Fever in the ICU

- 30% of medical patients will become febrile during their hospitalization in the ICU

- > 90% of critically ill patients with severe sepsis will experience fever during their stay in the ICU

A newly elevated temperature in critically ill patients

At a certain time of their hospitalization

Trigger a set of many diagnostic and laboratory tests

A cost-effective manner of assessment is necessary

• COMMON
• YES
• YES

Late fever in critically ill patients

Traditionally, a pharmacologic and/or mechanical antipyretic therapy is administered before the confirmation of the cause.

- a) misconceptions about the detrimental effects of fever especially in the children (e.g., seizures, brain damage)
- b) the response on the part of the physicians to the psychological pressure, especially from the family
Late fever in critically ill patients

- **Origin** = infectious, non-infectious, mixed
- **Difficult** = Confirmation of the source
- **Treating response** = a variability from the medical and nursing staff

“to treat or not to treat”...
Febrile response

A complex physiologic reaction to inflammation and/or infection

- cytokine-mediated rise in core body temperature
- generation of acute phase reactants
- activation of numerous physiologic, endocrinologic and immunologic systems

Definition, physiology and pathogenesis of the fever
Definition of the fever

Healthy individuals

- 36.8°C with a range 35.6°C–38.0°C and a slight diurnal/circadian variation 0.5°C–1.0°C
- During the heavy exercise a rise by 2°C to 3°C is observed

Neutropenic patients

- A core temperature >38.0°C or in two consecutive measurements >38.3°C

## Measurement of fever

<table>
<thead>
<tr>
<th>Site</th>
<th>Method</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery</td>
<td>Mixed venous blood</td>
<td>Pulmonary artery catheter complications</td>
</tr>
<tr>
<td>Infrared ear</td>
<td>Thermometer</td>
<td>Values a few tenth 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 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>

Pathogenesis of the fever

Exogenous stimuli

Release by monocytic cells of endogenous pyrogens (IL-1, TNF, IL-6, IFNs) binding to specific receptors located in the preoptic region of the anterior hypothalamus

1. A blood-brain barrier acts as a valve - permits the entrance of a limited quantity of those proteins into the brain.

2. These pyrogens come into contact with neurons with the aid of small neuronal cells with fenestrated capillaries called "circumventricular organs" and a direct response of the neurons within the organum vasculosum of the lamina terminalis or of astrocytes or microglia to cytokines is noted.

arachidonic acid metabolites production (prostaglandin E2 and thromboxane A2) and an up-regulation of the thermostatic set point.
Response of the brain

By sending signals able to activate effector mechanisms through the spinal / supraspinal motor system or throughout the sympathetic nervous system

generate heat
reduce heat loss and increase core body temperature to match the upregulation of the thermostatic set point

Activation of arachidonic acid metabolites act as substrate for the cyclo-oxygenase-2 (COX-2) pathway which in turn leads to:

- elevation of prostaglandins levels
- increased heat production.

Its activity is inhibited by selective inhibitors, including nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

Different organs (Responses to fever)

Metabolic

- Production of glucosteroids
- Secretion of growth hormone
- Secretion of aldosterone

FEVER

Metabolic

- Secretion of vasopressin
- Levels of divalent cations in plasma
- Secretion of acute-phase proteins

Autonomic Different

- Blood flow from cutaneous to deep beds
- Pulse and blood pressure

Different Signs

- Shivering (rigors)
- Chills
- Anorexia
- Somnolence
Effects of fever

For every degree centigrade increase in temperature, oxygen demand and energy expenditure 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.

Dimopoulos G. PACT modules updated 2011, European Society Intensive Care Medicine
Deleterious effects of fever

Fever affect mainly

- patients with cardiorespiratory diseases
  - poorly tolerated because of
    - $\uparrow$ CO
    - $\uparrow$ VO$_2$
    - $\uparrow$ CO$_2$
    - $\uparrow$ energy expenditure

- neurosurgical patients
  - moderate elevations of brain temperature
  - exacerbate the injuries

Upon the appearance of fever:

- elevated oxygen consumption
  - for each $\degree C$ increase in body temperature a 13% increase in oxygen consumption is noted
- increased heart rate
- elevated cardiac output
- increased serum catecholamine

Beneficial effects of fever

- The beneficial effects have been shown in
  - mammalian models
    - an increased body temperature was associated to enhanced resistance to infection
  - in clinical trials in adults
    - a positive correlation was recorded
      - between maximum temperature on the bacteremia day and survival
      - between a temperature of >38°C and survival in spontaneous bacterial peritonitis

In critically ill patients.................

- Single spike of elevated temperature that return to normal without treatment = **frequent**
  - without clinical significance
  - interventions, endotracheal suctioning, urinary catheter, transfusion of blood products

- Fever related to invasive procedure or manipulation of an indwelling device with or without transient bacteremia resolves spontaneously = **often**

- Fever caused by underlying chronic diseases, current medical illness or its complications, or reactions following drug therapy = **may be persistent**.
Fever in critically ill patients

Half of fever episodes in the ICU are of

- Non-infectious origin
- The temperature usually non-exceeding 38.3°C
- Additional necessary diagnostic procedures
  - medical history (recent interventions)
  - physical examination

- Type of ICU population
- Specific type of patients
- History of recent epidemics
- Local epidemiology
Main causes of non-infectious fever
In cardiac care units CCUs

- Myocardial infarction
- Dressler’s syndrome with pericarditis
- Thromboembolism
- Thrombolytic therapy
  - hemorrhagic complications and antiarrythmic medication (eg, procainamide, quinidine)
- Deep venous thrombosis

In neurosurgical ICUs

- Posterior fossa syndrome (mimics meningitis)
- Central fever
  - intracranial lesion /trauma affecting the brain or hypothalamus
  - exceeding 39C (106F), resistant to antipyretics
  - characterized by absence of perspiration
- Anticonvulsive agents
- Fat embolism in trauma patients

In acute phase after head injury pyrexia

- extremely frequent /deleterious for cerebral perfusion (CCP) and intracranial pressure (ICP)
- Lack of treatment by antipyretics = longer ICU stay

Acalculus cholecystitis

- Frequently unrecognized
  - gallbladder ischemia and bile stasis
  - estimated incidence of 1.5%
- Radiologic investigation
  - Ultrasound (wall thickness > 3 mm, intramural lucencies, gallbladder distension, pericholecystic fluid, intramural sludge)
  - CT scanning (high sensitivity and specificity)
  - Hepatobiliary scintigraphy: > 50% false-positive rate
- Diagnosis is often delayed
  - ischemia, gangrene, perforation
- Percutaneous cholecystectomy

Drug–related fever or “drug fever”

✓ Unknown incidence
  o 3%-7% of febrile episodes are attributed to drug reactions, but many cases remain undiagnosed

✓ Temperature
  o ranges from 38.8°C(102°F) to 40°C(104°F)

✓ Difficult diagnosis
  o usually established by exclusion because of the non-specific signs and laboratory tests

✓ Maculopapular rash
  o in only 5%-10% of case

✓ Increased WBC count (rarely)

✓ Moderate elevation of serum transaminases

✓ Peripheral eosinophilia

✓ Elevated sedimentation rate (>100 mm/h)

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## Agents associated to drug-fever

### High-risk agents
- Antibiotics
  - β-lactams
- Anti-epileptic
  - Phenytoin
- Anti-arrhythmics
  - Quinidine, procainamide
- Anti-hypertensives
  - Alpha-methyldopa
- Diuretics
- Anti-seizures drugs
- Stool softeners

### Antibiotics with lower risk
- Clindamycin,
- Vancomycin
- Chloramphenicol
- Aztreonam
- Doxycycline
- Erythromycin
- Imipemen
- Quinolones
- Aminoglycosides

Issues on drug-fever

Time between initiating a drug and drug fever
- 21 days (median 8 days)

Resolution
- usually within 72 hours after removing the offending drug
- when a rash is present it persists for days or week

Usual scenario

A patient with an already diagnosed infection

- The infection is resolving
- Initial defervescence in temperature
- Recurrence of fever is noticed
  - if the infection has been resolved or another infectious site has not been detected
  - Antibiotics should be discontinued

- If the patient is stable but the infection has not been resolved
  - The presumed offending agent should be removed and a modification to antibiotics, without potential sensitizing, according to the spectrum of pathogens should be performed
Postoperative fever

Within the first 72 hours after surgery

- release of endogenous pyrogens into the bloodstream
- careful evaluation to rule out infection
  - after a patient is >96 hours febrile
  - specific predisposing factors
  - type and site of surgery
  - underlying comorbidities


I AM HERE TO HELP YOU!!!
### Malignant Hyperthermia (MH) and Malignant Neuroleptic Syndrome (MNS)

#### MH
- Operating room mainly
  - after general anesthesia with depolarizing agents
  - Succinylcholine, inhaled anesthetics (halothane)

#### MNS
- Blockade of dopamine receptors from antipsychotic agents (phenothiazines, thioxanthenes, butyrophenones)
- Central initial muscle contraction (mainly difference)

Inhibit hypothalamic heat-conserving mechanisms, generating high fever, muscular rigidity, and increased creatinine phosphokinase concentrations

Heiman-Patterson TD. Med Clin North Am 1993;77:477-92
Other non–infectious causes of fever in critically ill patients

✓ Heatstroke
✓ Withdrawal of drugs
  o tachycardia, diaphoresis, and hyperreflexia
    (eg, alcohol, opiates, barbiturates, benzodiazepines)
✓ Atelectasis, ARDS without pneumonia
  o result of inflammatory process
✓ Blood transfusion
  o especially platelets
  o incidence of 0.5%
  o appears 30 min to 2 hours after the transfusion is begun
  o last 2–24 hours preceded by chills

Main causes of infectious fever
ICU–acquired infections

Prevalence

✓ 10% (NNIS), 20.6% (EPIC I,II study)
✓ VAP the most common followed by
  • Sinusitis
  • Bloodstream infections
  • Catheter–related infections
  • Nosocomial diarrhea and
  • Wound infections

Infections of the respiratory system

- VAP = 25% of mechanically-ventilated patients
  - Leukocytosis
  - Purulent tracheal secretions
  - New or worsening infiltrates on CxR
  - In immunocompromised patients, especially in solid organ transplant patients could be developed without the presence of the above clinical manifestations

- Differential diagnosis
  - ARDS, LVF, VAT (mainly)

Evaluation of infections of the respiratory system

- **Chest imaging study**
  - Chest radiograph, CT scan

- **Cultures of secretions**
  - before antibiotics administration
  - expectorated sputum, tracheal secretions, BAL
  - quantitative cultures

- **In case of pleural effusion**
  - stain culture, cytology of the pleural fluid

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**CLINICAL PULMONARY INFECTION SCORE**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp °C</td>
<td>36.5-38.4</td>
<td>38.5-39.0</td>
<td>&lt;36.0 or &gt;39.0</td>
</tr>
<tr>
<td>Neutrophils, x10³/L</td>
<td>4-11</td>
<td>≤4 or ≥11</td>
<td>≤4 or ≥11 + band forms ≥0.5</td>
</tr>
<tr>
<td>Secretions</td>
<td>+/-</td>
<td>+</td>
<td>++/purulent</td>
</tr>
<tr>
<td>Arterial PO₂ (kPa)/Inspiratory O₂ fraction</td>
<td>&gt;33 or ARDS</td>
<td>&lt;33 and no ARDS</td>
<td></td>
</tr>
<tr>
<td>Radiographic infiltrates</td>
<td>clear</td>
<td>patchy</td>
<td>localised</td>
</tr>
</tbody>
</table>

ARDS = acute respiratory distress syndrome

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Catheter–related infections

- Incidence
  - 10 infections/1.000 catheter days

- Relative risk for their appearance depends on
  - length of time with the catheter in situ
  - number of ports
  - manipulations
  - type of the device
  - patient population
  - techniques used in insertion
Catheter–related infections
Diagnosis

* Diagnosis is based on clinical signs
  - difficulty of drawing or infusing through the catheter
  - presence of inflammation at the insertion site and
  - the recovery of microorganisms in multiple blood cultures

* Two peripheral blood cultures or
  - one drawn percutaneously and one through the catheter
  - blood cultures drawn through intravascular devices (excellent sensitivity)

* Removal and culture of the catheter followed by
  semiquantitative or quantitative catheter tip methods

**GOLD STANDARD**

Sinusitis

Incidence = 5% of all nosocomial infections in the ICU
- Affecrs mainly trauma or neurosurgical patients, fever ↑ WBC
- Purulent nasal discharge present in only 25% of proved cases

Predisposing factors
- Nasotracheal or nasogastric tube placement
- Nasal packing, Facial fractures
- Steroid administration

Diagnosis
- Plain radiographs
- CT scan or magnetic resonance imaging of the sinus
- Nasal endoscopy

Intra–abdominal and surgical site infections

- Could be the main cause of ICU admission or a secondary cause after abdominal surgery

- Diagnosis is facilitated by CT scan of the abdomen, ultrasound and nuclear medicine techniques (gallium–67, indium–111, white blood cell scintigraphy)

- Contamination of the surgical incision
  - medical comorbidities
  - duration of the operation
  - whether antimicrobial prophylaxis was administered before incision

Nosocomial Diarrhea

More than two stools per day

- *Clostridium difficile* = commonest cause of febrile diarrhea
- 10%–25% of all cases of antibiotic-associated diarrhea
- clindamycin, ceplalosporins, fluoroquinolones

Diagnosis

- tissue culture assay
- enzyme immunoassay test (EIA) for toxin A and B
- flexible sigmoidoscopy

Cytomegalovirus antigenemia

CMV antigenemia = a cause of unexplained prolonged fever?
- emerging isolate in severely ill, immuno-competent patients in ICU patients
- the significance of CMV detection is unknown
- higher morbidity and mortality compared with patients in whom the virus remains undetectable

Fungal Infections

**Diagnosis is often made late**
- Non-specific early manifestations
- Blood cultures = gold standard positive in only approximately 50% of patients
- Cultures may become positive late
- Serologic tests or molecular methods
  - not currently used in clinical practice

Main causes of fever in the ICU according to the systems (I)

<table>
<thead>
<tr>
<th>System</th>
<th>Infectious Causes</th>
<th>Non–infectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Meningitis, Encephalitis</td>
<td>Posterior fossa syndrome, central fever, seizures, cerebral infraction, hemorrhage, cerebrovascular accident</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Central line, Infected pacemaker, endocarditis, sternal osteomyelitis, viral pericarditis</td>
<td>Myocardial infarction, myocardial / perivalvular abscess, balloon pump syndrome, post–pericardiectomy syndrome</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>VAP, mediastinitis, tracheobronchitis, empyema</td>
<td>Pulmonary emboli, ARDS, atelectasis (without pneumonia), BOOP, bronchogenic carcinoma without postobstructive pneumonia, systemic lupus erythemaosus pneumonitis</td>
</tr>
</tbody>
</table>
## Main causes of fever in the ICU according to the systems (II)

<table>
<thead>
<tr>
<th>System</th>
<th>Infectious Causes</th>
<th>Non-infectious Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Intra-abdominal abscess, cholangiitis, cholecystitis, viral hepatitis, peritonitis, diarrhea (Clostridium difficile)</td>
<td>Pancreatitis, acalculus cholecystitis, ischemia of the bowel, bleeding, cirrhosis, ischemic colitis, irritable bowel syndrome</td>
</tr>
<tr>
<td>UTIs</td>
<td>Catheter-associated bacteremia, urosepsis, pyelonephritis, cystitis</td>
<td>Underestimates core temperature, lacks reproducibility</td>
</tr>
<tr>
<td>SSIs</td>
<td>Decubitus ulcers, cellulitis, wound infection</td>
<td>—</td>
</tr>
<tr>
<td>Bone / joint</td>
<td>Chronic osteomyelitis, septic arthritis</td>
<td>Acute gout</td>
</tr>
<tr>
<td>Other</td>
<td>Transient bacteremia, sinusitis</td>
<td>Adrenal insufficiency, phlebitis / thrombophlebitis, neoplastic fever, alcohol / drug withdrawal, delirium tremens, drug fever, fat emboli, deep venous thrombosis, post-operative fever (48 h), fever after transfusion.</td>
</tr>
</tbody>
</table>
Approaching the febrile critically ill patient

The initial approach includes:

a) the overview of the medical record
b) the physical examination and
c) the evaluation of characteristics of the fever
   - magnitude
   - duration
   - relationship to:
     ✓ pulse rate
     ✓ diagnostic and therapeutic interventions

Approaching the febrile critically ill patient

Fever (>38.3°C or 101°F)

2 sets of blood cultures, urine and sputum cultures

The clinician must consider

- that chills and fever appear 1–2 hours after the presence of microorganisms in the blood
- explains the commonly observed negative blood cultures at the time of the temperature

Unexplained or unknown origin late fever

- Leukocytosis, anion gap acidosis, hypotension or persistent tachycardia and tachypnea
  - septic syndrome?
  - where is the source / site of infection?

✓ Immediate initiation of antibiotics empirically after the cultures have been obtained
✓ All the central lines must be removed
✓ Physical examination, laboratory evaluation
✓ Radiological evaluation
Biomarkers

Adjunctive markers for the evaluation of fever, aiming to discriminate true infection from noninfection or other inflammatory diseases

- serum procalcitonin assays
- endotoxin detection systems
- trigering receptor xpressed on myeloids cells–1 (TREM–1)
- C–reactive protein
- tumor necrosis factor–a and Interleukin–6

Methods for the suppression of the fever in the ICU

• Antipyretic agents
  – acetaminophen, cyclooxygenase 2 nonsteroidal agents, metamizol and propacetamol

• External cooling techniques
Antipyretic agents

- Block or reverse the cytokine-mediated rise in core temperature caused by fever without affecting body temperature

- Must be distinguished from hypothermic agents that are able to lower core temperature even in the absence of fever

External cooling methods

✓ Hypothermia blankets
  - Associated however with some side effects
    - large temperature fluctuations
    - development of rebound hyperthermia
    - appearance of hypermetabolism
    - increased oxygen consumption leading to elevated levels of epinephrine / norepinephrine.

ACCM/SCCM and IDSA guidelines

.....the goal for the treatment of a new temperature elevation in a previously afebrile, critically ill patient in whom the source of the fever is not obvious merits

a) a detailed evaluation (medical history)
b) careful physical examination before the order of any laboratory or imaging procedure
or
before the administration of any drug

Approach to the febrile patient in the ICU

Fever (temperature >38.3°C or 101°F)

- Infection site
  - Non-obvious
    - Consider Non-infectious causes
    - Observe 48 hours
    - If the fever persists
      - Central lines (>48 hours) → remove and culture
      - Nasal tubes → remove, CT of the sinuses
      - Diarrhea → stool culture and empiric antibiotic therapy
      - Observe 48 hours
      - If the fever persists
        - Antifungal therapy
        - Venography
        - Imaging for abdominal infections

In conclusion

Late fever in the ICU
- Frequent
- Infectious, non-infectious, mixed origin
- Difficult differential diagnosis
- Detailed (medical history, physical examination, laboratory evaluation)