


**Systemic inflammatory response syndrome (SIRS)**

In any patient with fever, one has to consider the likelihood of microbial infection and sepsis as opposed to SIRS which has been defined as:

- Fever (>38 °C) or hypothermia (<36 °C)
- Tachycardia (>90 b/min)
- Tachypnoea (>20/min), or fall in arterial PCO2 (<32 mmHg)
- Leukocytosis (>12.0 x 10⁹/L) or leukopenia (<4.0 x 10⁹/L) or >10% immature (band) forms.

See PACT module on Sepsis and MODS.

Sepsis is defined as SIRS in the presence of a clinical or microbiologically proven infection. Infection is indicated by a host response to micro-organisms or the invasion of otherwise sterile host tissues by (replicating) micro-organisms.

However, the predictive value of SIRS for severe microbial infection may be poor; specificity is low and sensitivity high. For example, the criteria are often met in trauma patients even in the absence of microbial infection. Hence, the clinical value of SIRS is in doubt. Nevertheless, meeting severe sepsis (organ dysfunction associated with sepsis) and septic shock criteria (hypotension below 90 mmHg in sepsis despite volume resuscitation) carries a higher mortality rate than meeting SIRS criteria alone, so that the latter classifications may have prognostic (rather than diagnostic) significance.

**THINK:** The usefulness of SIRS and sepsis criteria in patients with fever remains unclear. The sensitivity of the syndrome may be too high and specificity too low for microbial infection, even when supplemented by other 'sepsis signs'.

You may wish to consider the following references.


Determine the prevalence (number of cases per total number of patients) and incidence (number of new cases per total number in a given time period) of SIRS and sepsis in your ICU population over three days, assuming that criteria must be met within a six-hour time window. What percentage is associated with positive culture?
2/ Determining the cause of fever in the critically ill patient

Causes of fever of recent onset in the critically ill patient, in descending order of likelihood.

**Infective causes**
- Ventilator-associated pneumonia
- Catheter-related infection
- Upper respiratory tract infection and sinusitis
- Gastrointestinal infection: *Clostridium difficile*
- Urinary tract infection
- Acalculous cholecystitis
- Endocarditis
- Primary Gram-negative bacteraemia
- Malaria.

**Non-infective causes**
- Pulmonary aspiration
- Postoperative fever (<48h)
- Trauma/haematoma
- Thromboembolism
- Gastrointestinal bleeding
- Drug-induced fever
- Febrile non-haemolytic red cell and platelet transfusion reactions
- Alcohol withdrawal
- Neuroleptic malignant syndrome
- Cerebral disease, including subarachnoid haemorrhage
- Gout
- Transplant rejection
- Neoplasia, including lymphoma
- Haematoma
- Myocardial infarction
- Addisonian crisis, acute adrenocortical insufficiency
- Acute pancreatitis.

For surveys of the evolution of the epidemiology of nosocomial infections in the ICU see:


**Infective causes**

**Ventilator-associated pneumonia**

The longer the duration of mechanical ventilation the greater the risk of developing ventilator-associated pneumonia (VAP). Sinusitis is also a risk factor for VAP. Early diagnosis and effective treatment is associated with a lower morbidity and mortality. Confirmation of the clinical diagnosis in a ventilated patient developing fever, impaired oxygenation and purulent sputum may be obtained by means of tracheal aspirates and a new infiltrate on chest radiography. The additional presence of pathogenic micro-organisms with leukocytes is diagnostic – see pulmonary infection score below.

The preceding table is adapted from:


CT scanning of the thorax provides better visualisation of infiltrates than bedside chest radiography. In selected cases of suspected VAP, CT scanning can therefore be useful, even though transportation to the CT department is necessary. It may also help to recognise and allow drainage of empyema.
Task 2. Determining the cause of fever in the critically ill patient

**Tracheal aspirates:** their diagnostic significance is greater if (semi-)quantitative rather than qualitative cultures are performed; this helps to obviate false-positive results by colonisation of upper airways in the absence of lower respiratory tract infection by the bacteria. Usually, a cut-off point of $10^5$ cfu/mL is taken. Indeed, some micro-organisms are obligatory pathogens while the low-grade presence of others, such as Gram-negative bacilli, may merely represent colonisation. Microscopy of the aspirates is necessary to exclude saliva with many epithelial cells, and elastin staining may confirm a lower (versus upper) respiratory tract origin of the aspirate. In the case of VAP, the aspirate typically contains numerous neutrophils.

**Distal bronchial specimens:** tracheal aspirate results are less specific than those of Gram stains, microscopy and cultures of lower (distal) pulmonary secretions obtained by bronchoscopy and bronchoalveolar lavage (BAL) or protected specimen brush (PSB). It remains unclear, however, whether antibiotic guidance based on the latter is associated with lower morbidity and mortality for suspected VAP than antibiotic treatment guided by tracheal aspirates. Nevertheless, utilisation of these invasive tools may prevent overtreatment by antibiotics and reduce antibiotic pressure. This may be increasingly relevant because of the increase in multiresistant pathogens causing VAP.

Finally, positive blood or, when present, pleural fluid cultures with the same organism as recovered from the airway can be found in VAP.

Before proceeding to the next section, consider searching the Web for evidence that treatment guided by BAL/PSB specimens is superior to that guided by conventional, less invasive techniques and also for more specific clinical indications for the use of the invasive technique. Then assess the views expressed below.

The table below outlines a diagnostic approach to VAP when invasive procedures are performed.

<table>
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<th>Criteria for the diagnosis of VAP</th>
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<tr>
<td>I Three or more of the following:</td>
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<tr>
<td>a) Rectal temperature $&gt;38.0$ °C or $&lt;35.5$ °C</td>
</tr>
<tr>
<td>b) Leukocytes ($&lt;10.0 \times 10^9$/L) and/or left shift or leukopenia ($&lt;3.0 \times 10^9$/L)</td>
</tr>
<tr>
<td>c) $&gt;10$ leukocytes per high power field in Gram stain of tracheal aspirate</td>
</tr>
<tr>
<td>d) Positive (qualitative) culture of tracheal aspirate</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>II New, persistent or progressive infiltrate on chest radiograph</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>III One or more of the following</td>
</tr>
<tr>
<td>a) Positive quantitative culture of bronchoalveolar lavage fluid ($&gt;10^4$ cfu/mL) or PSB ($&gt;10^3$ cfu/L) or $&gt;5%$ of leukocytes containing phagocytosed bacteria.</td>
</tr>
<tr>
<td>b) Positive blood culture with the same micro-organism as that present in the airway</td>
</tr>
<tr>
<td>c) Positive culture of pleural fluid</td>
</tr>
</tbody>
</table>
The following reference is in favour of invasive technique for VAP diagnosis to reduce antibiotic usage and to improve outcome.


A CDC paper on the diagnosis of VAP favouring invasive techniques can be found on the following e-reference http://www.cdc.gov/ncidod/eid/vol7no2/mayhall.htm

but the following papers oppose this approach:


Hence, choosing among strategies remains hard, is controversial and is dependent in part on local practices.

For review:


Q. Look at the chest radiographs of this ICU patient who developed fever of 38.5 °C and a deterioration in his oxygenation. The initial CXR is on the left and shows right lower lobe volume loss and some patchy infiltrate; the CXR on the right was taken 48 hours later. The patient was a 72-year-old male with cerebellar haemorrhage, a
Task 2. Determining the cause of fever in the critically ill patient

tracheal tube for mechanical ventilation and his sputum had become purulent. Interpret the CXRs and give your presumptive diagnosis.

Day 1       Day 3

A. The chest radiograph two days later (right), shows the development of a pleural effusion. Taking the radiological infiltrates together with the clinical signs (purulent secretions, gas-exchange deterioration and fever), there is presumptive evidence of ventilator-associated pneumonia.

Q. How would you prove a diagnosis of VAP?

A. Microbiological proof may be obtained by a positive culture from sputum or distal bronchial sample (see microbial diagnostic criteria above) or from the pleural fluid. In this instance, the cultures of tracheal aspirate and pleural fluid yielded *Serratia marcescens* which was subsequently successfully treated by ceftriaxone.

**Central venous catheter-related infections**

Catheter infection should be suspected in the febrile ICU patient with an intravascular catheter when

- There is fever or a positive blood culture in the absence of another evident source of infection
- The CVC dwell time exceeds 3 days
- Fever abates after catheter removal
- There are signs of local (exit-site) infection.

Signs of exit-site infection include redness and purulent discharge.

The definitive diagnosis of central venous catheter-related infection is normally made after CVC removal and demonstration of a positive catheter tip culture with an identical micro-organism grown from a percutaneous ‘clean-stick’ culture(s), drawn peripherally and simultaneously, from blood.

**Some important definitions**

Exit-site catheter infection is defined as the presence of positive quantitative catheter culture in the presence of symptoms of local infection (erythema, tenderness, induration, or purulence), in the absence of other foci.

Catheter-related blood stream infection (CRBSI) is diagnosed when the same organism is isolated (at higher concentrations – see below) on quantitative culture of the distal catheter segment and from the blood of a patient with
clinical symptoms of local or systemic infection and no other source of infection evident.

In the absence of laboratory confirmation, defervescence after removal of an implanted catheter from a patient with blood stream infection is considered indirect evidence of CRBSI.


Catheter colonisation is diagnosed when bacteria are cultured from catheter segments (more than 15 CFU for the semi-quantitative roller plate method or >100–1000 CFU for quantitative techniques) or blood drawn through the catheter; in the absence of local or systemic infection symptoms, or of positive cultures from peripherally taken blood.

Catheter contamination is diagnosed when bacteria are cultured from catheter segment (more than 15 CFU bacteria for the roller plate method or >100–1000 CFU for quantitative techniques) or blood drawn through the catheter, in the presence of systemic infection symptoms and positive cultures from peripherally obtained blood, that do not resolve after removal of the catheter.

The following sets of diagnostic criteria are variously used:

<table>
<thead>
<tr>
<th><strong>Catheter-related Blood Stream Infections (BSI) criteria</strong></th>
<th><strong>HELICS</strong> criteria</th>
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</thead>
<tbody>
<tr>
<td><em><em>CDC</em> criteria</em>*</td>
<td>Criterion 1 – catheter-related infection (CRI) 1</td>
</tr>
<tr>
<td>Criterion 1</td>
<td>Local central venous catheter (CVC)-related infection (without positive blood cultures).</td>
</tr>
<tr>
<td>Patient has a recognised pathogen cultured from one or more blood cultures and organism cultured from blood not related to an infection at another site.</td>
<td>• Quantitative CVC culture $10^3$ colony forming units (CFU)/ml or</td>
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<tr>
<td>Criterion 2</td>
<td>• Semi-quantitative CVC culture &gt;15 CFU and</td>
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<tr>
<td>Patient has at least one of the following signs or symptoms: fever (&gt;38 °C), chills, or hypotension and signs and symptoms and positive laboratory results not related to an infection at another site and common skin contaminant (i.e., diphtheroids [Corynebacterium spp.], Bacillus [not B. anthracis] spp., Propionibacterium spp., coagulase-</td>
<td>• Pus/inflammation at the insertion site or tunnel.</td>
</tr>
<tr>
<td></td>
<td>Criterion 2 (CRI 2) General CVC-related infection (without positive blood cultures).</td>
</tr>
<tr>
<td></td>
<td>• Quantitative CVC culture $10^3$ CFU/ml or</td>
</tr>
</tbody>
</table>

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negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.) cultured from two or more blood cultures drawn on separate occasions.

Criterion 3

Patient <1 year of age with at least one of the following signs or symptoms: fever (>38 °C core) hypothermia (<36 °C core), apnoea, or bradycardia and signs and symptoms and positive laboratory results not related to an infection at another site and common skin contaminant (i.e., diphtheroids [*Corynebacterium* spp.], *Bacillus* [not *B. anthracis*] spp., *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp.) is cultured from two or more blood cultures drawn on separate occasions.

See Mermel LA et al below for the 2009 updated guidelines of the Infectious Diseases Society of America (IDSA) which state that a definitive diagnosis of CRBSI requires

- the same organism grow from at least one percutaneous blood culture and from a culture of the catheter tip or
- that two blood samples be drawn (one from the catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or differential time to positivity (see below under ‘CRI diagnosis without CVC removal’).

- Semi-quantitative CVC culture >15 CFU and
- Clinical signs of systemic sepsis improve within 48 hours after catheter removal.

Criterion 3 (CRI 3)

- Blood stream infection (BSI) occurring 48 hours before or after catheter removal and
- Positive culture with the same micro-organism of either:
  - Quantitative CVC culture $10^3$ CFU/ml
  - Semi-quantitative CVC culture >15 CFU or
  - Pus from the insertion site

Alternatively, if paired blood samples are taken from blood and from the CVC:

- Quantitative blood culture ratio CVC blood sample/peripheral blood sample >5 or
- Differential delay to positivity of blood cultures: CVC blood sample culture becomes positive 2 hours or more before peripheral blood culture (blood samples drawn at the same time)

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Causative micro-organisms include coagulase-negative staphylococci, *S. aureus*, *Enterococcus*, Gram-negative and *Candida* spp. The following references describe these criteria and preventable risk factors for infection.
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CRI diagnosis without CVC removal

Two recognised methods of catheter-related blood stream infection diagnosis are:

- Differential time to positivity: a relatively rapid (by at least 2h) onset of a positive culture in blood drawn via the CVC as compared to a paired sample from peripheral blood.
- Quantitative blood cultures: a quantitative organism ratio of at least 3:1 colony forming units (CFU) per ml between paired samples drawn from the catheter hub and peripheral blood cultures respectively.

Hence, paired blood cultures may be used, one taken through the catheter and the other via a ‘clean-stick’ (percutaneous) blood culture and presuming the patient is reasonably stable, the CVC may remain in situ until results from such cultures become available.


Other methods that have also been reported to be able to help diagnose catheter-related BSIs without catheter removal include acridine orange/Gram staining of blood drawn through the catheter, brush specimens of endoluminal contents and cultures from the hub surface and skin at the catheter exit-site. Indeed, direct (acridine orange/Gram) staining techniques of bacteria (in

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leukocytes) from catheter segments and blood may give results earlier than cultures.

Non-removal of the CVC is only acceptable in stable patients. If it is decided to remove the catheter, both the tip and the intradermal part should be cultured (semi-) quantitatively (roller plate method). A change of catheter over a guide wire in case of suspected catheter-related infection carries a risk of reinfecting the new catheter, such that infection does not resolve, and it is not recommended. The risk should be weighed against the mechanical risks associated with a new puncture and insertion site.

For an overview and guidelines in diagnostics, see:


Incidence of CRBSI

Depending on the type of unit and patient, among other factors, the rate of catheter-related blood stream infection varies between 0 and 33% (mean 5%) of catheters, or an incidence density of 2.8 to 12.8 episodes per 1000 catheter days.

Implementation of a multiple approach prevention strategy can decrease the number of catheter blood stream infections from 11.3 episodes per 1000 patient days to 3.8 episodes.

Prevention of catheter-related infection is of utmost importance, see:


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or

http://www.cdc.gov/ncidod/dhqp/gl_intravascular.html

What is the incidence of central venous catheter-related infection in your unit and does this necessitate a change of insertion and maintenance policy?

Complications of catheter-related infection other than severe sepsis and septic shock include endocarditis, and metastatic abscesses, thrombosis and supplicative phlebitis.

Management of CRI

Treatment is outside the scope of this module but the guidelines on the management of CRI of the Infectious Diseases Society of America (IDSA) is recommended and is available (http://www.idsociety.org/) – see Mermel LA et al below


http://cid.oxfordjournals.org/content/49/1/1.full#sec-3

Sinusitis

Nasogastric and nasotracheal tubes are important risk factors, and should be removed if present during treatment of sinusitis. Prolonged nasotracheal intubation is particularly associated with sinusitis; this type of airway is often converted to an oral tube when prolonged intubation is anticipated. Sinusitis is a risk factor for ventilator-associated pneumonia (VAP). Hence, a search for and treatment of sinusitis in febrile patients may prevent VAP and associated mortality. Fever and purulent nasal discharge in the presence of nasal tubes may point to nosocomial sinusitis. The maxillary sinuses are most commonly affected, but sphenoidal or ethmoidal sinusitis, whether or not accompanied by maxillary sinusitis, is increasingly recognised. The diagnosis is difficult, even in the case of maxillary sinusitis, since bedside plain radiograms (Caldwell and Waters’ view) may not be sensitive and specific. This may be overcome by a CT scan.


Q. Considering the risks involved in transporting a critically ill patient to the radiology department, in what circumstances might it be justified to perform a CT examination to confirm a diagnosis of sinusitis?

A. If the patient has to be transported for investigation of another major problem. Some institutions may also perform a CT scan when sinusitis persists or recurs despite adequate treatment (drainage and lavage) for 72h.

Opacification or fluid-air levels necessitate needle aspiration, microscopy and culture of secretions to confirm a radiologic diagnosis. Only half the patients with a radiological diagnosis are confirmed to have sinusitis on aspiration. A radiological diagnosis is confirmed on aspiration if staining and culture yield neutrophils and micro-organisms at a concentration >10³ CFU/ml. Gram-negative bacteria are often involved, and polymicrobial infections are relatively common. Treatment of maxillary sinusitis includes needle aspiration, lavage and, sometimes, systemic antibiotics. The clinical and radiographic features of infection should abate within a few days, following the start of appropriate treatment. Rarely, persistent or recurrent sinusitis may necessitate surgical exploration.

Q. Examine this CT scan from a 54-year-old male admitted because of respiratory insufficiency in the course of Legionella pneumonia. Day 11 of mechanical ventilation was complicated by fever, leukocytosis, and purulent nasal discharge, in spite of systemic antibiotics. What is your presumptive diagnosis and how would you prove it?
Task 2. Determining the cause of fever in the critically ill patient

A. The CT scan demonstrates fluid levels in both maxillary sinuses. The diagnosis of sinusitis can be confirmed if aspiration reveals microscopic and culture evidence for bacterial infection. Specimens obtained by aspiration revealed some leukocytes on Gram staining and Gram-positive cocci. Cultures from both sinuses grew *Candida albicans*. The condition cleared following repeated lavages.

**Urinary tract infections**

Most critically ill patients will have indwelling urinary bladder catheters. Nevertheless, a urinary tract infection is rarely the cause of fever in the critically ill, even though colonisation (bacteriuria at $>10^5$ CFU/ml) is common. Fever, leukocytosis, pyuria and a known pathogen in urine with the same pathogen cultured from blood points to a urinary tract infection in the febrile critically ill patient that should be treated by antibiotics. Obstructed catheters should be replaced.


Acute acalculous cholecystitis

After multiple trauma, burns, severe sepsis and major surgery, the gallbladder may become inflamed in the absence of gall stones. This inflammation, called acalculous cholecystitis, has an estimated incidence of 1.5% especially in septic patients or in patients recovering from abdominal sepsis. The low incidence is probably because of the non-specific clinical signs (pain in the right upper quadrant and nausea) and laboratory work-up. The detected wall thickness >3 mm, intramural lucencies, gallbladder distension, pericholecystic fluid, and intramural sludge are helpful radiological findings while hepatobiliary scintigraphy is characterised by a high false-positive rate (>50%). Frequently, the diagnosis is delayed and the disease progresses to ischaemia, gangrene and perforation, indicating the necessary high index of suspicion while the treatment of choice is cholecystectomy. However, in very unstable patients, radiologic percutaneous drainage (cholecystostomy) may be preferred as a temporary measure and has replaced surgical cholecystectomy as a first choice treatment in many centres. In many patients, antibiotics will be prescribed, aimed at the causative organism, identified after percutaneous puncture and culture of the bile. For further details see:


Other causes

Be aware of central nervous system infections in patients with (internal or external) neurosurgical monitoring or draining devices. Coagulase-negative staphylococci are often involved. Suspected infection should prompt obtaining cerebrospinal fluid (CSF) for Gram stain and culture.

Pseudomembranous colitis caused by Clostridium difficile has become a prevalent problem in many ICUs. In milder forms of the infection, diarrhoea may be the only feature. C. difficile-related diarrhoea is a relatively frequent occurrence in the critically ill, particularly if there has been treatment with multiple courses of broad-spectrum antibiotics. More severe forms of the disease are frequently characterised by a marked leukocytosis and elevated creatinine. Occasionally, an acute abdomen may result from C. difficile infection and surgical colectomy may be required. More virulent strains causing severe disease have recently emerged.

The bacteria can be transmitted from patient to staff and vice versa, so that inadequate handwashing (alcohol gel is inadequate and soap and water is required for spore removal) may result in small outbreaks in the ICU. The diagnosis is established by a positive faecal toxin A and B (or tissue culture cytotoxicity) assays and increased faecal leukocytes. A negative...
immunoassay does not rule out the diagnosis. For further reading:


Non-infective causes

Half of fever episodes in the ICU are of non-infective origin without the temperature usually exceeding 38.3 ºC. The medical history, including recent interventions along with the physical examination aids the clinician in narrowing down the differential diagnosis. However, the type of ICU population (e.g. medical vs surgical patients), the specific type of patients (e.g. immunocompromised, elderly), the history of recent epidemics and the local epidemiology must be taken into account.

**Drug-fever**: has an unknown incidence (3%–7% of febrile episodes are attributed to drug reactions but many cases remain undiagnosed), a temperature range from 38.8 ºC (102 ºF) to 40 ºC(104 ºF) and is a difficult diagnosis (usually established by exclusion because of the non-specific signs and laboratory tests), shaking chills and spiking temperatures. A concomitant maculopapular rash makes the diagnosis simple but accompanies fever in only 5%–10% of cases. Rarely an increased leukocyte count with a left shift, peripheral eosinophilia, a moderate elevation of serum transaminases, and a markedly elevated erythrocyte sedimentation rate (>100 mm/h) are recorded.

The signs that are associated with drug-fever are a lack of appropriate pulse rate response and a relative bradycardia in the absence of intrinsic conduction.
defects or beta-blockade. Any drug can cause fever due to hypersensitivity producing fever alone, with local inflammation at the site of administration (phlebitis, sterile abscess, soft tissue reaction) or because of the delivery systems (diluent intravenous fluid, intravascular delivery devices). The high-risk agents for drug-fever are all antibiotics (especially β-lactams), anti-epileptic drugs (especially phenytoin), anti-arrhythmics (mainly quinidine and procainamide), anti-hypertensives (α-methyldopa), diuretics, and stool softeners. Antibiotics with a lower risk for drug-fever development are: clindamycin, vancomycin, chloramphenicol, aztreonam, doxycycline, erythromycin, imipemen, quinolones, and aminoglycosides.

The time between initiating a drug and fever appearance is estimated to be 21 days (median 8 days) while the fever resolves usually within 72 hours after removing the offending drug. When a rash is present it may persist for days or weeks. The usual scenario of drug-fever in the ICU includes a patient in whom an already diagnosed infection is resolving and after an initial defervescence in temperature, a recurrence of fever is noticed. In this type of patient, the antibiotics should be discontinued if the infection has resolved or another infected site has not been detected. If the patient is stable, but the infection has not resolved, then the presumed offending agent should be removed and a modification to antibiotics, without potential sensitising, according to the spectrum of pathogens should be performed.


In cardiac care units (CCUs), the main causes of non-infective fever include: myocardial infarction, Dressler’s syndrome with pericarditis, thromboembolism, thrombolytic therapy with haemorrhagic complications and anti-arrhythmic medication (e.g. procainamide, quinidine), and deep venous thrombosis.

In a neurosurgical ICU, the posterior fossa syndrome is a common cause of non-infective fever that mimics meningitis with stiff neck, low level of glucose/increased level of protein in cerebrospinal fluid, and predominance of polymorphonuclear leukocytes in cerebrospinal fluid (CSF) as a result of blood leakage into CSF. The differential diagnosis from bacterial meningitis is based on the negative cultures and the gradual lessening of meningeal symptoms as the number of red blood cells decreases in the CSF with time.

Other causes are: central fever (caused by intracranial lesion or trauma affecting the brain or hypothalamus that is resistant to antipyretics, exceeds 39 °C or 106 °F and is characterised by absence of perspiration); the use of anticonvulsive medications; deep venous thrombosis and fat embolism syndrome in trauma patients. In the acute phase after head injury, the appearance of pyrexia is extremely frequent and deleterious to cerebral perfusion (CCP) and intracranial pressure (ICP); while lack of treatment by
antipyretics has been correlated with a longer ICU stay. Other causes of nosocomial fever in the ICU include adrenal insufficiency, acute pancreatitis, decubitus ulcers and gastrointestinal haemorrhage.


Blood transfusions may elicit acute febrile reactions, even in the absence of bacterial contamination or haemolysis. Both acute, but more often, delayed haemolytic transfusion reactions may also be responsible for the fever. (Sub) acute febrile reactions without haemolysis (negative direct antiglobulin test) are caused by antibodies present in the recipient’s plasma and directed against HLA antigens on leukocytes in the donor’s blood. Occasionally, the donor’s blood is contaminated by micro-organisms and elicits fever in the recipient. Acute or subacute febrile reactions during red cell and platelet infusions should lead to discontinuation of the transfusion. Both donor and recipient blood should be sent for culture and haematological investigation.

Alcohol withdrawal is often seen in the first 48 to 72 hours following hospitalisation and can often result in confusion with infection. Infection, hepatitis or pancreatitis should therefore be sought and excluded. Alcohol withdrawal leads to autonomic disturbances with sweating and fever. Benzodiazepines are the drug of choice for treatment. An overview is given in:


Contrary to common belief, atelectasis does not cause fever. However, atelectasis may become infected and constitute a nidus of pneumonia.
3/ Fever in specific categories of critically ill patient

Some categories of critical care patients deserve special mention. In some centres, surgical ICU is a separate entity but even where surgical patients are part of a general critical care population, some distinctive considerations pertain particularly in the early postoperative period. Fever in the immune suppressed and in neurological patients is also included here.

The surgical critical care patient – determining the cause of fever

The normal response to trauma and surgery includes release of pro-inflammatory mediators and an elevation of body temperature that usually does not exceed 38.5 °C and does not last longer than two days, unless the surgery was done for infection itself, e.g. peritonitis. Hence, any elevation of temperature above 38.5 °C, lasting longer than two days or developing on the third day, may indicate concomitant microbial infection and sepsis. About 10% of trauma patients develop a nosocomial infection.

Trauma has some immunodepressant effect thereby increasing the risk for infection.

Other risk factors relate to advanced age, underlying morbidity and extent of trauma and surgery. Risk factors also include prolonged hypotension, haematoma, foreign bodies and blood transfusion. Repeated and careful searches for a source and micro-organisms are mandatory in these patients. Gram-negative pneumonia and wound infection are among the most common sources. Careful search should be made for an infective focus, including removal of dressings and wound inspection. Bear in mind, however, that at least 35% of episodes of fever after trauma or surgery are of non-infective origin, and thromboembolism may lead the list of causes.

Causes of fever of recent onset and infection in descending order of likelihood are:

- Nosocomial pneumonia (and rarely empyema)
- Urinary tract infection
- Wound infection
- Catheter-related infection
- Sinusitis
- Gram-negative bacteraemia
- Miscellaneous.

Empirical antibiotics should only be given after appropriate clinical assessment and provisional diagnosis, imaging and obtaining specimens for culture. Antibiotic therapy if started should be reviewed, in the clinical context, once staining and culture results become available.
**Wound infection**

Obviously, wound infection is a major cause of fever after trauma and surgery. The frequency after surgery varies between 3.5 and 5%.

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**Q. Name at least four risk factors for surgical site infection (SSI).**

A. Risk factors include advanced age, prolonged hypotension, haematoma, malnutrition, diabetes mellitus, foreign bodies, blood transfusion, and ‘dirty’ surgery.

The infections are mostly caused by coagulase-negative staphylococci (and *S. aureus*), enterococci, Gram-negative bacteria and *Candida albicans*. Redness, discharge, swelling and pain are features of infection, and have a peak on the seventh postoperative day. Early (within three days) wound infections include necrotising fasciitis caused by virulent Streptococcus species, gas gangrene and abscesses with *S. aureus*. Later infections may harbour mixed flora or Gram-negative rods, either as cellulitis, necrotising fasciitis or abscess.

Wound infections may thus include clostridial cellulitis (caused by *Clostridium perfringens*), synergistic necrotising soft tissue infections including Meleney’s synergistic gangrene (advancing gangrene of the abdominal wall) caused by microaerophilic streptococci and *S. aureus*, and Fournier’s gangrene (of perineum and scrotum) caused by obligate anaerobic streptococci and facultative anaerobes. Necrotising fasciitis can be polymicrobial (aerobic and anaerobic Gram-negative bacilli, enterococci, *S. aureus*) or can be caused by *Streptococcus pyogenes* Group A.

A wound infection by toxin producing *Staphylococcus* or Streptococcus spp. can cause a toxic shock (like) syndrome. Any wound should be opened and cultured if there is a high index of suspicion of wound infection. Necrotising fasciitis is an emergency, the management of which includes necessary wide excision and drainage.

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**Q. How would you treat toxic shock syndrome?**

A. The toxic shock syndrome is treated by wound drainage (or wide excision in the case of necrotising fasciitis), removal of foreign bodies associated with development of the syndrome, and an extended spectrum penicillin combined with clindamycin. The treatment of shock consists of fluid loading and, if needed, inotropic agents.
Q. What is the role of immunoglobulins in the treatment of toxic shock syndrome?

A. Their value of immunoglobulins and hyperbaric oxygen is unclear. In life-threatening cases, the potential advantages may outweigh the current lack of positive randomised clinical trials. For further reading on this subject, see the references below. A study comparing intravenous immunoglobulins in toxic shock syndrome with historical controls, not receiving such treatment, suggested a reduced mortality rate.


The abdomen

In patients with suspected intra-abdominal sepsis, the decision to proceed with laparotomy is hard, particularly after a prior laparotomy, with or without peritonitis. Leakage of anastomoses and ischaemia/perforation leading to intra-abdominal abscesses, are most often involved, followed by postoperative cholecystitis and diverticulitis. Conversely, shock in the course of extra-abdominal sepsis may occasionally result in ischaemia, necrosis and perforation of (small) bowel segments, necessitating laparotomy, resection and drainage, if the patient is considered appropriate for surgery.

After a primary laparotomy, persistent fever and leukocytosis, in spite of antibiotics and in the absence of an overt extra-abdominal source, may be indicative of intra-abdominal infection. Other signs that may point to (recurrent) intra-abdominal sepsis and should lead to consideration of relaparotomy are respiratory failure, renal failure, ileus, wound infection, mental changes, abdominal pain, and previous contaminated surgery.

On the basis of these variables, scoring systems have been developed to help decision-making for relaparotomy. Careful imaging procedures (CT scan) are helpful in guiding surgery, while laboratory tests are not. Nevertheless, laparotomy without specific indications appears diagnostic in more than half of cases of suspected intra-abdominal sepsis. The mortality risk of a negative laparotomy in the critically ill is about 15%, while unrecognised intra-abdominal sepsis may have a mortality rate exceeding 50%. A laparotomy should not be withheld in such patients when there is a high index of suspicion for intra-abdominal sepsis. Most common micro-organisms include Gram-negative and Enterobacteriaceae.
The decision for relaparotomy should, on every occasion, be based on a careful consideration of possible benefits and harm in the individual patient. Scheduled or planned relaparotomies may be of doubtful value. You may wish to discuss this statement with surgical colleagues.

Determine retrospectively the frequency of a correct diagnosis for the last ten (re)laparotomies performed in your unit on the basis of suspected intra-abdominal sepsis.


Fever in immunocompromised patients

See PACT module on Immunocompromised patients

The immunocompromised host includes patients with immunological or haematological disease or those receiving immunosuppressive therapy, including steroids and anticancer drugs, for autoimmune disease or after organ transplantation. Moreover, the hypo-gammaglobulinaemic or post-splenectomy patient may have some immune defect, as shown by their susceptibility to pneumococcal sepsis and shock, often with a fatal outcome. Cellular immune defects predispose to infections with intracellular micro-organisms. Other risk factors for infection in cancer patients include the invasive procedures these patients undergo and the devices they receive. Neutropenic cancer/haematologic patients (neutrophil count <1.0 x 10⁹/l) with fever may have fewer clinically obvious signs and symptoms of infection than non-neutropenic patients. They are therefore treated more often on an empirical basis, even before a source and associated micro-organisms have been identified. The risk of microbial infection increases with the severity and duration of neutropenia. Nevertheless, microbiological cultures are positive for bacteria in less than 40% of febrile episodes during neutropenia. Pneumonia and catheter-related infections are the most common sources. Treatment with growth factors may not help to overcome infection developing during neutropenia in the critically ill. Nonetheless, in many centres growth factors are used routinely post chemotherapy (with the exception of haematological malignancies). Their use in non-neutropenic patients is also controversial. Overviews are given in the following references:

Task 3. Fever in specific categories of critically ill patient


Review the practice in your own unit concerning the administration of growth factors in neutropenic patients. What evidence is available for giving this? Is there a difference in practice worldwide?

Patients with human immunodeficiency virus (HIV) infection, whether or not complicated by AIDS, may require admission to the ICU, mainly because of respiratory insufficiency associated with pneumonia. Pneumonia is the major source of infection in AIDS patients with fever in the ICU. The latter still most often involves Pneumocystis jirovecii. Identification of the micro-organism on methenamine silver stains of respiratory secretions or with help of immunofluorescent monoclonal antibody techniques establishes the diagnosis. HIV infection also increases the risk of (penicillin-resistant) pneumococcal pneumonia. Opportunistic infections further include Mycobacterium avium complex disease, tuberculosis, cytomegalovirus infection, histoplasmosis, toxoplasmosis and leishmaniasis.

Non-infective causes of fever include lymphomas and thrombophlebitis. Other conditions requiring intensive care may include the recently recognised complications of extensive and aggressive antiretroviral therapy including hepatic steatosis and lactic acidosis. The immune reconstitution syndrome at the start of antiretroviral therapy and pancreatitis associated with these drugs may be causes of fever in HIV-infected persons in the ICU.


http://journals.lww.com/co-criticalcare/Abstract/2000/10000/The_HIV_infected_patient_in_the_intensive_care.5.aspx

Q. How would you treat Pneumocystis jirovecii pneumonia in a mechanically ventilated patient?

A. The standard treatment includes cotrimoxazole (sulfamethoxazole and trimethoprim) at high doses intravenously and systemic steroids. Oxygen therapy or mechanical ventilation may be required for supportive care. Compliance of the lung is often quite low, so that permissive hypercapnia may be necessary to limit high inflation pressures.
Fever in neurological disease

Fever in patients with cerebral disease is especially dangerous. After acute stroke and head injury, brain temperature (directly measured) may even exceed body temperature. After stroke or neurotrauma, fever may be associated with increased damage and a worse neurological outcome. It is believed that increasing oxygen demand of the brain augments susceptibility to hypoperfusion. Fever in the neurological critically ill patient therefore warrants a rapid assessment of potential infective causes, including meningitis. This may be particularly difficult, since fever may have a non-infective origin, i.e. reset of the hypothalamic thermostat by the cerebral damage. Only a minority of febrile patients with serious cerebral disease have an identifiable infective source. Regardless of the origin, it is generally recommended that a febrile patient with serious cerebral disease be treated with antipyretics, in order to lower cerebral oxygen demand, decrease secondary brain damage, and improve (neurological) outcome.

Antipyretics may include paracetamol (acetaminophen) by the oral, nasogastric, intravenous or rectal routes and/or by enteral or intravenous diclofenac (0.04 mg/kg/hour by continuous i.v. infusion – max daily dose 150 mg – not available in the US). The benefit of lowering the temperature to prevent secondary brain damage is probably greater than the disadvantage of losing a marker for the response to antimicrobial drugs. Obviously, antimicrobial agents are required in the presence of infection.

Examine the changing opinions over the past decade of the value of therapeutic cooling to reduce/prevent secondary brain damage. Is there now a consensus? Examine current practice in your institution.

In the following references the authors suggest that body temperature be maintained in a safe, normothermic range (e.g. 36.7 °C to 37.0 °C) for at least the first several days after acute stroke or head injury.


This recent ESICM Flash Conference addresses the current knowledge of the role of hypothermia in a variety of brain injury circumstances. Peter Andrews, Edinburgh, UK. Resuscitating the brain from global ischemia: hypothermia and beyond. Summer conference, Dublin, 2010.
Identifying special forms of fever

Heat stroke is included in the module on Environmental hazards. Other circumstances where the fever may be especially high are malignant hyperthermia, neuroleptic malignant syndrome and lethal catatonia. See PACT module on Environmental Hazards.

Malignant Hyperthermia (MH) can be caused by succinylcholine and inhaled anaesthetics administration (especially halothane). MH is more common in the operating room than in the ICU and occurs after general anaesthesia with depolarising agents in patients with a mutation in the calcium channel of sarcoplasmic reticulum.

The Neuroleptic Malignant Syndrome (NMS) resembles malignant hyperthermia and may occur after single or repeated doses of neuroleptic drugs in any patient. It is thought to be a consequence of blockade of dopamine receptors from antipsychotic agents such as phenothiazines, thioxanthenes or butyrophenones e.g. haloperidol.

Both MH and NMS inhibit hypothalamic heat-regulation mechanisms generating high fever, muscular rigidity, and increased creatine phosphokinase concentrations. The main difference between these two clinical entities is the initial muscle contraction which is centrally mediated in NMS and peripherally mediated in MH. The Serotonin syndrome caused by excessive stimulation of the 5-HT1A-receptor by various psychiatric medications may be confused with NMS. It may be exacerbated by the concomitant linezolid therapy.

The central problem of these syndromes is calcium overload in muscle consequent on certain stimuli. There is an in vitro (caffeine-halothane contracture) muscle test to detect susceptibility to malignant hyperthermia. The family of a patient with malignant hyperthermia should be counselled. Malignant hyperthermia is a dangerous syndrome and since core temperature may exceed 41 °C, severe brain injury and even brain death may occur if the condition is unrecognised and untreated.

The onset of MH is sudden and, in addition to fever, is associated with tachycardia, arrhythmias, arterial desaturation and metabolic acidosis; oxygen consumption and carbon dioxide production (as measured via capnography) are increased. These abnormalities may persist after transfer to the ICU. Mental disturbances (progressing to coma), muscular cramps or rigidity and signs of altered autonomic function (tachycardia and hypertension) may predominate. Creatine phosphokinase (CK) levels are elevated (particularly the muscular MM band) as a consequence of rhabdomyolysis, and dangerous hyperkalaemia may ensue. Dantrolene is a recognised therapy in addition to cooling and supportive measures – see Task 4.

THINK: Given the lethality of malignant hyperthermia and the existence of a test for susceptibility, consider the ways in which the condition might be prevented. What is your local practice? How would you advise a patient, and the family, after suffering from malignant hyperthermia?
The Lethal Catatonia syndrome is a neuropsychiatric disorder that may overlap the neuroleptic malignant syndrome. Fever, stupor, mutism, coma, muscle rigidity and autonomic instability are amongst the most prominent features. The differential diagnosis includes thyrotoxic crisis, anticholinergic drug overdose (anticholinergic syndrome), sepsis, pheochromocytoma and central nervous system abnormalities.

A 47-year-old woman was admitted to the neurological ward because of mutism. She had a history of paranoid psychosis. The psychiatrist prescribed haloperidol 2.5 mg bd, and a few days later she developed fever without a clinically evident infective focus. There was muscle rigidity and hypertonia. CK was 300 U/l, slightly elevated. After discontinuation of haloperidol and start of oxazepam and dantrolene orally, hyperthermia and coma persisted and the patient was transferred to the ICU. Dantrolene was continued by the intravenous route, and after some days the patient’s condition improved sufficiently for her to be returned to the ward. During the subsequent neurological course, discontinuation of dantrolene again elicited a syndrome of coma, hyperthermia, hypertonia, accompanied by arterial hypertension and hyperglycaemia which was attributed to neuroleptic malignant syndrome. However its severity led lethal catatonia to be considered and, at one stage, electroconvulsion therapy was considered. Nonetheless, dantrolene was recommenced with an efficacious clinical response and a subsequent slow withdrawal of the drug was achieved without untoward effect. The case illustrates the prolonged nature of the condition and the disadvantages of too rapid a discontinuation of dantrolene.

In a patient with at risk of malignant hyperthermia, the following drugs can be given safely:
- Paracetamol (acetaminophen)
- Propofol
- Thiopentone (thiopental)
- Droperidol
- Non-depolarising muscle relaxants
- Neostigmine
- Atropine
- Nitrous oxide
- Benzodiazepines
- Lignocaine.

For an overview, see:


The Malignant Hyperthermia Association of the US, www.mhaus.org, has educational material on the website.
4/ UNDERSTANDING AND TREATING FEVER

Knowledge concerning fever and its influence on disease progression, its relative importance in infective and non-infective circumstances and the merit of controlling fever is incompletely understood. Although fever control is commonplace in medicine and in ICU, there is conflicting evidence on the efficacy of such therapy, using paracetamol or NSAID (non-steroidal anti-inflammatory drugs) for example. Furthermore, infective and non-infective fever may differ in their effect. However, an understanding of its pathogenesis is useful and its control in highly febrile states is unquestioned.


Pathogenesis and pathophysiology

Several conditions, such as malnutrition, uraemia and immunosuppression, may modify the body’s thermoregulatory responses. Uraemic or immunosuppressed patients (such as those receiving steroids which are inherently antipyretic) may manifest little febrile response to bacteraemia. Hence, bacteraemia or infection in these patients may be associated with a less marked elevation of body temperature. Modest elevations, or even a fall, in body temperature in patients with these conditions may therefore be worthy of prompt investigation.

Rigors can be associated with a sudden rise in body temperature and energy expenditure, leading to cardiorespiratory instability. In these circumstances, increased dependency on inotropic or ventilatory support may develop and ICU patients may suddenly begin to trigger the ventilator or manifest tachycardia and hypotension. Sudden wheezing may also point to bacteria entering the blood stream, mirroring the effect of increased airway resistance and bronchoconstriction seen in animal experiments during the infusion of endotoxin.

The transfusion of contaminated blood products (now rare in regulated environments) has been known to result in sudden bacteraemia and thus serve as an unintentional model of sepsis. You may wish to read more about transfusion-related sepsis in:


Rigors are unpleasant for the patient, and the symptoms can be alleviated with opioid drugs.
Although fever can be regarded as a beneficial component of the host response to invading micro-organisms and tissue injury, deleterious endocrine and metabolic side effects can occur, including increased protein breakdown (catabolism) and cerebral damage. The latter is imminent when temperature exceeds 42 °C for one hour or longer. The effect of raised ambient temperature on the endocrine and metabolic response is displayed in the figure:


A warm nursing environment (e.g. a fluidised bed at 32 °C) after trauma, burns or surgery, for instance, may attenuate these effects. The diminished gradient between body and ambient temperature decreases heat production, metabolic stress and the catabolic response. See the following reference:


A number of exogenous stimuli (e.g. infections, inflammatory or autoimmune diseases, vascular occlusive diseases, drugs) lead to the release of large proteins called ‘endogenous pyrogens’ which bind to specific receptors in the preoptic region of the anterior hypothalamus where a blood-brain barrier acts as a valve permitting the entrance of a limited quantity of these proteins into the brain. Pyrogen access and contact with neurons is achieved with the aid of small neuronal cells with fenestrated capillaries called ‘circumventricular organs’.

Fever is normally good for the patient but can be bad

Responses of different organs to fever
This results in a direct response of the neurons within the organum vasculosum of the lamina terminalis or of the astrocytes or microglia to circulating cytokines such as interleukin-1 and -6, resulting in arachidonic acid metabolite production (prostaglandin E2 and thromboxane A2) and upregulation of the thermostatic set point. The brain responds by sending signals that activate effector mechanisms (through the spinal/supraspinal motor system or throughout the sympathetic nervous system), which in turn generate heat production (in brown adipose tissue), reduce heat loss and increase core body temperature to match the upregulation of the thermostatic set point (see diagram).

The activation of arachidonic acid metabolites acts as a substrate for the cyclooxygenase-2 (COX-2) pathway, which in turn leads to further elevation of prostaglandin levels, a decreased rate of firing of sensitive neurons and an increased heat production. The role of COX-2 is important for the development of fever although its activity is inhibited by selective inhibitors, namely non-steroidal anti-inflammatory drugs (NSAIDS) and acetaminophen. Thermal imbalance may of course occur in the absence of a reset of the thermostat, when heat loss is less than heat production as, for example, in hyperthyroidism, salicylate and anticholinergic drug overdose, skin disease and heat stroke.


The following figure illustrates the time course of thermostat resetting and the consequences for the time course of body temperature (green line) as a function of heat gain, when the thermostat is set at a higher level (grey line), and of heat
loss, when the thermostat is set again to the normal level. Shivering occurs in the first period (heat gain) and sweating in the second one (heat loss).

For every degree centigrade increase in temperature, oxygen demand and energy expenditure are said to increase by about 6–10%. Sedation, anaesthesia and cooling may decrease oxygen demand while shivering has the opposite effect. When cooling results in shivering, oxygen demand may also increase.

**Treating fever**

There is ongoing debate as to the benefit of physical or pharmacologic lowering of core temperature exceeding 40 °C with the attendant risk of cerebral damage. Indeed, we previously noted that brain damage may be anticipated when the duration of fever of >42 °C exceeds one hour; higher temperatures may be tolerated for much shorter periods. In patients with sepsis, NSAIDs may attenuate the febrile response. In patients with severe sepsis, ibuprofen has been shown to lower body temperature, tachycardia and lactic acidosis but no other haemodynamic, respiratory, or survival benefit was demonstrated. Although this type of drug may be associated with renal dysfunction, particularly in hypovolaemic subjects, the administration appeared safe. Antipyretics may also include paracetamol (acetaminophen) (orally or rectally) or diclofenac (0.04 mg/kg/h continuous i.v. infusion) if available. Overzealous treatment with NSAIDs may augment inflammatory responses.


Task 4. Understanding and treating fever


THINK: Are there any specific infective conditions in which NSAIDs contribute to the cause?

Malignant hyperthermia, neuroleptic malignant syndrome and lethal catatonia

The treatment of these syndromes consists of eliminating underlying causes, cooling (initially by infusion of cold intravenous fluids – see below), rehydration and benzodiazepines. Intravenous dantrolene sodium to treat muscle contraction (1 mg/kg bolus) which may be repeated during the course of the illness is followed by 4–8 mg/kg per day in 3–4 doses, orally, for 3–4 days as ongoing prophylaxis. Bromocriptine, other dopamine agonists (levodopa) and amantadine may also be used for neuroleptic malignant syndrome. Electroconvulsive therapy may be necessary for catatonia if refractory to drug treatment. NSAIDs are not efficacious.

Cooling techniques

In highly febrile states (usually quoted as >40 °C), treatment of the fever per se (in addition to managing the underlying cause) may be required. Cooling is also a recognised therapy of coma following cardiac arrest.

The cooling techniques in practice in ICU include the conventional cooling (rapid infusion of 30 ml/kg cold fluids, ice and/or coldpacks), cooling with water circulating blankets, air circulating blankets, water circulating gel-coated pads and intravascular heat exchange systems. Cooling blankets are used mainly in patients with hyperthermia. The use of such devices lowers oxygen requirement in paralysed or heavily sedated patients, thereby reducing demand on the cardiorespiratory system. In unparalysed patients, cooling may have the undesirable effect of inducing shivering and a rise in oxygen uptake to augment heat production and compensate for the increased loss. Otherwise, temperature fluctuations and rebound hyperthermia may occur. There are some reports on the maintaining of the target temperature where intravascular cooling was superior to all other cooling methods. See the references below.


[43]

Unintended cooling may occur during continuous renal replacement therapy (CRRT) techniques, when the extracorporeal circuit is exposed to environmental (room temperature) and heat is lost via the ultrafiltrate. The decrease in core temperature may contribute to vascular stability, and hypotensive episodes may be shortened or prevented. These effects may explain the reversal of the hypermetabolic and vasodilated state sometimes noted in patients with septic shock and acute renal failure on whom CRRT is initiated, and may be independent of possible filtration or absorption of the toxic mediators of sepsis, including cytokines.

**Q. Does cooling, by continuous haemofiltration techniques, decrease oxygen requirements of the body? Is the cooling effect dependent on the ultrafiltration rate? Explain your answer.**

A. Yes, the fall in temperature during high (and less so during low) ultrafiltration rates results in a decrease in O2 uptake. This may partly explain the beneficial haemodynamic effect of the technique in patients with septic shock, when clearance of absorption via the artificial membrane of cytokines and other inflammatory mediators is minimal.

For information on haemofiltration techniques:


CONCLUSION

This module helps to recognise and manage the cause of febrile diseases in critically ill patients. Early recognition and proper diagnosis is dependent on the differentiation between infective and non-infective causes. There will be differences of emphasis between the surgical and the medical patient and also in the immune suppressed patient. A full clinical evaluation and supplementary imaging or other testing as indicated by clinical evaluation, is the most important process in identifying the cause of the fever. A supplementary step in identifying an infective origin of a fever is having knowledge of surveillance cultures from the patient and also of the local microbial epidemiology and antibiogram pattern. Such knowledge can facilitate early adequate and appropriate empiric treatments, pending specific information from targeted, patient diagnostic sampling. Cooling, when indicated, is best accomplished in an easy, controllable, minimally invasive and well-tolerated way. Little is known about the optimal method of temperature control. The cooling devices in practice include the water circulating external cooling methods, the air circulating external cooling device, the water circulating external cooling device using self-adhesive gel-coated pads and the intravascular heat exchange system.
SELF-ASSESSMENT

EDIC-style Type K

1. Clinical signs or measurements associated with fever include:
   A. Rigor
   B. Increased oxygen consumption
   C. Decreased energy expenditure
   D. Tachycardia

2. Fever in a patient on the second day after major trauma:
   A. Is a common phenomenon
   B. Is abnormal when it occurs
   C. Is a strong indication of an infection
   D. Usually does not exceed 38.5°C

3. Fever above 39°C in a patient with head injury
   A. Is normal and does not need treatment
   B. May increase cerebral damage
   C. Should immediately be treated with broad-spectrum antibiotics
   D. Acetaminophen (paracetamol) is the first treatment of choice

4. Clinical manifestations of heat stroke include
   A. Core temperature above 42°C required for diagnosis
   B. Reduced consciousness
   C. Convulsions
   D. Hypertension

5. The Neuroleptic Malignant Syndrome is caused by:
   A. Mutation in calcium channels of sarcoplasmatic reticulum
   B. Excessive stimulation of beta receptors in the musculature
   C. Drug-induced blockade of dopamine receptors
   D. Inactive Na/K channels in myocytes

6. Safe drugs to use in a patient at risk of malignant hyperthermia include:
   A. Thiopentone (thiopental)
   B. Propofol
   C. Succinylcholine
   D. Lignocaine

7. Important pathways responsible for increasing heat production and temperature include:
   A. Activation of arachidonic acid metabolites
   B. Down-regulation of prostaglandin levels
   C. Activation of α receptor activity
   D. Increase in cyclo-oxygenase-2 (COX-2) pathway activity
8. The definition of fever in an ICU patient is temperature above:
   A. 38.0
   B. 38.3
   C. 38.5
   D. 38.8
   E. 39.0

9. The part of the brain mainly involved in the pathogenesis of fever is:
   A. Hypothalamus
   B. Hippocampus
   C. Cerebellum
   D. Pons
   E. The 4th ventricle

10. Core temperature is measured in all of the following anatomical sites EXCEPT the:
    A. Pulmonary artery
    B. Bladder
    C. Oesophagus
    D. Rectum
    E. Femoral artery

11. Non-infective causes of fever in an ICU patient include all of the following EXCEPT:
    A. Thromboembolism
    B. Drugs
    C. Central venous catheter
    D. Myocardial infarction
    E. Acute pancreatitis

12. Central venous catheter (CVC)-related sepsis is a frequent cause of sudden fever in the ICU. This complication is most commonly reported to occur at a rate of:
    A. 0–2 episodes/1000 CVC days
    B. 2–15 episodes/1000 CVC days
    C. 16–30 episodes/1000 CVC days
    D. 30 episodes/1000 CVC days
    E. 15–20% of CVCs

13. Effective prevention strategies to reduce central venous catheter (CVC)-related sepsis includes all of the following EXCEPT:
    A. Prophylactic antibiotic intravenously
    B. Use of alcohol-based skin disinfection
    C. Use of sterile gloves and gown
    D. Protocol-based care and maintenance of the CVC
    E. Antibiotic coating of the CVC
14. The most likely cause of fever (of new onset) and infection in a critically ill surgical patient is:
   A. Wound infection
   B. Catheter-related infection
   C. Nosocomial pneumonia
   D. Urinary tract infection
   E. Sinusitis

15. Treatment of heat stroke includes the following EXCEPT
   A. Infusion of cold fluids
   B. External cooling
   C. Intravascular cooling
   D. Dantrolene
   E. Supportive cardiovascular therapy
**Self-assessment answers**

**Type K**

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**Type A**

8. Answer B is correct
9. Answer A is correct
10. Answer D is correct
11. Answer C is correct
12. Answer B is correct
13. Answer A is correct
14. Answer C is correct
15. Answer D is correct
PATIENT CHALLENGES

A 63-year-old woman, previously operated on for ischaemic heart disease, underwent elective redo coronary artery bypass graft (CABG) and mitral valve repair. Because of persistent hypoxaemia after 24h, she remained intubated and ventilated. Haemodynamic evaluation revealed an elevated pulmonary capillary wedge/occlusion pressure (PCWP/PAOP) of 22 mmHg. The ejection fraction was 50% but mild mitral regurgitation, as judged by echocardiography, had been present since the day of surgery. Vasodilators and diuretics were administered with a definitive decrease in wedge pressure and there was an improvement in the blood gas values and ventilatory parameters – at an inspiratory \( O_2 \) fraction of 0.3, a positive end-expiratory pressure (PEEP) of 5 cm H\(_2\)O and a pressure support of 10 cm H\(_2\)O, the arterial PO\(_2\) was 9.31 kPa (66 mmHg) and PCO\(_2\) 5.05 kPa (36 mmHg). However on the fourth postoperative day, the patient developed a fever.

The chest X-ray was abnormal: right lower lobe atelectasis and bilateral infiltrations were evident but no clear differences from the previous examinations were noted. The white blood cell count was 13.0 \( \times \) 10\(^9\)/l (previously 8.5 \( \times \) 10\(^9\)/l) with 80% neutrophils and 9% band forms. The tracheal aspirate was not macroscopically abnormal. The Gram stain registered the presence of bacteria but the sample was judged unreliable because of the presence of numerous epithelial cells. The figures below show the chest X-ray appearance on admission to the hospital and on the day when fever appeared.

**Learning issues**
Assessment of fever
Evaluation of bronchial aspirates

![X-ray on admission](image)

![X-ray when fever appeared](image)

**Q.** The patient is probably developing an infective problem. Which type of further examination (if any) would you do?

**A.** A strategy of identifying the source of infection should be undertaken followed by appropriate treatment. First and foremost, clinical examination must take into account all the possible sources of infection in a postoperative patient.
Q. Outline the particular features of the clinical evaluation of sepsis that would be appropriate in this surgical patient.

A. Wound margins are examined for erythema or infiltration of the soft tissues and drains (including their content) are checked. Tracheal and pharyngeal secretions are reviewed together with catheter sites for possible cellulitis.

Q. In this intubated patient, might any additional respiratory investigation be indicated?

A. Bronchoalveolar lavage or protected specimen brush specimens may be examined if pneumonia is suspected and initial tracheal aspirates are unhelpful.

Since the patient is still invasively monitored, catheter infection has to be considered. Even in the absence of external signs of infection (local inflammation or pus formation) catheter infection should always be strongly suspected especially if there is no other evident source of infection or a positive blood culture has been obtained. Blood cultures, urinalysis and, even though fever has occurred only a few days postoperatively, an echocardiogram may be useful. If endocarditis is suspected, transoesophageal echocardiography is utilised when transthoracic (valvular) images are suboptimal.


While waiting for the microbiological results, the temperature rose to 39.3 °C and the patient developed tachycardia and respiratory distress. Ventilatory assistance was increased (inspiratory O₂ fraction 0.4; pressure support 15 cm H₂O). Antibiotics were started after a septic work-up which included bronchoscopy and distal bronchial sampling by bronchoalveolar lavage (BAL).

Q. Are there particular indications in this patient to treat fever?

A. Patients with impaired myocardial reserve tolerate the increase in oxygen demand poorly because of the increased myocardial workload. While keeping clearly in mind that the key issue is the treatment of the underlying infection, a symptomatic approach to fever may be indicated. Several drugs have been proposed for the treatment of fever and no clear consensus has been reached as to the drug of choice. However, it is mandatory to consider their potential side effects.

Learning Issues

Antipyretic treatment
Antipyretic drugs
The urgent Gram stain and microscopy of the protected bronchial specimen has now revealed Gram-negative rods >10⁴ CFU/ml together with leukocytes and bronchial cells; no epithelial cells are detected.

**Learning Issues**

Assessment of bronchial aspirates

Q. Would you consider the specimen suggestive of infection?

A. In an intubated patient, in the presence of systemic and radiological signs suggestive of infection and with a microbiological specimen compatible with the diagnosis of pneumonia, the presumptive diagnosis of ventilator-associated pneumonia is appropriate and antibiotic therapy should be immediately initiated.

**Learning Issues**

Ventilator-associated pneumonia

After a further three days, the fever appears to be well controlled below 38 °C and does not require continued antipyretic therapy. The patient was progressively weaned from the ventilator, the chest X-ray which had developed obvious consolidation was now clearing (figure below); she had stable cardiovascular function and she was extubated successfully. *Pseudomonas aeruginosa* grew in the BAL culture.

*The chest radiograph of the patient with residual basal infiltrate (right greater than left)*

While transfer to the surgical ward was being planned, the patient became confused and agitated, her temperature rose to 39 °C and she became hypotensive: 70/40 mmHg. The electrocardiogram did not show a change compared to previous ones. The echocardiogram showed a normally contracting ventricle without wall motion abnormalities. Fluid resuscitation was started and despite a fluid load of 1500 ml, the arterial blood pressure rose to only 80/40 mmHg, and the patient became anuric. The oxygen saturation started to decrease despite supplemental O₂ by mask. Nasotracheal intubation was performed and vasoactive drugs were administered.
A cardiogenic cause to explain the clinical picture was excluded by previous examinations. In a patient with reduced cardiovascular reserve however, a pulmonary artery catheter was inserted to guide the titration of fluid and haemodynamic therapy. With dopamine at 10 mcg/kg/min and a further 1000 ml of colloids to obtain a wedge pressure of 18 mmHg, the arterial blood pressure rose to 120/80 mmHg. However, the patient remained anuric for three additional hours and despite its known lack of efficacy as a renal conservation measure, frusemide was administered.

See PACT module on Oliguria and anuria (AKI part 1)

Blood tests were as follows: white blood cell count 35 x 10⁹/l (band forms 20%; neutrophils 80%); platelets 150 x 10⁹/l; haematocrit 35%; aspartate aminotransaminase (ASAT AST) 30 U/l; alanine aminotransaminase (ALAT ALT) 50 U/l; bilirubin 1.4 mg/dl; creatinine 176.8 micromol/l; blood urea nitrogen 14.28 mmol/l; lactate 10 mmol/l; sodium 143 mmol/l; potassium 4.3 mmol/l. Blood was taken for culture.

**Note**

Haemodynamic monitoring during septic shock: see PACT module on Haemodynamic monitoring.

Q. What other source of infection do you look for?

A. The development of such a dramatic clinical course in a postoperative patient should always remind us that infection can arise from the surgical wound or at the valvular level. Moreover the patient still has devices in situ such as a central venous catheter and urinary catheter. *Clostridium difficile* infection (non-diarrhoeal) needs to be included in the differential diagnosis.

**Learning issues**

SIRS, infection, sepsis and shock definition

Despite the administration of paracetamol (acetaminophen), the patient remained febrile (39 °C) and although restoration of blood pressure stability allowed some weaning of dopamine, tachycardia (135 bpm) persisted. The electrocardiogram showed diffuse ST segment depression which appeared to be tachycardia-associated. Because the patient has been in hospital for a number of days, had not responded to current antimicrobial therapy, and catheter or surgical site infection were possibilities, intravenous vancomycin was added and deeper sedation and analgesia were instituted.

The presence of fever and leukocyte abnormalities together with shock and organ dysfunction were consistent with a diagnosis of septic shock. The appropriate response included: first, resuscitation and treatment of the haemodynamic derangement; second, rapid investigation to detect the source of infection and third, treatment and consideration of any additional issues.

The first goal had been successfully achieved. The second goal in this complicated patient still requires further consideration.
Learning issues

Treatment of septic shock
Complications of pneumonia
Catheter-related infection

Q. The patient had pulmonary infection that is apparently resolving. Which further respiratory diagnostic test would you consider and why?

A. It is possible that a pulmonary abscess or empyema is complicating the original pneumonia. A CT scan may be indicated.

In the presence of such complex radiological findings where abnormal features exist, a CT scan may be helpful to diagnose or exclude complications (see figure below). A CT scan revealed bilateral pleural effusion and posterior bilateral consolidation. The pleural effusion was drained and cultured and therapy with vancomycin, ceftazidime and amikacin is continued.

Learning issues

CT scan indications

Q. The pleural fluid proves not to be infected and the source of the infection remains unclear. What additional diagnoses might you now consider?

A. The presence of a nasotracheal tube should raise the possibility of sinusitis and CT scan of the head might be considered. Other possibilities include:

- Endocarditis
- Has sufficient time elapsed to see an improvement in infective endocarditis, if present?
- Has serial physical examination shown evidence of new murmurs; further transoesophageal echocardiographic examination (TOE) should help in detecting abnormal valvar vegetations if suspected?
- Vascular CVCs are always a possible source of infection
- Wound infection including mediastinitis
- Non-diarrhoeal Clostridium difficile is a possibility
- Urinary tract infection is kept under review

Q. Which type of further therapeutic manoeuvre might be considered to treat the remaining fever (of 39 °C)?

A. External cooling should be considered.
Cooling techniques

External cooling is started and temperature is decreased to 36 °C. The heart rate decreased to 100 bpm. ECG disturbances disappear. Arterial blood pressure stabilises at 120/60 mmHg. Cardiac output is 3.5 l/min. Mixed venous oxygen saturation is 72%.

*Staphylococcus aureus* was cultured in the blood culture. The central venous catheter was removed and catheter tip sent for culture. Transoesophageal echocardiography was performed and was negative for vegetations on the cardiac valves. The culture of the tip of the catheter also (in addition to the blood) grew *Staphylococcus aureus*, thus complying with the criteria for catheter-related blood stream infection (CRBSI) or CRI3 by HELICS criteria.

**Learning issues**

Diagnostic criteria for catheter-related infection

The antibiotic therapy is rationalised to target *Staphylococcus aureus* CRBSI. The haemodynamic support is progressively decreased and cooling is stopped after 24 hours and deep sedation and paralysing drugs are discontinued. Two days after the shock episode, the patient was weaned off the ventilator. After three days the patient was afebrile, the white blood cell count was 12 x 10⁹/l and she was eventually transferred to the ward to continue out her course of Flucloxacillin for *Staphylococcus aureus* CRBSI.


Following a motorcycle accident, a 24-year-old man was admitted to the Emergency Department. Pelvic and femoral fractures were confirmed on radiographic examination. On admission the patient was hypotensive; resuscitation was promptly instituted. Subsequently his haematocrit fell to 22%. Blood alcohol was negative. Twelve hours later, while awaiting femoral stabilisation, he became severely dyspnoeic and arterial blood gas analysis (breathing room air) revealed an arterial PO2 of 4.65 kPa (33 mmHg), PCO2 of 2.66 kPa (19 mmHg) and pH of 7.5. Oxygen was administered; the chest X-ray revealed diffuse bilateral interstitial infiltrates. Platelet count was 55 x 10^9 /l. He was transferred to the ICU where after an initial trial of non-invasive ventilation (pressure support 15 cm H2O, inspiratory O2 fraction 1.0 with PEEP of 15 cm H2O), his oxygenation improved. No haemodynamic derangement developed but the patient became febrile (38.8 °C).

**Learning issues**

Non-invasive ventilation (see PACT Module on Mechanical ventilation)

Q. Are there reasonable grounds to suspect a non-infective problem?

A. In this trauma patient, fever could have several non-infective explanations including:
   - Haematoma
   - Drug reaction
   - Fat embolism

The patient probably has extensive retroperitoneal haematoma due to the pelvic fracture and this, per se, could explain the febrile response.

**Learning issues**

Other causes of fever

Blood platelets are, however, considerably decreased and although this could be explained by dilution following resuscitation, the fat embolism syndrome should also be suspected. Clinical diagnosis and physical examination is mandatory looking for petechiae, characteristically located near the axilla, around the nipples, and in the conjunctivae and fundi.

Q. Is the distinction between infective and non-infective causes easy? If infection is still suspected, are there additional blood tests which might be helpful in the diagnosis of infection?

A. There can be lack of clarity initially as infection is associated with non-specific symptoms and signs. Bacteriological evidence of infection can be absent despite the presence of relevant symptoms and signs. On the other hand, positive microbiological results may be due to contamination. The diagnosis in these situations can be further supported by specific markers including procalcitonin, C-reactive protein, urine test for lipiduria and examination of the tracheal aspirate for macrophages with lipid globules.

CRP was within normal range and the fever gradually disappeared. The patient was stable and a weaning protocol was initiated. Microbiological results were all negative. After three days, the patient was afebrile, the clinical diagnosis of the fat embolism
syndrome was clear and antibiotics, which had been started for the fever, were stopped.

**Learning issues**

Value of laboratory diagnosis of fever
A 64-year-old female psychiatric patient was scheduled for cholecystectomy. There was no history of previous surgical procedures, abnormal reactions to drugs, asthma or other cardiorespiratory diseases. The arterial blood pressure was 130/70 mmHg and heart rate 96 bpm. The electrocardiogram and chest X-ray were normal. The haemoglobin content was 14 g/dl and serum electrolytes and arterial blood gases were in the normal range. On the day of surgery, the patient received diazepam 10 mg and atropine. Anaesthesia was induced with propofol and suxamethonium (succinylcholine). Desflurane 2%, nitrous oxide and fentanyl were used to maintain anaesthesia. Twenty minutes after induction of anaesthesia, the arterial blood pressure rose to 170/100 mmHg and the heart rate to 120 bpm. Additional fentanyl did not control the hypertension. The end-tidal PCO₂ increased from 4.79 kPa (34 mmHg) to 5.72 kPa (40 mmHg) without apparent technical problems with the anaesthetic apparatus. The arterial blood gas analysis was as follows: PO₂ 7.19 kPa (51 mmHg), PCO₂ 7.19 kPa (51 mmHg) and pH 7.21

Q. Pneumothorax was immediately excluded on clinical grounds. The increase in arterial PCO₂ was at first thought to be responsible for the clinical findings. Could the hypercarbia account for the physiological pattern evident?

A. Yes. Hypertension and tachycardia frequently accompany hypercarbia and acidosis.

Arterial PCO₂ may increase for two reasons: decreased elimination and increased production. The former and more common is due to reduction in alveolar ventilation, possibly from some malfunction of the anaesthetic breathing circuit. Increased production can happen during a laparoscopic procedure when CO₂ is used to distend the abdominal cavity or when endogenous CO₂ production is increased (e.g. associated with fever, adrenal hormone excess and malignant hyperthermia). Technical reasons for decreased CO₂ elimination were excluded, as were surgical explanations for increased CO₂ production.

PMID 9798607

Inspiratory O₂ fraction and ventilation were increased. Muscle rigidity became evident and core temperature rose to 40 °C.

Q. What is the most likely diagnosis at this time?

A Malignant hyperpyrexia

Anaesthesia was discontinued. Iced bags were positioned over the patient and dantrolene was administered. Core temperature started to decrease after iced gastric lavage was initiated. The patient was admitted to the ICU and the temperature aggressively controlled. She later awoke and was eventually extubated without untoward sequelae. A more detailed history taken from a brother living abroad revealed that malignant hyperthermia was diagnosed in the patient’s mother during a hysterectomy performed 15 years earlier.
An 18-year-old male with congenital hydrocephalus, permanent celiot-peritoneal drainage and epilepsy controlled with lamotrigine and oxcarbazepine, was admitted to the hospital because of respiratory failure due to lower respiratory tract infection. He needed ICU admission for endotracheal intubation, mechanical ventilation and central venous cannulation. During the seventh ICU day, he developed septic shock and blood cultures revealed three positive consecutive cultures for both methicillin-resistant *Staph. aureus* (MRSA) and *Candida albicans*. The tip of the central venous catheter (after removal) was also positive for *Candida albicans*.

The main risk factors for invasive fungal infection development were considered the prolonged use of antibiotics and catheter devices, and the moderately prolonged stay in the ICU. The course of the fever, despite the administration of broad-spectrum antimicrobials including vancomycin and antifungals, is shown below. No specific temperature lowering measures were required.

The main findings from the detailed diagnostic evaluation of the patient included:
- CT scan of the lungs – infiltrates compatible with pneumonia
- CT scan of the abdomen – negative
- Cerebrospinal analysis – no signs of infection
- WBC: 12.4 x 10⁹/L, Biochemistry: unremarkable
- Ophthalmology – negative for *Candida* endophalmitis
• Transthoracic and transoesophageal echocardiography – no signs of endocarditis.

The final diagnosis from thoracic CT (see below) was: Septic thromboplebitis of the left subclavian and jugular vein due to MRSA and *Candida albicans*.

The thrombophlebitis with its septic complication was not associated with a prolonged central venous cannulation while no MRSA colonisation that might have predisposed to this infection has been detected from patient’s ICU admission surveillance screening.

The patient received treatment with linezolid 600mg x 2 and anidulafungin 100mg x 1 IV (after a loading dose of 200 mg) for three and two weeks (for MRSA and *C. albicans* respectively). A step down modification of the treatment to linezolid at the same dose and voriconazole (4 mg/kg x 2) orally was performed at the time of discharge from ICU to the ward with an anticipated total duration of antimicrobial therapy of eight and 12 weeks respectively. She remained under the ongoing consultative advice (including monitoring for drug toxicity – especially for linezolid) of the microbiological/infectious diseases team.

The patient was also anticoagulated but this was stopped at six months after his discharge after follow up evaluation was negative for signs and symptoms of thrombophlebitis.

**On reflection, pyrexia is a frequent observed clinical sign in the ICU.** The four patients described represent examples of the diagnostic and therapeutic challenge to ICU clinical staff when confronted with this problem. Although pyrexia is
often a transient, minor sign it may be the harbinger of serious illness. Rapid identification of the underlying cause is imperative if life-threatening complications are to be avoided and differentiation between infective and non-infective causes is a priority. It is important to obtain samples for microbiological evidence in patients with suspected infection before starting antibiotic treatment although in the critically ill, when severe sepsis is present, a ‘best guess’ approach, based on thorough clinical evaluation, will be indicated pending results from the microscopy/culture examinations. Source control of infection may also require consideration of surgical or radiological intervention.

You will have noted the importance of clinical acumen in reaching diagnostic and therapeutic decisions. No fool proof laboratory tests are available although selected investigations can be helpful, particularly when part of a collaborative strategy with colleagues from other disciplines.