Saturday night fever: finding and controlling the source of sepsis in critical illness

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Fever is a daily concern in the intensive care unit. Although about half of all febrile cases are due to non-infectious causes, fear of sepsis frequently leads to diagnostic tests and escalation of therapy, including broadening antibiotic therapy. Using a case to illustrate this dilemma, we discuss the commonest non-infectious and infectious causes of fever, and suggests approaches to their management. Any unexplained fever in intensive care unit patients warrants investigation, which includes complete clinical assessment and blood cultures. When the source of fever is not immediately apparent, non-infectious and infectious causes should be considered. If stable, non-neutropenic patients should be monitored before further tests or empiric antibiotics are started. In an era of rapid emergence and spread of antimicrobial-resistant pathogens and intense scrutiny of resources, optimal diagnosis and management of patients with suspected infection entails much more than the escalation of antimicrobial therapy.

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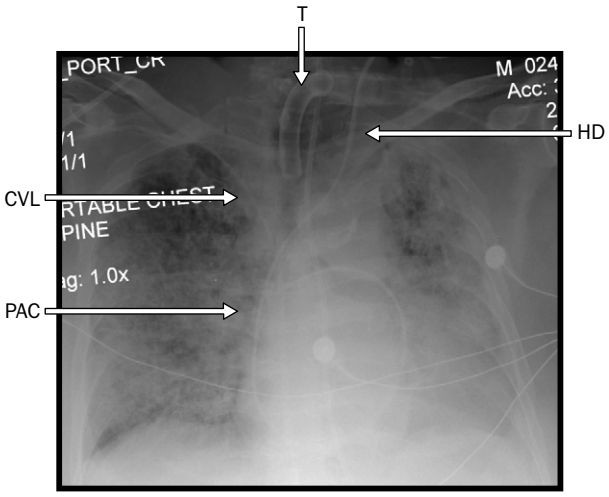

Figure 1. Mr B's portable chest radiograph shows bilateral fluffy infiltrates, compatible with acute respiratory distress syndrome, and both non-infectious and infectious causes of fever. In addition, he has multiple invasive devices, all of which serve as potential sources of infection. T=tracheotomy tube, HD=haemodialysis catheter, CVL=central venous line, PAC=pulmonary artery catheter

Temperature is routinely measured in every intensive care unit (ICU) around the world, and fever is common.[1] Its development in an already critically ill patient raises immediate concerns about further deterioration, and typically prompts the clinician to order a battery of diagnostic tests, change supportive care, and initiate empiric broad-spectrum antibiotics.

Fewer than half of all febrile episodes in the ICU, however, can be attributed to infection,[2] and empiric therapy is often initiated unnecessarily. Furthermore, repeated blood sampling and exposure to radiation, contrast, and invasive diagnostic procedures not only disrupt and prolong ICU stay but, more importantly, expose patients to unnecessary risk, including the adverse effects of antibiotics. The rapid emergence and spread of antibiotic-resistant bacteria argues for greater restrictions on the indiscriminate use of antibiotics.[3]

In this review we will focus on the assessment of the ICU patient who has a fever without an obvious source, the approach to differentiating infectious from non-infectious causes for fever, and the optimum strategies to investigate such patients in a clinically appropriate and cost-effective manner.

Clinical scenario

It is Saturday night and Mr B is febrile. He is 72 years old, with a medical history of laryngectomy, carotid endarterectomy, and ischaemic heart disease. After an uneventful elective colon resection 4 weeks ago, Mr B had a myocardial infarction with cardiogenic shock, and needed haemodynamic support including an intra-aortic balloon pump. Large doses of vasopressors resulted in ischaemic necrosis of all fingers and toes. Other complications included an anastomotic dehiscence of the colon which required reoperation and an ileostomy, recurrent intra-abdominal abscesses that were drained percutaneously, acalculous cholecystitis treated by percutaneous cholecystostomy, congestive heart failure, acute respiratory distress syndrome (figure 1), acute renal failure, and recurrent pneumonia. Mr B remains fully ventilated, and has a tracheotomy, multiple intravenous sites, and a

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Table 1. An approach to the ICU patient with suspected infection

What is the underlying diagnosis?	Consider the admission diagnosis, and all co-morbid conditions that might predispose to infection In our patient, predisposing conditions include colonic surgery with anastomotic dehiscence, raising the possibility of intra-abdominal infection, high-dose vasopressor use, raising the possibilities of extremity or intestinal ischaemia
What has been done in the ICU?	Consider all the interventions performed in the ICU, especially those that involve insertions of tubes, catheters, and other foreign bodies. Our patient is intubated and ventilated, raising the possibility of pneumonia, particularly in the presence of the acute lung injury of acute respiratory distress syndrome, has a Foley catheter, raising the possibility of urinary tract infection, has multiple intravascular lines for monitoring and support,raising the possibility of catheter-related bacteraemia, has a nasogastric tube, raising the possibility of sinusitis, and has been on broad spectrum antibiotics, raising the possibilities of a superinfection, typically fungal, antibiotic-associated colitis, or a drug reaction.
The likelihood of a new infection unrelated to either the acute problem that led to admission or the interventions undertaken in the ICU is very small.	In the absence of a source related to either of the two considerations above, the clinical picture of sepsis is almost certainly arising from a non-infectious source.

pulmonary artery catheter. He is receiving multiple medications, including meropenem and ciprofloxacin for a multidrug-resistant klebsiella.

Does he have a fever?

The definition of fever is arbitrary and varies for different purposes. The guidelines of the Society of Critical Care Medicine (SCCM) and Infectious Disease Society of America (IDSA)[4] define fever as a temperature of or above 38·3°C, and recommend that any new fever in an ICU patient be investigated for a potential infectious source.[4]

Characterising fever magnitude, pattern, and relation to pulse could provide important diagnostic clues.[5-7] Fevers higher than 41·1°C are more likely a result of non-infectious causes such as malignant hyperthermia, heat stroke, drug fever, adrenal insufficiency, or thyroid storm.[4,6] Temperatures between 38·3 and 41·1°C could be equally infectious or non-infectious, but in this range certain patterns might suggest the cause. Continuous fever, or an unusual temperature pattern, has been associated with Gram-negative pneumonia, central nervous system fever (ie, encephalitis), drug fever, or salmonelosis.[5] Relative bradycardia during fever, especially when accompanied by leucocytosis, eosinophilia, or cutaneous rash, suggests a fever induced by medications.[8,9] Other well-characterised patterns are postoperative fevers. Fever in the first 2–3 postoperative days is usually non-infectious, self-limited, and benign,[2] whereas fever arising 5–7 days postoperatively could indicate a surgical site infection.[10] Another common pattern is that of fever arising after 10–14 days of antibiotic treatment, and as a consequence of fungal infection.[11]

Fever is neither sensitive to nor specific for infection. Not all septic patients are able to amount a febrile response, one-third of septic patients present with normal temperatures, and 10% are hypothermic.[12,13] In certain patient groups such as those at extremes of age, or those with extensive burns or open wounds, the reasons for the absence of fever might be self-evident; however, in most cases, the reasons are poorly understood. The absence of fever in sepsis is associated with significantly higher mortality,[12,13] validating experimental evidence that fever has a protective function. Fever enhances immune responses, inhibits the proliferation of pathogens, and improves general outcome from infectious diseases.[14,15] Consequently, there is no scientific justification for the routine use of antipyretics, cooling blankets, or other forms of temperature reduction in febrile patients. It is important to note that cooling blankets are often ineffective, increasing rather than reducing the fever, increasing oxygen consumption due to shivering, and causing intense thermal discomfort for the patients.[16] Only in a few situations, where fever is clearly detrimental, is it advisable to lower the body temperature. These exceptions include extremes of hyperpyrexia (≥41·1°C), and patients having severely limited cardiorespiratory reserve, recent strokes, or traumatic brain injury.[6,17,18] In all other cases, antipyretics not only remove an important immunological defence but also prevent the physician from characterising the fever, which could help in identifying the source or assessing the response to treatment.[6,19]

Back to our scenario; Mr B's temperature is 38·8°C, he does have fever according to our definition. This is the second spike over the past 12 hours, and is accompanied on this occasion by shaking chills. His last operation was weeks ago; investigations are in order (table 1).

Initial approach

Fever in a critically ill patient calls for a systematic clinical assessment. Physical examination of ICU patients is often not very informative.[3] Nonetheless, a thorough physical examination should be done, focusing on wounds and invasive devices; on occasion it is conclusive, establishing the origin of fever and defining further management.

The physical examination is complemented by a review of the patient's history, of all medications, therapies, blood products, laboratory tests, and imaging studies. The goal of this initial assessment is to understand the host—eg, underlying diseases, immunocompetence—to establish how ill he is and to find clues about the origin of the fever. Moreover, organisms isolated from previous episodes of infection commonly persist or recur.

What happens next depends on the initial assessment and will vary depending on whether patients are neutropenic, rapidly deteriorating, or stable. Management decisions are not based solely on clinical assessment, but will also take into account local characteristics of the ICU such as specific policies, recent epidemics, endemic pathogens, and antibiotic susceptibility.

Both infectious and non-infectious causes are sought during the initial assessment. For fever without an obvious source, the first recommended step is to order blood cultures.[4,17] Positive blood cultures have serious therapeutic and prognostic implications; therefore, SCCM/IDSA guidelines recommend drawing blood cultures, even when the evidence could suggest a non-infectious cause. The recommendation is to draw two blood cultures from two separate sites for any ICU patient with a new episode of fever.[4]

What to do next? Our bias, in agreement with a recent proposal,[17] is that the next reasonable and prudent step is simply to observe the stable non-neutropenic patient regularly over 24–48 h. While establishing possible causes of the fever, we favour a policy of waiting before beginning empiric antibiotics or further tests.

The initial assessment of Mr B did not establish a cause for his fever. His clinical status remains unchanged and now he has a notable leucocytosis. Two blood cultures are ordered but no antipyretics given. In the meantime, we will focus on the many possible non-infectious sources of fever and leucocytosis.

Searching for non-infectious causes

Non-infectious processes are a common cause of fever in critically ill patients. Common causes include early postoperative fever and single fever spikes after blood transfusion, or after insertion/removal of devices, or manipulation of infected areas. These fevers resolve spontaneously within 24 h.[6,7]

Postoperative fever

Early postoperative fever is common in the ICU, and inappropriate management can be costly. Perlino[20] recently reviewed some of the largest clinical studies on postoperative fever published over the past 20 years. He concluded that fever occurring within 2–3 postoperative days does not need investigation beyond clinical assessment, and should not be treated with antibiotics.[2,6,20] Within the first 48 h, fever is almost exclusively due to surgical trauma rather than infection.[20] In a prospective study of surgical ICU patients, Circiumaru et al[2] reported that 70% of all febrile episodes were non-infectious, especially those happening within 3 days of surgery.

Post-surgical fever is the result of an inflammatory response to tissue trauma and is more common after major operations. Yet another cause for early postoperative fever is the effect of anaesthetic drugs on thermoregulation in the hypothalamus.[2,21] Neither needs any intervention.

Early postoperative fever is most likely non-infectious, but pulmonary aspiration, a major break in sterile technique, or an uncommon infection such as clostridial myonecrosis or group A streptococcal cellulitis, need to be considered and ruled out as causes. Anaerobic wound infections could happen within hours to days after surgery but are usually evident on clinical inspection alone.[4,6] New or persistent fever arising more than 96 h after surgery strongly suggests an infectious origin.

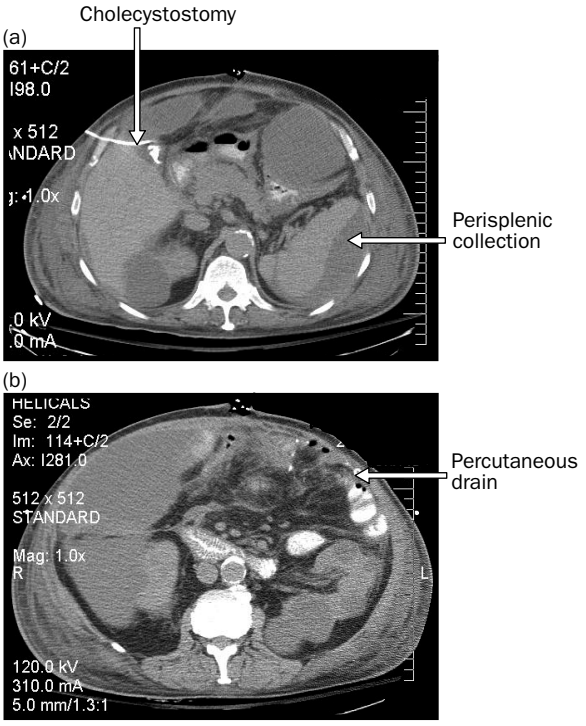

Figure 2. An abdominal CT scan showing (a) percutaneous cholecystotostomy tube and perisplenic fluid collection. The latter is homogeneous, without intracavitary air or rim enhancement that might suggest an abscess. (b) After the previous drainage of an intra-abdominal abscess, the CT scan shows no residual cavity or fluid, but marked mesenteric streaking, compatible with persistent inflammation.

Atelectasis

Atelectasis is often implicated as the source of early postoperative fever. The association between atelectasis and fever is controversial. Clinical studies of surgical and non-surgical patients have shown that significant atelectasis often fails to cause a febrile reaction.[17,22] Similar conclusions have been drawn from animal experiments in which atelectasis in the absence of pulmonary infection does not cause temperature elevation.[17] On the other hand, macrophages retrieved from atelectatic lung produce increased quantities of interleukin-1,[23] a cytokine previously known as endogenous pyrogen. Atelectasis and fever are often concomitant but could well be unrelated.

Drug-induced fever

Medications are a common non-infectious cause of fever in ICU patients. Up to 10% of all hospitalised patients have at least one episode of fever as a result of drugs.[6] Although any drug can cause fever,[4,8,20] the ones most frequently implicated are actually antibiotics, especially beta-lactam antibiotics. Other drugs commonly thought to induce fever are antiseizure medications, especially diphenylhydantoin, and antiarrhythmics such as quinidine and procainimide.[8,20]

Medication-induced fever is difficult to diagnose. Diagnosis requires that other sources of fever be excluded, and that a temporal association between drug administration and fever be established. Resolution of the fever after withdrawal of the drug is diagnostic. The temporal association between drug administration and fever might not be easy to establish.

Table 2. Approaches to the diagnosis and management of common ICU-acquired infections

Site	Diagnostic approach	Treatment
Ventilator-associated pneumonia	Chest radiograph or CT scan; semiquantitative culture of bronchoalveolar lavage fluid	Antibiotics as guided by culture; extubate if possible
Catheter-related bacteraemia	Line removal with culture of tip; blood culture	Line removal; antibiotics only for persistent bacteraemia or high-risk patient
Urinary tract infection	Quantitative culture of urine Gram-negative infections; antibiotics for high-risk patients	Change or remove catheter
Sinusitis	CT scan of sinuses; sinus acidification of urine for puncture for culture and sensitivity	Remove nasal tubes; sinus drainage
Surgical site infection		
Superficial	Examine and open wound	Open and pack wound
Deep	CT scan	Percutaneous or operative drainage
Diarrhoea	Culture and ELISA for *C difficile* toxin	Stop antibiotics; probiotics (*S boulardii*); metronidazole or vancomycin
Fungal infection	Culture; tissue biopsy; cryptococcal antigen	Stop antibiotics; systemic antifungal therapy as indicated

The onset of fever could happen hours to days after the administration of the drug and disappearance of the fever could be delayed for several days after drug withdrawal.[6,8] Eosinophilia, cutaneous rash, and relative bradycardia happen infrequently but are very suggestive of drug-induced fevers.[6]

Another commonly overlooked cause of medication-associated fever in the ICU is substance withdrawal—not only alcohol and recreational drugs, but also sedative-hypnotic medications given during the ICU stay.[20] In a recent study, one-third of patients spending longer than 7 days in the ICU had withdrawal symptoms such as fever, hypertension, tachycardia, sweating, or dysphoria.[24] In view of the number of patients using alcohol or recreational drugs, or receiving therapeutic narcotics or sedative-hypnotics in the ICU, withdrawal-induced fever is almost certainly more common than is appreciated.

Transfusion of blood products

Fever can be a complication of blood-product transfusion. Febrile transfusion reactions are most often attributed to the presence of granulocytes and platelets, but could also be caused by plasma factors such as exogenous immunoglobulins.[20,25] Haemolytic transfusion reactions manifest rapidly with hypotension, capillary leak, fever, and oliguria; the most common febrile transfusion reactions occur 30 min to 2 h after the beginning of the transfusion.[26] Simple febrile transfusion reactions do not need further investigations. Patients with repeated febrile reactions to blood transfusion benefit from receiving leucocyte-filtered blood.

The abdomen as the source of fever

The abdomen can harbour a broad range of infectious and non-infectious disorders, with minimal evidence of their presence. Conversely, significant abdominal findings, such as pain, distension, or paralytic ileus, can be unrelated to intra-abdominal pathology, but rather be due to pneumonia or metabolic disorders. The list of possible non-infectious intra-abdominal processes causing fever includes hepatobiliary diseases, pancreatitis, malignancies, intestinal obstruction, infarction, inflammation, and many others.

Abdominal sources of fever, especially in patients with recent abdominal surgery, are best investigated with imaging tests. Computed tomography (CT) scan with intravenous and oral contrast is the procedure of choice and is far superior to clinical examination. Abdominal CT scans correctly identify pathologic disorders in 90–95% of cases, whereas clinical assessment was correct in 60–76%.[27,28] The CT scan is superior also to plain films, ultrasound, barium studies, and radionuclide scans in diagnosing the source of abdominal pain and fever.

Plain films are of limited use in assessing fever in ICU patients, in part because of technical limitations in obtaining adequate abdominal films with portable radiograph machines. Even when adequate films are taken, plain radiographs simply do not add information to a contrast CT scan.[28] Ultrasound imaging is portable, and might be very useful in assessing hepatobiliary disorders, but is limited by the presence of increased bowel gas, free air, or subcutaneous emphysema, and is highly operator-dependent.[28]

Reviews by the American College of Radiology confirm the superiority of CT scan imaging in investigating intra-abdominal sources of fever. They report a general CT scan sensitivity of 86–100% for the diagnosis of bowel obstruction and its cause, and 82% for the diagnosis of bowel infarct.[27,28] CT scan is also the procedure of choice for the diagnosis of intra-abdominal abscesses, phlegmonous masses, Crohn's disease, pseudomembranous colitis (correct in 88% of cases), perforations, mesenteric pathology, fistulas, and sinus tracts.[27,28] Moreover, a negative CT scan is reliable evidence of the absence of a significant problem needing surgical intervention.

Acalculous cholecystitis

Acalculous cholecystitis can cause non-infectious fever in the ICU, although results are often nonspecific.[3,17] The most severely ill patients are at highest risk for acalculous cholecystitis. Risk factors include mechanical ventilation with positive-end expiratory pressure, gastrointestinal tract inactivity, and parenteral nutrition, which leads to bile stasis and ischaemia.[29,30] Delayed diagnosis could result in progression to gangrene, perforation, or secondary infection of the gallbladder, with subsequent high mortality. Acalculous cholecystitis has become less common with increased use of enteral nutrition in the critically ill.

Ultrasound is the most commonly used tool for investigating cholecystitis and has a specificity of 90% and sensitivity of 100%.[3,17,30] Although the commonly recommended treatment is open cholecystectomy, for critically ill patients this option carries a significant risk of morbidity and mortality.[3] Most ICU patients today can be treated by percutaneous cholecystostomy, with few complications and resolution of the process in over 90% of cases.[31,32]

Other non-infectious causes

Consideration should also be given to other potentially life-threatening causes of fever in the ICU, including haematomas located anywhere in the body, gastrointestinal bleeding, deep vein thrombosis, pulmonary embolus/infarct, myocardial infarction, subarachnoid haemorrhage, fat emboli, transplant rejection, hyperthyroidism, and acute adrenal insufficiency.[4,20]

Possible non-infectious sources of fever for Mr B, in addition to those mentioned, include ischaemic necrosis of his extremities, the fibroproliferative phase of his acute respiratory distress syndrome,[17] and intravenous contrast reaction.[4,17] The diagnosis of a non-infectious cause of fever is made by excluding infection as the cause: the next section will be devoted to exploring the many possible infectious causes.

Searching for infectious causes

Ventilator-associated pneumonia

The most common infectious causes of fever in ICU patients are pneumonia, urinary-tract infection, sinusitis, surgical-site infections, and bloodstream infections, typically a result of colonised intravascular catheters. Ventilator-associated pneumonia (VAP) is a particular diagnostic challenge, in part because it is so common. In a European prevalence study of ICU-acquired infection, VAP accounted for half of all infections in ventilated patients,[33] whereas in a Canadian study of ICU patients at risk for stress-induced gastrointestinal bleeding, 17·5% of patients developed VAP.[34] Reported incidence rates range from 12% to 63%.[3,34] VAP prolongs the ICU stay by about 4 days and increases mortality by 20–30%.[35]

The classic diagnosis of pneumonia is based on the development of fever, rales, purulent endotracheal secretions, leucocytosis, and new infiltrates on the chest radiograph. However, these findings are all non-specific, and often result from other pathologies (figure 1). In fact, fewer than one-third of the patients diagnosed by these criteria will be shown to have pneumonia.[17,35–37] Chest imaging is of limited diagnostic value in the critically ill. Portable chest radiograph has a diagnostic accuracy of 0·5, with sensitivity of 0·6 and specificity of 0·28.[38] Higher resolution studies, such as CT scans, are occasionally used to aid in the diagnosis. This discrepancy between clinical suspicion and documented infection prompted new techniques to confirm the presence of infection, and to guide antimicrobial therapy. Direct examination and culture of secretions from the distal respiratory tract establish the bacteriologic diagnosis of VAP.[4] However, since sputum is typically obtained by either expectoration or deep tracheal aspiration, and since colonisation of the proximal airway or endotracheal tube is common, it is impossible to differentiate infection from simple colonisation. In fact, most ICU patients have Gram-negative colonisation of their upper airway within 48 h of admission.[4]

Invasive techniques such as bronchoscopy-directed bronchoalveolar lavage (BAL) and protected brush sampling, or semi-invasive techniques such as blind BAL, have been used for improved sampling and confirmation of infection.[39] Yet the very number of such techniques underscores the general sense that a gold standard diagnostic method does not yet exist for VAP.

Although the effect of invasive methods on clinical decision-making and patient outcome remains a matter of controversy,[34] evidence suggests significant benefits. Invasive methods result in more appropriate antibiotic therapy compared with non-invasive testing,[36,40–42] and allow safe and early discontinuation of antibiotic therapy by excluding the diagnosis of VAP in a significant number of patients. By identifying the responsible pathogen, these methods enable the clinician to narrow the antibiotic spectrum, reduce costs, and prevent the selection of resistant organisms and superinfection.[40] One report in which antibiotics were started empirically, according to the American Thoracic Society recommendations, reported that 43% of antibiotic prescriptions needed later modification.[43] Few studies have shown conclusive evidence of improvement when semi-invasive microbiological tests are used,[40,41] and the effect of these diagnostic tests on outcome remains unknown.

Several case series argue that the most important factor affecting outcome is not establishing a diagnosis, but instituting appropriate antibiotics promptly.[42,44,45] Use of an inappropriate antibiotic was associated with higher mortality, even when the antibiotic was eventually changed on the basis of BAL findings.[42,45,46] There is, however, a general sense that patients suspected of having VAP are already over-treated with antibiotics.[47] A study by Singh et al[48] adds to the complexity of managing patients with VAP. Patients classified as having a low likelihood of pneumonia, based on the clinical pulmonary infection score, were treated exclusively with ciprofloxacin. The antibiotic was discontinued if after 3 days the patient's status remained unchanged.[48] Compared with standard antibiotic therapy, the 3-day monotherapy group had a significantly shorter ICU stay, lower hospital cost, lower antimicrobial resistance, and less superinfection, with no adverse effect on mortality.[48] This study raises the question of whether ICU patients with pulmonary infiltrate and low likelihood of pneumonia should be treated with antibiotics at all.

Catheter-related sepsis

Intravascular devices are a common, although often overlooked, source of fever. The risk of catheter-associated sepsis varies depending on the length of time since insertion, the type of device, the number of ports, the insertion technique, and the frequency of manipulation.[4,17,49] The highest risk is with temporary haemodialysis catheters (five to ten cases/1000 catheter days) and the lowest is with short peripheral catheters (<0·2 cases/1000 catheter days).[4] A recent randomised controlled trial showed that central venous catheters inserted through the femoral vein carry a

significantly higher risk of infectious (19·8% *vs* 4·5%) and thrombotic (21·5% *vs* 1·9%) complications than those inserted through the subclavian vein.[50] The risk of infectious complications associated with internal jugular vein insertion is reportedly comparable to or slightly lower than the femoral route.[49,51–53]

Catheter-related infection should be suspected when bacteraemia or fungaemia develop in an immunocompetent patient, when there is inflammation or pus at the catheter insertion site, or when blood cultures are positive for organisms otherwise considered contaminants, especially coagulase-negative saphylococci, *Corynebacterium* spp, *Bacillus* spp, or *Candida* spp.[4,49]

Investigations for a catheter source of fever include a meticulous examination of all intravenous sites. Exudate or pus around insertion sites or tunnels should be sent for Gram stain and culture. Blood cultures should be drawn both retrograde through the catheter and from peripheral venipuncture sites. Catheter-related sepsis can be diagnosed when a higher concentration—usually tenfold higher—of organisms is identified in the retrograde blood culture compared with the blood culture from separate venipuncture.[49,54] The catheter is also implicated as the source of sepsis when semiquantitative (catheter tip rolled over solid media) or quantitative (sonication or catheter flush on liquid media) culture counts are high—ie, more than 15 colony-forming units (CFU) for semiquantitative or more than 100 CFU in quantitative cultures.[4,49]

Local infection, documented catheter-related bacteraemia, or remote complications such as septic thrombosis, endocarditis, or metastatic seeding, usually require immediate removal of the vascular line.[4,49] An exception to this general rule involves the use of antibiotic lock therapy in implantable devices or tunnelled central lines, reserved for those patients with very poor vascular access.[49] Depending on the virulence of the pathogen and host factors, removal of the infected catheter might be the only treatment necessary.[49] Routine exchange of catheters does not prevent infection.[3]

Urinary-tract infections

Another therapeutic dilemma is the management of an ICU patient with fever and a positive urine culture.

Almost all ICU patients have a bladder catheter that rapidly becomes colonised by the patient's colonic flora. Catheter-associated bacteriuria occurs in at least 30% of these patients.[55] But the differentiation of bacteriuria from urinary-tract infection (UTI) has not been well established. Fewer than 3% of patients with bacteriuria develop bacteraemia with the organism isolated in the urine culture.[17] Pyuria could differentiate bacteriuria from UTI, however it is not a useful marker for the diagnosis of invasive infection since most episodes of catheter-associated bacteriuria present with a significant number of white cells in the urine.[4,56]

The current recommendation is that urine cultures should be obtained only when clinically indicated—eg, in patients with an anatomic abnormality or recent surgery of the urinary tract—and that isolated bacteriuria should not be treated.[4,56] Antibiotic treatment should be started only in patients who have symptoms, with concomitant bacteraemia, with urinary tract obstruction, or after urinary tract surgery.[17]

Sinusitis

Sinusitis is another common but difficult to diagnose source of fever in critically ill patients. The clinical diagnosis of sinusitis is made in only one-quarter of ICU patients with proven sinusitis,[57] because few have characteristic physical indications or are able to give a classic history of facial pain, headache, or purulent nasal discharge.[57]

Sinusitis in critically ill patients results from obstruction of the draining ostia of the sinuses by nasotracheal or nasogastric tubes.[4] Removal of the tube is essential for the treatment of an established infectious sinusitis. Tube removal could also prevent sinusitis. It has been shown that avoiding the nasal passage for the insertion of endotracheal and gastric tubes reduces the incidence of sinusitis.[58,59]

Initial investigation of suspected sinusitis is by CT scan of the face, since plain films or ultrasound examinations are limited in their ability to detect the disorder.[60,61] But the CT scan only shows opacification or air fluid levels in the sinus cavities, an abnormality that does not necessarily indicate infection: in one report, only 38% of radiologically detected abnormalities proved to be infectious sinusitis.[17] To establish the diagnosis it is necessary to puncture, aspirate, and culture the fluid from the sinus cavities.[57,58] Transnasal puncture serves two purposes: it establishes the diagnosis and drains the infected sinus cavity. Drainage alone often resolves the infectious process, even when intravenous antibiotics are not used.[57,58]

Diarrhoea and fever

Fever might also occur in patients with diarrhoea, defined as two or more loose bowel movements a day. In the ICU, diarrhoea is typically caused by either enteral feeds or antibiotic use. We will focus on the latter.

Clostridium difficile is responsible for one-quarter of all cases of antibiotic-associated diarrhoea[62] and has been reported to infect as many as 20% of all hospital in-patients.[63–65] *C difficile*-induced diarrhoea should be suspected in patients with fever and diarrhoea who have received antibiotics within 3 weeks of the onset of diarrhoea.[62] Systemic manifestations include fever, nausea, and marked neutrophilia. Rare cases may present without diarrhoea and a fulminant and life-threatening toxic megacolon.

Any ICU patient at risk of developing *C difficile* colitis and having more than two loose stools per day should have two stool samples sent for a toxin ELISA.[62] Even though tissue culture for *C difficile* is the gold standard for diagnosis, in practice it has been replaced by the quicker and less expensive toxin ELISA. CT scan is another excellent tool in the diagnosis of *C difficile* colitis, with CT results suggestive of pseudomembranous colitis in 88% of the cases.[27,28] For patients with severe forms of colitis an immediate diagnosis can be made by visualisation of pseudomembranes with a sigmoidoscope. Sigmoidoscopic examination has a good sensitivity (71%) in severe forms of pseudomembranous colitis, but a low sensitivity (23%) in mild disease.[4] Because sigmoidoscopy or colonoscopy have significant cost and carry the risk of perforation, many clinicians prefer to introduce empirical antibiotic therapy while waiting for laboratorial diagnosis. Except for the most severe presentations, the

empirical use of antibiotics, especially vancomycin, should be discouraged because of the risk of producing even more resistant pathogens.[4] Some recent studies in patients with *C difficile* colitis reported that adding the probiotic agent *Saccharomyces boulardii* to conventional antibiotic therapy reduced subsequent recurrences compared with antibiotic alone.[66] The use of *S boulardii* remains controversial since other studies have reported no benefits with this therapy and it is not FDA approved.[67]

Wound infection

Another common cause of infection and fever in the ICU is postoperative wound infection, the second most common hospital-acquired infection.[4] Most wound infections are subcutaneous abscesses, and are diagnosed by the presence of erythema, pus, or tenderness of the surgical incision. Treatment involves opening the wound and drainage. Antibiotics are reserved for immunocompromised patients or for the treatment of cellulitis.[68]

Wound infection can develop in the deeper layers of the incision, and involve fascia and muscles. When such infections develop in the early postoperative period, or are accompanied by findings such as disproportional pain, rapidly advancing borders, blisters, necrosis, and systemic toxicity, the possibility of clostridial myonecrosis should be considered.[68] Deeper infections need immediate and aggressive resuscitation, surgical debridement, and appropriate antimicrobial therapy.[68]

Other infectious causes

Other potential infectious sources in ICU patients include fungal infection, an important diagnosis to pursue in febrile ICU patients who have been receiving multiple antibiotics for more than 10 days,[69] bacterial endocarditis, and septic thrombophlebitis, which typically occurs in patients with chronic intravascular catheters.

Conclusion

Let us return to Mr B. A systematic clinical assessment showed no obvious infectious cause for his fever (figures 1 and 2), and two blood cultures have been drawn. Although he is febrile, he is physiologically stable. His treatment remained unchanged.

The next morning Mr B's antibiotics were withheld, despite the recent and repeated episodes of fever, and his persistent leucocytosis. Plans were made to repeat cultures 24–48 h after stopping antibiotics, with the understanding that broad-spectrum antibiotic coverage would be started immediately were Mr B to show any evidence of deterioration. He remained stable and 24 h after withdrawing the antibiotics he was no longer febrile. Follow-up blood cultures were negative and the leucocytosis resolved. Saturday night fever had passed; it was the start of a new week.

Sepsis is the leading cause of death in the ICU. Not surprisingly, therefore, intensive-care specialists commonly have a low threshold for starting antibiotics empirically as soon as patients show clinical signs of sepsis. This practice, however, carries the risk of over-treating suspected infections, and promoting the emergence of multidrug-resistant pathogens.

Several guidelines have been proposed to avoid unnecessary antibiotic use, and to increase the effectiveness of those that are employed[46,70] Restriction of the use of antibiotics reduces infection with pathogens such as vancomycin-resistant enterococcus and *C difficile*, and reduces the number of nosocomial infections such as VAP,[70–72] but these protocols have limitations.

Our bias in managing ICU patients with fever has been increasingly towards a more restrictive approach. Empiric antimicrobial therapy should be reserved for the high-risk patient—eg, those who are deteriorating rapidly or who are neutropenic. Patients without an obvious source of sepsis are better served by continued vigilance and repeated assessment. The work up of fever includes not only changing central lines or searching for sinus infections, but also stopping antibiotics. Most nosocomial infections in critically ill patients will respond satisfactorily to physical source-control measures (table 2). In this new century, the management of fever in the ICU entails much more than simply initiating antibiotic therapy. For many patients, careful diagnosis with the use of source control techniques, and even the discontinuation of systemic antimicrobial agents is the more appropriate therapeutic response.

Search strategy and selection criteria

References selected for this review were identified by searches of Medline, using the search terms "fever", "ICU", and specific topics—ie, acalculous cholecystitis, and by searches of practice guidelines of diverse infectious disease and critical care societies. The references were chosen mostly for their relevance to clinical practice and up-to-date concepts. Several studies were chosen based on their impact on the authors' practice, their ease of access, and on the additional information they provide.

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