New Onset Fever in the Intensive Care Unit

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Abstract

Fever is defined as a core body temperature of >38.3°C or 101°F. About 50% of fevers in the ICU are due to infectious causes. Absence of fever in patients with infection heralds a poor prognosis. Temperatures between 102°F-106°F are more likely to be due to infection. The common infectious causes of fever are pneumonia, sepsis, line infections and intra-abdominal infections. Temperatures <102°F or >106°F are usually due to non-infectious causes like deep venous thrombosis, infusion reactions, aspiration, drug fever and the neuroleptic malignant syndrome. Fever should be distinguished from hyperthermia as antipyretics are ineffective in the latter. Inappropriate use of antibiotics selects resistant bacterial strains, but delay in treating infection could increase mortality. A structured approach is therefore required in order to correctly diagnose and treat fever in critically ill patients.

Fever is a daily concern in the ICU as sepsis is a leading cause of death. However, many cases of fever are due to non-infectious causes. In spite of that patients undergo extensive investigation and are often started on antibiotics as soon as they develop fever. This leads to the development of drug-resistant pathogens and exposes the patient to serious side effects.

PATHOPHYSIOLOGY OF FEVER

Fever is a coordinated neuroendocrine, autonomic and behavioural response that is adaptive, and an essential part of the acute-phase response to immune stimulus or tissue injury. Like other integrated homeostatic responses of the body, fever is co-ordinated largely by the hypothalamus, which receives neural input from peripheral thermoreceptors and humoral cues, produced by inflammation or infection.

Temperature is sensed by A-delta fibres (cold signals), and unmyelinated C fibres (warm signals). These receptors are distributed throughout the body with the largest contribution from the thermal core. Signals from these receptors ascend via the spinothalamic tracts to the hypothalamic thermoregulatory centre located in the preoptic region near the floor of the third ventricle. This region has fenestrated capillaries (called the Organum Vasculosum of the Lamina Terminalis), which allow the neurons to come in contact with a wide variety of substances directly from the blood stream.

The systemic inflammatory response syndrome is characterized by synthesis and release of pyrogenic cytokines (IL-1, TNF, IL-6) from a variety of cells. These cytokines, in turn, trigger specialized endothelial cells of the hypothalamic vascular organs, which release PGE2, and other substances resulting in a resetting of the hypothalamic thermostat from normothermic to febrile levels. This brings about both heat conservation (through cutaneous vasoconstriction) and increased heat production (through shivering and uncoupling of oxidative phosphorylation), resulting in fever. The core body temperature rarely exceeds 106.0°F (41.1°C) during fever. This suggests that fever has a thermal ceiling designed to protect the host against the deleterious effects of temperatures higher than 106.0°F (41.1°C) which is partly mediated by endogenous ‘cryogens’.

Fever appears to be a preserved evolutionary response within the animal kingdom and even reptiles, amphibians, fish, as well as several invertebrate species manifest fever in response to challenge with bacteria. Although fever can have deleterious effects, it helps to rid the host of invading pathogens. Plasmodium species, causing malaria, spirochaetes, and bacteria such as Streptococcus pneumoniae are inhibited by elevated body temperatures. Elevated body temperature has been shown to enhance several parameters of immune function, including antibody production, T-cell activation, production of cytokines, and enhanced neutrophil and macrophage function.

An elevated body temperature may, however, be associated with a number of deleterious effects, most notably an increase in cardiac output, oxygen consumption, carbon dioxide production, and increase in BMR. Oxygen consumption increases by approximately 10% per degree Celsius. These changes may be poorly tolerated in patients with limited...
cardiorespiratory reserve. In patients who have suffered a cerebrovascular accident or traumatic head injury, moderate elevations of brain temperature may markedly worsen the resulting injury. Maternal fever has been suggested to be a cause of foetal malformations or spontaneous abortion.

**Definition of Fever**

One of the largest studies of oral temperature in healthy subjects yielded a mean temperature of 98.2°F (36.8°C). The upper limit of normal temperature (i.e. greater than the 99th percentile), varied according to the time of day from an low of 99.0°F (37.2°C) in the early hours of the morning to as evening rise of 100°F (37.8°C) due to circadian rhythmicity. Thus the guidelines of the Society of Critical Care Medicine (SCCM) and Infectious Disease Society of America (IDSA) recommend that any new fever in an ICU patient should be investigated only if the temperature is 38.3°C (101°F) or higher. The guidelines recommend that a well-maintained and suitably calibrated electronic device be used for measurement of tympanic, oral or rectal temperatures and the measurement of axillary temperatures be abandoned.

Characterising fever magnitude, pattern, and relation to pulse could provide important diagnostic clues. Fevers less than 102°F are usually due to non-infectious causes as given in Table 1. Fevers higher than 106°F are often a result of non-infectious causes such as malignant hyperthermia, heat stroke, drug fever, adrenal insufficiency, or thyroid storm. Temperatures between 102 and 106°F could be both due to infectious or non-infectious causes, but certain patterns might suggest the cause. Continuous fever has been associated with Gram-negative infections, drug fever and fever due to central nervous system disease (i.e., encephalitis, subarachnoid haemorrhage). Relative bradycardia during fever, especially when accompanied by leucocytosis, eosinophilia, or cutaneous rash, may occur in drug fever. Fever in the first 2–3 postoperative days is usually non-infectious, and benign due to tissue injury or atelectasis, whereas fever arising 5–7 days postoperatively usually indicates a surgical site infection. Fever arising after 10–14 days of antibiotic treatment could be due to infection by resistant organisms especially candida or other fungi.

**Hyperthermia versus Pyrexia**

In contrast to fever, hyperthermia is characterized by an elevation of the core body temperature without a change in the hypothalamic set point and occurs essentially due to a failure to dissipate heat in relation to its rate of production. Common causes include pontine haemorrhage, heat stroke, malignant hyperthermia and the neuroleptic malignant syndrome.

A diagnosis of heat stroke is suggested when hyperthermia is associated with altered mentation after exposure to high environmental temperatures or vigorous exercise, with core body temperature often exceeding 42°C (107.6°F). Investigations reveal metabolic acidosis and electrolyte abnormalities like hyperkalemia, hypocalcemia and hyperphosphatemia. Treatment involves cooling by evaporation (tepid water sponging), conduction (immersion in cold water), and management of fluid, electrolyte and acid-base balance.

Malignant hyperthermia is an autosomal dominant myopathy. The genetic defect is on chromosome 19, which codes for the ryanodine receptor that regulates the calcium channel. Release of large amounts of calcium from the sarcoplasmic reticulum occurs on exposure of a susceptible individual to anaesthetic triggering agents and depolarizing muscle relaxants. This causes intense muscular contraction, with subsequent muscular rigidity and hyperthermia. Other manifestations include metabolic acidosis, disseminated intravascular coagulation and renal failure. Management includes stopping all triggering agents, use of dantrolene sodium and treatment of organ failure.

The neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to neuroleptic drugs characterized by encephalopathy, muscle rigidity, hyperthermia and dysautonomia. These drugs appear to block dopamine receptors in the hypothalamus with consequent altered thermoregulation and heat dissipation. Rhabdomyolysis and renal failure may occur. Management involves discontinuation of the offending drugs, cooling, and use of dopamine agonists like bromocriptine and muscle relaxants like dantrolene. Gratz and co-workers have also used anticholinergic agents for the treatment of NMS.

**Noninfectious Causes of Fever**

Several non-infectious conditions may cause fever in the ICU (Table 1). The pathogenesis involves the release of cytokines following tissue injury. A study by Circiumaru and Baldock found that non-infective causes accounted for about half the cases of fever in the ICU.

**Approach to Fever in the ICU**

This is best done in a systematic manner (Fig. 1). Answers to some basic questions, often leads one to the diagnosis.

1. Is there any chronic predisposing condition? Are there any conditions that have a greater incidence of specific bacterial infections like diabetes, COPD, HIV infection, corticosteroid therapy, malignancy?
2. What is the acute condition leading to ICU admission? Could the condition itself explain the fever? Examples include sepsis, stroke, obstructive uropathy, pancreatitis, congestive heart failure, ARDS, traumatic brain injury.
3. Have any invasive procedures been carried out?
Diagnostic and therapeutic procedures could result in a portal of entry for common ICU organisms. Such procedures include, central venous catheterization, dialysis, urinary catheterization, tracheal intubation and emergency or elective surgery.

4. What is the maximum temperature and pattern of the fever?²⁰

- Temp > 106°F (41.1°C): consider malignant hyperthermia, neuroleptic malignant syndrome, drug fever, heat stroke and hypothalamic injury
- Temp < 102°F (38.9°C): consider deep venous thrombosis and pulmonary embolism, superficial phlebitis, gastrointestinal bleeding, pancreatitis, bacteriuria, myocardial infarction, drug and alcohol withdrawal, post operative fever, post transfusion fever, subarachnoid haemorrhage, ischemic bowel and atelectasis.
- Temp 102°F-106°F: consider infections like ventilator associated pneumonia, sinusitis, catheter related sepsis, primary Gram-negative sepsis, abdominal sepsis like acalculous cholecystitis, wound infection, C. difficile diarrhea, drug fever and adrenal insufficiency.

5. Does the patient have any localizing signs that indicate specific organ involvement?

**COMMON INFECTIOUS CAUSES OF FEVER IN THE ICU**

Infectious causes of fever require antibiotic therapy. Febrile patients with localizing signs present few difficulties in diagnosis. Diagnosing patients without localizing signs, however, is a challenge. This is usually empiric to start with, and is often guided by the probable site of infection. The approach to the common causes of infections is described in Table 2. Once antibiotics are started, and microbiological tests are done, the diagnosis should be reviewed after 48 hours if fever persists or if laboratory tests are negative.

**Rational use of antimicrobials in the ICU**

1. Empirical antibiotic regimens should cover the most likely pathogens, should be initiated promptly after taking suitable cultures and should be given in high doses to provide optimal therapy.

2. Antimicrobial resistance patterns must be factored in the initial choice of antibiotic(s), especially the growing threat of ESBL's, to decrease mortality and morbidity.²³

3. The results of culture and susceptibility tests should be utilised to make suitable changes to initial empiric antibiotic regimens.

4. The pharmacologic activity of the antibiotic agent (MIC on in-vitro testing) and the pharmacokinetic properties (distribution in various body compartments and routes of metabolism and excretion) should be considered in the selection of antibiotic agents.

5. Protocol driven antibiotic cycling in which specific antibiotics are periodically withdrawn and replaced by drugs from a different class should be considered for prevention of emergence of drug resistant organisms.²⁴

6. Combination microbial regimens should be used in the treatment of mixed infections or organisms like *Pseudomonas aeruginosa* which are often resistant to multiple antibiotics.

7. Shorter courses of antibiotics e.g. 8 days versus 15 days to treat VAP may be equally efficacious and
### Table 2: Infectious causes of fever in the ICU

<table>
<thead>
<tr>
<th>Infection</th>
<th>Clinical pointers</th>
<th>Diagnostic Approach</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>Purulent secretions. Bronchial breath sounds, new or progressive infiltrate on Xray. Worsening PaO₂/FiO₂. Systemic inflammatory response.</td>
<td>Tracheal secretions - Gram stain, culture, blood cultures, bronchoalveolar lavage fluid with quantitative cultures esp. for PCP, CMV or mycobacteria. <strong>Differential diagnosis:</strong> CHF, ARDS, atelectasis</td>
<td>Broad spectrum antibiotics e.g. piperacillin-tazobactam or a carbapenem modified according to culture results; wean and extubate as soon as the patients condition allows.</td>
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<tr>
<td>I.V catheter-related sepsis</td>
<td>Inflammation or purulence at insertion site. Thrombosis of catheter. Systemic signs of infection.</td>
<td>Semiquantitative culture of catheter tip + blood cultures (bacterial and fungal); &gt;15 colony forming units from tip + positive blood culture of the same organism + SIRS is catheter related blood stream infection(CRBSI).</td>
<td>Line removal; antibiotics for persistent bacteraemia, high-risk patient or progressive sepsis. Vancomycin for MRSA and cloxacillin for sensitive staph. Consider cover for Gram –ve organisms and Candida.</td>
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<tr>
<td>Urosepsis</td>
<td>SIRS plus lower abdominal/flank pain or tenderness</td>
<td>Urine exam and culture. Blood cultures. USG and CT to look for obstruction or complications</td>
<td>Broad spectrum antibiotics if evidence of a systemic response, or immunocompromised pts, change or remove catheter</td>
</tr>
<tr>
<td>Intraabdominal infection e.g. Peritonitis, abscesses due to intestinal perforation</td>
<td>Localized tenderness, palpable abdominal mass, absent bowel sounds</td>
<td>Peritoneal tap, USG followed by CT abdomen with oral and iv contrast</td>
<td>Antibiotics to cover aerobic and anaerobic organisms</td>
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<tr>
<td>Paranasal sinus infection</td>
<td>Presence of nasogastric or nasotracheal tube. Purulent discharge, periorbital edema, headache, fever</td>
<td>CT scan of sinuses; sinus puncture for confirmation, culture and sensitivity</td>
<td></td>
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<tr>
<td>Surgical wound infection</td>
<td>Important whether surgical field contaminated by bowel contents or entry into respiratory or urinary tract</td>
<td>Superficial - Examine wound Deep - CT Scan</td>
<td>Open, debride and pack wound Percutaneous or operative drainage, Antibiotics</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Rule out food intolerance, drug, HIV, consider <em>C. difficile</em> if antibiotics within last 3 weeks</td>
<td>ELISA for <em>C. difficile</em> toxin A and B or tissue culture assay and flexible sigmoidoscopy for detection of pseudomembranes.</td>
<td>Stop antibiotics; probiotics (<em>S. boulardii</em>); Oral metronidazole or vancomycin for <em>C. difficile</em>.</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>Consider if febrile inspite of broad spectrum antibiotics</td>
<td>Fungal blood cultures</td>
<td>Stop antibiotics Systemic antifungal therapy as indicated</td>
</tr>
<tr>
<td>Disseminated candidiasis</td>
<td>Immuno compromised e.g. diabetes, HIV infection, neutropenia.</td>
<td>Fundoscopy, liver biopsy, culture of urine, sputum and vascular catheters</td>
<td>Systemic antifungal therapy as indicated e.g amphotericin B or voriconazole</td>
</tr>
<tr>
<td>Acalculous cholecystitis</td>
<td>Fever, nausea, vomiting and right hypochondrial tenderness. Predisposing conditions: Shock, TPN, major surgery, burns, HIV</td>
<td>USG: gallbladder sludge and distension. Gallbladder wall thickness ≥3.0 mm and pericholecystic collection. Suberosal edema (halo sign)</td>
<td>Cholecystectomy / cholecystotomy, empiric broad spectrum antibiotics</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Fever, heart murmur, unexplained heart failure or embolic phenomena</td>
<td>Blood cultures, transthoracic and transesophageal echocardiography</td>
<td>Antibiotics especially to cover for <em>Staphylococcus</em> and Gram negative organisms</td>
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<tr>
<td>Meningitis</td>
<td>Fever, altered sensorium, neck stiffness</td>
<td>CT scan (to assess for complications), CSF, blood cultures</td>
<td>Vancomycin + Meropenem</td>
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**Does the Patient Warrant Antipyretic Therapy?**

The absence of fever in sepsis is associated with significantly higher mortality, thus proving that fever has a protective function. Patients with septic shock had a higher mortality if they were hypothermic than if they were febrile.26 Fever upgrades immune responses and inhibits the proliferation of pathogens. Therefore the use of antipyretics, cooling blankets, or other forms of associated with decreased incidence of side effects, emergence of drug resistance and costs of therapy.25

8. Monitoring of antibiotic therapy should include clinical response, changes in organ function requiring changes in drug dosing, drug related adverse events, drug interactions and monitoring of serum antibiotic levels.

9. Initial route of administration should be IV but can later be changed to the oral route once patients are stable.
temperature reduction in febrile patients should not be routinely utilized. It is important to note that cooling blankets often increase fever by inducing shivering, thus increasing oxygen consumption, and causing discomfort for the patients. There are only a few situations where fever is clearly detrimental and it is advisable to lower the body temperature. These include temperature >41.1°C (106°F), patients having limited cardiorespiratory reserve, recent stroke, traumatic brain injury and possibly pregnancy. In these conditions, the elevated temperature itself, or the associated increase in cardiac output can worsen outcome of the underlying acute disorder. Antipyretic drugs like paracetamol are preferred to physical cooling in most cases, as the latter may induce shivering and further increase cardiac output and oxygen demand. However, in patients with fulminant hepatic failure, paracetamol is best avoided as abnormal metabolism may lead to the formation of toxic metabolites and liver injury.

**CONCLUSION**

Treat fever more as a friend than as a foe. Fever in the critically ill patient is a marker of an underlying problem which needs to be unearthed and suitably dealt with, rather than reacting to an elevated body temperature in a knee jerk fashion. In about 50% of patients, fever is due to non-infective causes. When infection is suspected, the choice of antibiotic therapy differs according to the site of infection and predisposing factors. Hence efforts must be made to identify the source of infection and the causative organism, which may be a resistant hospital pathogen. Finally, fever has myriad immunostimulatory effects, and it is useful to remember the age-old adage when treating it: Primum non nocere (First do no harm).

**REFERENCES**