Fever in Intensive Care Unit

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1.1 Introduction

The development of fever in a critically ill patient in ICU should not trigger panic, but it should be considered as a sign, which requires appropriate attention and management. Fever is commonly a physiological expression of host response to infectious or non-infectious agents. Fever is also considered to be host defense against external exposure and the raised body temperature helps in better immune response by promoting synthesis of antibodies, cytokines, activated T cells, polymorphs, and macrophages. There is some medical evidence to suggest, raised body temperature may be harmful in patients with acute brain injury and in patients with compromised cardio-respiratory reserve (e.g., cardiac arrest) and pharmacological treatment in these critically ill patient is beneficial. Fever should also be treated in patient who complains of discomfort due to high body temperature.

For an intensivist, fever is most often the starting point for detailed clinical evaluation and prompts him to initiate important diagnostic and treatment decisions. As our knowledge of pathogenesis of fever is expanding along with availability of better diagnostic tools, the perimeter of fever is expanding well beyond bacterial infections. Fungal, viral, and immunological etiologies of fever are now well known and not uncommon. Sometimes a simple drug fever may perplex an intensivist, leading to extensive unfruitful investigations. We will discuss about various infectious and non-infectious causes of fever and briefly discuss the approach to fever management in ICU care.
1.2 Definition of Fever

The normal body temperature varies with the time of measurement as well as by the method of measurement, the body temperature of approximately 37 °C (98.6 °F) is considered to be normal. The definition of fever is also arbitrary considering the time of day and method of measurement. The most accepted definition of fever in ICU by 2008 Infectious Disease Society of America (IDSA) and American College of Critical Care Medicine (ACCM) is temperature of >38.3 °C (101 °F). This definition has several caveats as it may not be true for the immunocompromised patients, in elderly, patients on immunosuppressant therapy (e.g., corticosteroids), pediatric population, and severe form of sepsis where hypothermia may be the presenting sign instead of fever.

1.3 Measurement of Fever

The fever can be measured by central and peripheral thermometers. Their indications, advantages, disadvantages, and accuracy are given in the Table 1.1. The pulmonary artery catheter based core body temperature measurement is the gold standard and most accurate method, but it is not a feasible method in ICU. The reason includes non-availability of resources, requirement of technical competence, trained and experienced manpower and of course high cost. The peripheral thermometry is still extensively utilized in most of the ICU, although it is less reliable, with average sensitivity and specificity being 64% and 96%, respectively, as compared to central thermometry.

As an intensivist, the dilemma of relying upon central verses peripheral thermometry do exist, especially in resource poor countries. One may prefer central thermometry if accurate measurement is necessary (hypothermia, neutropenic sepsis) or if the temperature is not fitting well with clinical condition. In rest of situation the peripheral thermometry is appropriate.

1.4 Etiopathogenesis of Fever

Fever or pyrexia in human being is thought to be a protective adaptive response secondary to release of cytokines in the circulation. Although the exact mechanism of cytokine release is not understood but it is thought to be related to endocrine and immune mediated. Heat is generated by chemical reactions during catabolism of

| Table 1.1 | Methods of temperature measurements in intensive care unit |
|------------|----------------------------------------------------------|
| Accuracy   | Method of temperature measurement                        |
| Most accurate | Pulmonary artery catheter, esophageal probe, bladder probe, rectal probe |
| Less accurate | Oral, temporal artery probe                              |
| Least accurate | Axillary, tympanic membrane, chemical dot                |
nutrient inside the cells. Human body generates a basal metabolic rate as well as basal heat production to maintain optimum cell function, and this generated heat is distributed to the whole body by circulatory system. The thermoregulation and control of body temperature is done meticulously by preoptic region of nervous system (hypothalamus, limbic system, lower brainstem, reticular formation, spinal cord, and sympathetic ganglia). The temperature sensitive area in this preoptic region regulates body temperature according to feedback signals as received from the peripheral sensors (skin) and core sensors of body. There are cold and warm sensing neurons in this region, which respond in a way to keep the body temperature in balance and at a set temperature.

Fever has been documented in up to 2/3rd of intensive care unit admissions and is commonly due to infections. Studies have shown that patient with fever in ICU setting is associated with higher mortality, increased length of stay, increased cost of therapy, and poorer outcome, especially in patients with head injury, subarachnoid hemorrhage (SAH), and pancreatitis. However, in few studies, fever in infectious diseases has been associated with less hospital mortality, and considered to be adaptive response to infection. Therefore, the pathophysiologic importance of process of fever is still incompletely understood and controversial.

The etiology of fever in ICU can be divided into infectious or non-infectious in origin (Table 1.2). The proportion of infectious versus non-infectious cause

Table 1.2 Infectious and non-infectious causes of fever

| Infectious Causes of Fever | Non-Infectious Causes of fever in ICU | Hyperthermia Syndrome |
|----------------------------|-------------------------------------|-----------------------|
| Bacteremia | Drug Fever | Drug Reaction |
| Intravascular Cather related infections | Drug Reactions: Steven Johnson syndrome. | Neuroleptic malignant syndrome |
| Surgical site infection | Drug overdose (aspirin, anticholinergic drugs) | Malignant Hyperthermia |
| Ventilator associated Infections (VAP) \ | Drug withdrawal | Serotonin Syndrome |
| Abdominal Causes (Bowel perforation, abdominal abscess, diverticulitis cholangitis, pseudomembranous colitis) | Abdominal (Acute cholecystitis, pancreatitis, ischemic colitis) | Thyrotoxicosis |
| Chest Infection (Pneumonia, Empyema) | Benign Post-operative Fever | Pheochromocytoma |
| Urinary tract (infection/ pyelonephritis) | Endocrine causes (Thyroid storm, adrenal crisis, pheochromocytoma) | Heat stroke |
| CNS (meningitis,encephalitis) | Rheumatic (vasculitis,SLE,Gout) | |
| Cellulitis/Necrotizing Fascitis/ Myonecrosis | Neoplastic (Reticuloendothelial malignancy, Solid Tumors) | |
| Septic arthritis | Transfusion reaction | |
| Sinusitis | Burns | |
| Thrombophlebitis | CNS (subarachnoid hemorrhage/ seizures) | |
| | Pulmonary Embolism | |
of fever in ICU is highly variable depending on population being studied, type of ICU, and definition of fever being used. The various studies on ICU infections suggest the relative frequency of infectious fever between 50 and 60%. The distinction between infectious and non-infectious fever is challenging for every intensivist. Few studies suggest the magnitude of fever or absolute body temperature may help in differentiation in few situations, in contrary to it others scientists are not fully convinced with importance of absolute temperature. Many experts believe, fever with temperatures between 38.3 °C (101 °F) and 38.8 °C (101.8 °F) can be due to infectious/non-infectious source, therefore not useful in differentiation; while patients with fever between 38.9 °C (102 °F) and 41 °C (105.8 °F) can be assumed to be infectious; patients with very high fever ≥41.1 °C (106 °F) are commonly non-infectious in origin (drug fever, hyperthermia, etc.)

1.5 Infectious Causes of Fever

The common infectious causes of fever in ICU includes ventilator associated pneumonia (VAP), central line associated blood stream infection (CLABSI), catheter related UTI, surgical site infections, and sinusitis. The few important infectious causes of fever in ICU will be discussed in next section.

Ventilator Associated Pneumonia (VAP) Pneumonia developing after >48 h of ventilatory care is called VAP. The triad of VAP consists of new or increase in pulmonary infiltrates on chest radiograph, increase or purulence of tracheobronchial secretions, and leukocytosis.

Central Line Associated Blood Stream Infection (CLABSI) Long term intravascular catheters are commonly associated with fever in ICU patients, who need central line for nutrition, fluid, chemotherapy, or antibiotics. They frequently present as uncomplicated fever without any localizing signs, but alternatively they may present with local abscess or visible purulent secretions from the catheter insertion site. Other manifestations include septicemia with or without multi organ failure or suppurative thrombophlebitis, endocarditis, or septic abscesses. The following points regarding indwelling catheter should be remembered:

1. There is increased use of iv devices (central and peripheral) for short/long term therapeutic goals.
2. Look daily at insertion site for local and possible systemic infection.
3. Culture of pus/discharge at insertion site is not routinely recommended; however, if done, it has got negative predictive value.
4. Please remember to remove iv catheter as soon it is not needed.
**Viral Infections**  Epidemiological studies show that the prevalence of viral respiratory tract infections can be as high as 41% in critically ill patients admitted to the ICU with a suspected CAP, and up to 34% in HAP. It is unclear if all patients admitted to the ICU with a suspected CAP should be tested for respiratory viruses. There are no recommendations for virus testing in patients admitted to the ICU due to HAP. The difficulty is that clinical signs and symptoms are rarely sufficient to make a specific diagnosis of a viral infection.

It is therefore a combination of clinical syndrome together with epidemiologic clues and specific laboratory tests which helps in arriving a diagnosis. Documented viral infections occur in up to 45% of episodes of exacerbation of COPD. Frequently identified viruses in acutely ill COPD patients are rhinoviruses, parainfluenza viruses, coronaviruses, and influenza viruses type A and B. In severely ill adult patients requiring hospitalization and mechanical ventilation, influenza viruses and coronaviruses are most common pathogens.

**Fungal Infections**  Contrary to popular believes that fungal infections occur in immunocompromised patients, there is growing body of evidence that suggest intensive care per se predisposes to fungal infections. The important factors for micro invasion are: prolonged ICU stay (>7 days), parenteral antibiotics use, total parenteral nutrition, major abdominal surgery, vascular access, patients with acute kidney injury. The preexisting conditions like diabetes, burns, prematurity, and neutropenia make fungal infections more likely.

**Sinusitis**  The common cause of sinusitis is anatomic obstruction of ostia draining from sinuses. Persons with deviated nasal septum (DNS) are more prone to some degree of chronic sinusitis. The clinical diagnosis of sinusitis suspected by purulent nasal discharge, fever, and malodourous breath. The ICU patients pose a different problem as many of them are intubated and therefore cannot be assessed routinely for headache, pain, or purulent discharge. In addition, a nasal intubation, orofacial trauma, fracture base of skull, and nasopharyngeal hematomas all contribute to sinusitis. A combination of CT scan along with nasal endoscopy increases diagnostic accuracy as the latter one helps getting the sinus fluid for examination. Regarding pathogens, pseudomonas accounts for 60% infections, *S. aureus* and streptococcus are implicated in 33% cases.

### 1.6 Non-infectious Causes of Fever

There are several non-infectious causes of fever in ICU. It is good practice to separate the hyperthermia syndrome from other non-infectious cause of fever as they usually present with very high absolute temperature and do not respond to antipyretics therapy, and instead need physical therapy for management. In next section, we
will discuss common causes of hyperthermia and few important causes of non-infectious fever in ICU.

### 1.6.1 Hyperthermia

Distinction between hyperthermia and fever is required for better management. The very high absolute body temperature which exceeds >41.0 °C and has no response with pharmacological treatment distinguishes between hyperthermia syndrome and fever/pyrexia. In hyperthermia syndrome, there is unregulated rise in body temperature associated with failure of thermoregulatory homeostasis. In routine fever, the adaptive mechanism resets the thermostat, leading to normalization of temperature after sometime. Malignant hyperthermia, neuroleptic malignant syndrome (NMS), serotonin syndrome secondary to antipsychotic drugs, heat stroke, and endocrine cause (thyrotoxicosis, pheochromocytoma, adrenal crisis, etc.) are common causes of hyperthermia (Table 1.2). Malignant hyperthermia occurs in genetically susceptible individuals and associated with use of anesthetic agents (e.g., halothane, succinylcholine, etc.) where dysregulation of intracellular calcium metabolism leads to increased skeletal muscle activity resulting in muscle rigidity, metabolic acidosis, and hyperthermia. The malignant hyperthermia usually occurs immediately after use of culprit anesthetic agents, but uncommonly it may occur up to 24 h later, especially if steroid has been used preoperatively. Dantrolene sodium inhibits calcium ion release from skeletal muscle by antagonizing ryanodine receptor on sarcoplasmic reticulum. It is the drug of choice for malignant hyperthermia as well as for neuroleptic malignant syndrome (NMS) and can be life-saving in critically ill patients. Neuroleptic malignant syndrome develops commonly in patients on antipsychotic (haloperidol) medicines. It is associated with excessive skeletal muscle activity leading to high fever, muscle rigidity, and raised creatinine phosphokinase enzymes levels. The supportive care to reduce body temperature with cold blankets and ice bath is usually required in critically ill patients of hyperthermia in ICU.

**Drug Fever**

Medicines may precipitate fever owing to their pharmacological properties. They may induce fever by allergic/anaphylactic/hypersensitivity reactions, inducing fever, decreasing heat dissipation or altering thermoregulatory mechanism, and inducing cytokine storm (Table 1.3). While suspecting drug as an offending agent for fever, the clinician needs to address two issues:

1. Is it really a drug fever?
2. If so, what is/are offending agents?

While finding the answer to the first question about the causality of drug fever, there may be a temporal profile, which may help in deciding if the drug is the cause of fever (Table 1.4). The review of history and/or medical records may help in knowing the exact day of onset of fever and duration of fever and its relation to drug introduction, which may help in identifying the cause of fever.
The second question is little difficult to answer as there is a long list of medicines which may cause fever and often patients are receiving different class of drugs in both inpatient and outpatient settings. The Table 1.5 lists the most common culprit drugs involved in drug fever. The astute clinician needs to use his knowledge and keep high index of suspicion in case no other cause is apparent and one of the mentioned drug is being used in ICU. We should remember any drug may cause fever, there has been rare case reports of dexmedetomidine and pantoprazole causing fever.

### 1.6.2 Connective Tissue Disease (CTD)

The CTD/vasculitis as an etiology in ICU patient is difficult to consider at first place as it does not develop acutely. There may be a coexisting undiagnosed CTD or a diagnosed patient with acute complication. Both types of patients pose different clinical problem in diagnosis and management (Table 1.6). The common CTD’s to be considered are RA, SLE, scleroderma, antiphospholipid syndrome, vasculitis, and dermatomyositis in decreasing order of prevalence.
A peripheral smear suggesting rouleaux formation along with urinalyses showing dysmorphic RBC’s (glomerulonephritis) points towards an ongoing immune insult and it should be further probed. Low complements level C3/C4 and CH50 may help to diagnosis of SLE activity. When suspecting CTD, a revision of history, medical records, treatment, and interview with relatives/friends may give you a valuable clue towards diagnosis.

### Table 1.6  Issues in diagnosis and management of CTD in ICU

| Clinical status | Probable outcome |
|-----------------|------------------|
| Undiagnosed CTD | Delay in treatment |
|                 | Unexplained/early multi organ failure |
|                 | Rapid downhill course |
|                 | Increased morbidity/mortality |
|                 | 20% are antibody negative |
| Diagnosed CTD   | Mortality is high |
|                 | Difficult to differentiate between inflammatory v/s infection as a primary insult |
|                 | Overlap syndrome often coexists |

1.7  Laboratory Investigation

1.7.1  Blood Culture

The growth of suspected organism along with sensitivity profile is still gold standard for selection/revision of antimicrobials therapy and antibiotic stewardship. The rapidity of MDR bugs development and paucity of newer antibiotics make situation very complex, leaving very little room to maneuver.

The following points should be remembered for blood culture sampling:

1. Multiple samples with aseptic precautions (at least 3–4 in 24 h) is must for detection/microbial growth.
2. Single sample is not recommended except for neonatal patients.
3. There is no difference of growth between arterial and venous samples.
4. Use different sites for each sample and at least 10–20 ml blood sample to be collected in blood culture bottle or BACTEC.
5. If intravascular device is in place, use separate site to obtain blood.
6. Do not use multiple port of same device.

1.7.2  Serum Procalcitonin (PCT)

The serum procalcitonin is a promising, cheap, and simple blood test to distinguish bacterial infection from other causes of infection or inflammation. PCT can be
positive in many non-infectious etiologies, especially in severe physiologic stresses (e.g., surgery, major trauma, burns, hemodialysis, multi organ failure). PCT values should always be interpreted carefully in light of history, clinical examination findings and microbiological assessment. The PCT test has following characteristics:

1. Reporting time <2 h.
2. Average sensitivity and specificity is 80–100%
3. Detectable within 2–4 h after stimulus (infection/inflammation)
4. Peaks by 12–24 h
5. Decline (half-life) 24–36 h.
6. Parallel increase with inflammation.
7. A declining trend is suggestive of resolving infection/inflammation.

1.7.3  Syndromic Testing

Rapid multiplex PCR based molecular diagnostic platforms have been developed which can screen for a wide variety of pathogens with a short turn around time. High cost remains a major bottleneck preventing the widespread use of such platforms.

1.7.4  Urine Culture

Urinary infections, especially urinary catheter infection is a major source of fever in ICU patients. Early morning mid-stream urine sample is best in a self-voiding patient. In a catheterized patient urine should be collected from Foley’s catheter port and transported immediately or at least within 2 h of sample collection for optimum results.

1.8  Radiologic Investigations

**Chest Radiograph**  Most common radiological investigation to order as it gives information about appearance of a new pulmonary lesion or worsening of the existing one. Respiratory system being the portal of entry second to genitourinary system and therefore more likely to get infected.

**CT Scan**  Though it is not done routinely required in all patients, it may have a role in specific subset of patients especially in ICU as it provides very important information about diagnosis of pulmonary embolism and mediastinal adenopathy which is otherwise difficult to diagnose on chest radiograph. It also helps to differentiate between new or worsening lung pathology. Regarding abdomen, it is much more sensitive in detecting hepatobiliary infection/inflammation, Psoas hematoma/abscess, pancreatic necrosis, adenopathy, and retro-peritoneal collection then ultrasound.
MRI  The MRI of brain becomes essential in evaluating CNS infections specially meningoencephalitis and posterior fossa lesions.

1.9  Approach to Patient with Fever in ICU

A thorough medical history and complete review of records followed by complete physical examination is paramount in localizing and identifying the cause of fever in ICU. Multiple blood culture is the only mandatory diagnostics test in patient with new onset fever in ICU as clinical examination alone cannot identify cause of fever in many critically ill patients because of low sensitivity. Further evaluation should be done in a systematic manner to find the cause of fever.

The systematic approach to patient with fever in critically illness in intensive care unit involves integration of following seven points:

1. Medical history and review of records.
2. Clinical examination.
3. Interpretation of investigative data.
4. Any chronic predisposing condition.
5. Acute condition leading to ICU admission.
6. Magnitude of fever.
7. Any recent invasive procedure.

1. Medical History and Review of Records  The complete medical history should be taken from the patient or from attendant depending upon circumstances and patient’s sensorium. The medical records of recent treatment, travel, or medication should be noted and confirmed from previous hospital records or prescription. The importance of good medical history in making a diagnosis cannot be ignored in ICU patients.

2. Clinical Examination  The patient needs to be thoroughly re-examined from head to toe, many a times the clues lie right there or developed recently before patient being shifted to ICU from general ward. The suggested search for infectious source should start with focused examination, which should include any evidence of: abscess, localized collection, thrombophlebitis, deep vein thrombosis, cellulitis, pressure ulcers/bed sores, indwelling catheter or catheter site infections. Although its well-known that in many ICU patient focus of infection could not be find even after complete thorough examination, thus bringing the role of blood culture and laboratory investigations.

3. Interpretation of Data  Any patient with fever undergoes a battery of test to ascertain the cause. The test ordered are blood culture, urine culture, chest radiograph, and examination of other relevant body fluids in descending order. However, it is the interpretation of laboratory and radiological data that differentiate between infectious from a non-infectious cause. Therefore, for interpretation of laboratory data the following points should be considered:
1. There are marked overlap of organism between normal and pathogenic, especially gastrointestinal tract, and genital systems.
2. For blood culture, compare the number of samples drawn with positive growth and organism grown.
3. For suspected UTI, the urinalyses should show >10 WBC/hpf and CFU > 10^7/ml unless the sample is collected by special procedure (i.e., suprapubic aspiration).

4. Any Predisposing Condition Patient with pancytopenia due to leukemia, post-chemotherapy is more prone to develop febrile neutropenia leading to gram negative sepsis or even fungal infection. Similarly, immunocompromised patients with HIV may have atypical infection from pneumocystis or mycobacterium. Knowing of predisposing condition will help in further investigation and arriving at diagnosis.

5. Acute Condition Leading to ICU Admission Rarely patients with congestive heart failure, ARDS, traumatic brain injury, Addison’s crisis, seizure or pulmonary embolism may present with fever due to primary illness only, instead of any infection.

6. Magnitude of Fever Body temperature above 41 °C is commonly seen in non-infectious causes, especially hyperthermia. This hyperthermia syndrome does not respond with antipyretics and is secondary to dysfunction of thermoregulatory centers in brain. Fever between 38.9 °C (102 °F) and 41 °C (105.8 °F) usually considered to be secondary to infectious source.

7. Recent Invasive Procedure Any diagnostic or therapeutic procedures done recently can be source or portal of infection in ICU patients. The fever can be due surgical site infection (>48 h of surgery) or benign post-operative fever. Common ICU procedures like CVP line insertion, urinary catheterization, tracheal intubation, arterial line can lead to fever in ICU patients.

1.10 Management

The management of fever in ICU is very challenging for intensivist. First and foremost, he has to investigate and decide if the cause of fever is infectious or non-infectious and then further proceed. The three most crucial decision an ICU specialist has to take in a febrile patient is to decide if patient should be started on empirical antibiotics (especially if the focus of fever is not found), secondly to remove or not to remove an indwelling catheter, and lastly if the patient should be treated with antipyretics or not.
1.10.1 Empiric Antibiotic Therapy for Suspected Infection in a Febrile Patient

If an infectious cause of fever is suspected in ICU patients, broad spectrum antibiotics should be started as soon as possible after taking appropriate cultures. There are studies which suggest that timely appropriate antibiotics in sepsis patients lead to reduced ICU stay and reduced mortality. Empirical antibiotics should be started on priority in patients in shock, neutropenia, and suspected infected ventricular assist device. Patients who are stable and whose temperature is below 102°F should be further evaluated before starting antibiotics therapy.

1.10.2 Removal of Catheter in Febrile Patient

Infected central venous catheter should be removed immediately in a catheter related blood stream infection (CRB). The consideration should be given to severity of illness, age of indwelling catheter, probability of catheter being infective source in an unproven case of blood stream infection.

1.10.3 Antipyretics or Cooling Therapy for Fever

There is conflicting data for treatment of fever with antipyretics or external cooling in ICU patients and therefore it should not be routinely treated especially in septic patients. Exceptions to it are patients having very high core temperature (>41 °C/106 °F), patients with acute stroke or traumatic brain injury (raised ICP), limited cardio-respiratory reserve (post cardiac arrest), as in these situations higher temperature may lead to tissue injuries. Patient having significant discomfort due to fever and pregnant female may also be treated with antipyretics as there is chances of fetal malformations. If decision is taken for treating fever, then it should be ideally treated with oral/intravenous acetaminophen.

1.11 Conclusion

Fever is seen in 2/3rd of ICU admission in some point of their care. It is recommended to follow a clinically driven, systematic, cost-effective approach for evaluation of febrile ICU patients. Empirical antibiotics should only be started as soon as possible in patients who are very sick, in shock, neutropenic, or having suspected infected ventricular assist device. As there is no robust data to suggest any benefit in treating fever with antipyretics, therefore, the lowering of temperature is only recommended in patients with acute brain injury, hyperthermia, and in patients with reduced cardiorespiratory reserve to prevent excessive tissue injury and mortality.
Suggested Readings

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