Diagnostic Approach to Fever in ICU

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- Fever
- Pathogenesis
- Measurement of Temperature
- Causes of Fever
  - ICU Environment
  - Hyperthermic Syndrome
  - Non-infectious
  - Infectious
- Investigations
- Treatment

Fever

- Fever appears to be a preserved evolutionary response within the animal kingdom in response to challenge with microorganism.

Mackowiak PA et al, Ann Intern Med 1994;120:1037-40

Kluger MJ et al,Infect Dis Clin N Am 1996; 10:1–20

Kluger MJ et al, J Physiol 1978; 282:243–251

Bernheim HA et al, Am J Physiol 1976; 231:198–203

D'Alecy LG et al, J Physiol 1975; 253:223–232

Vaughn LK et al, Nature 1974; 252:473–474.

Fever

- Complex physiologic reaction to disease involving a cytokine mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiologic, endocrinologic and immunologic systems

Arch Intern Med 2000, 160:449-456

Fever

- Normal body temperature 37 °C ± 0.5 to 1 °C, according to circadian rhythm and menstrual cycle.

Dinarello CA et al, *Rev Infect Dis 1988; 10:168–189*

- Heavy exercise can rise the temperature by 2 to 3°C .

Waterhouse J et al, *Chronobiol Int* 2004; 21:253–275

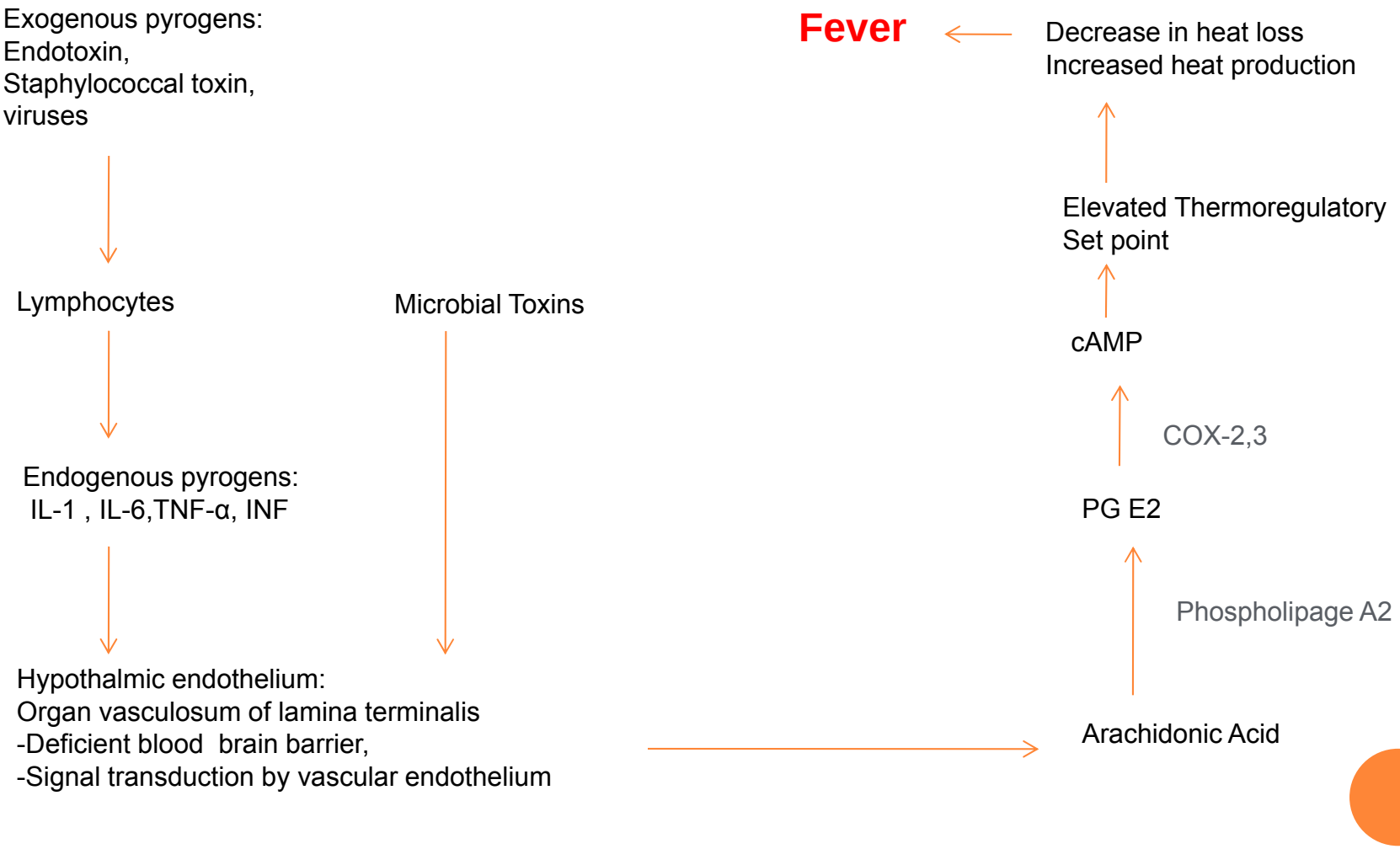
Fever

- Fever in patients admitted to ICUs:
  - Core body temperature $\geq$38.3°C (101°F)
  - Lower threshold for immunocompromised patients

    O'Grady NP et al, *Crit Care Med 2008; 36:1330–1349*

- Hyperthermia:
  - Increase body temperature with normal hypothalamic set point.
- Hyperpyrexia $\geq$ 40 °C
- Hypothermia $\leq$ 35 °C

PATHOGENESIS



Measurement of Temperature

Method	Merits	De-marits
Pulmonary artery thermistor	Most accurate (Gold Standard)	Invasive, Need equipment
Urinary bladder catheter thermistor	Most accurate	Costly Need equipment
Esophageal probe	Most accurate	Position diff. to confirm Uncomfortable Risk of perforation
Rectal probe	higher than core temperature	Unpleasant Rectal trauma Cl.difficle transmission
Oral probe	Acceptable	Food, drinks, intubated, un-cooperate pt
Infrared ear thermometry	acceptable	Risks trauma Inflammation Obstruction of the external canal
Axillary thermometer	Less desirable	Underestimates core temp.
Temporal artery thermometer	Less desirable	Underestimates core temp.
Chemical dot	Less desirable	Lack of agreement

Clin Pediatr(Phila) 1991; 30(4 Suppl):13–16
Crit CareMed 1991; 19:818–823
Crit Care Med 1993; 21:1528–153
*Am J Crit Care*1994; 3:40–54
Am J Crit Care 1995; 4:286–292

FEVER IN ICU

- Frequency of fever in ICU has been variably quoted between 26%* to 44%^

Intensive Care Med 2004; 30:811–816

**Intensive Care Med 1999; 25:668–673*

^Kevin B et al, *Crit Care Med 2008;36:1531-1535*

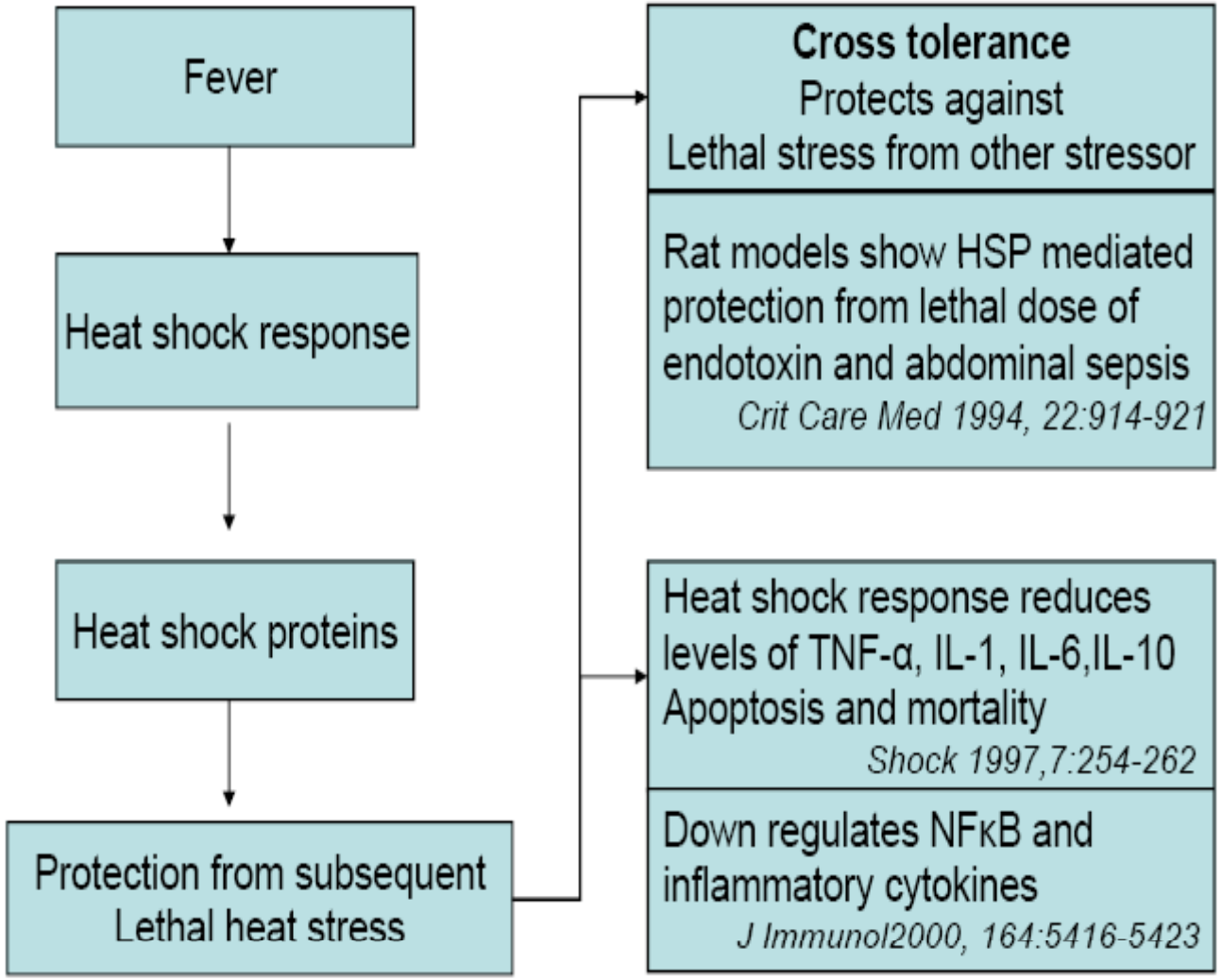
- Presence of fever often prompts changes to patient management.

O'Grady NP *et al, Clin Infect Dis 1998; 26:1042–1059*

- The acquisition of fever in the ICU is associated with adverse outcomes in medical ICU patients .

Kevin B et al, *Crit Care Med 2008;36:1531-1535*

Protective effects of fever



Protective effect of fever

- It helps to rid of the host from invading pathogens: eg
  - Plasmodium species,
  - Spirochaetes,
  - Bacteria such as Streptococcus pneumoniae are inhibited by elevated body temperatures.

Marik PE et al, Chest 2000;117:855-69.

PROTECTIVE EFFECT OF FEVER

- Enhance parameters of immune function
- Improves antibody production
- Activates T-cell
- Produces cytokines
- Enhanced neutrophil and macrophage function

Marik PE et al, *Chest 2000;117:855-69.*

Jampel HD et al, *J Exp Med* 1983;157:1229-38.

Sande MA et al, *J Infect Dis 1987;156:849-50.*

Bryant RE et al, *Arch Intern Med* 1971;127:120-8.

Weinstein MR et al, *Am J Med 1978;64:592-8*

The New England Journal of Medicine

THE EFFECTS OF IBUPROFEN ON THE PHYSIOLOGY AND SURVIVAL OF PATIENTS WITH SEPSIS

GORDON R. BERNARD, M.D., ARTHUR P. WHEELER, M.D., JAMES A. RUSSELL, M.D., ROLAND SCHEIN, M.D., WARREN R. SUMMER, M.D., KENNETH P. STEINBERG, M.D., WILLIAM J. FULKERSON, M.D., PATRICK E. WRIGHT, M.D., BRIAN W. CHRISTMAN, M.D., WILLIAM D. DUPONT, PH.D., STANLEY B. HIGGINS, PH.D., AND BRIDGET B. SWINDELL, R.N., FOR THE IBUPROFEN IN SEPSIS STUDY GROUP*

N Engl J Med 1997;336:912-8.

- BERNARD et al conducted a randomized, double-blind, placebo-controlled trial of intravenous ibuprofen in 455 patients.
- 10 mg/kg body weight [maximal dose, 800 mg] every six hours for eight doses.
- In the patients who had sepsis, defined as fever, tachycardia, tachypnea, and acute failure of at least one organ system.
- Infection sources were : Lung(47%), Peritoneum(15%), UTI(10%) & other/unknown(27%)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	IBUPROFEN (N=224)	PLACEBO (N=231)
Major prognostic indicators		
Age (yr)	54.0±18	56.0±16
APACHE II score	16±7	15±7
Mean blood pressure (mm Hg)	80±17	79±16
Positive culture (% of patients)		
At any site	75	76
Of blood	39	32
Mechanical ventilation (% of patients)	78	76
Adequate antibiotic treatment (% of patients)	96	96
Black race (% of patients)	32	25
Sex (% of patients)		
Female	59	66
Male	42	34
Classification of patient (% of patients)		
Surgical, no trauma	27	25
Surgical, trauma	7	9
Medical	67	66
Laboratory data†		
Serum creatinine (mg/dl)	1.7±1.7	1.5±1.7
Total bilirubin (mg/dl)	1.5±1.7	1.4±1.5
Arterial lactate (mmol/liter)	3.0±3.0	2.7±2.4
PaO_2/FiO_2	214±107	203±102
Pulmonary edema on chest film (% of patients)		
None	11	16
Mild	27	21
Moderate	36	37
Severe	26	26
Organ-system failure at entry (% of patients)‡		
ARDS	29	28
Pulmonary system	56	55
Central nervous system	26	26
Renal system	53	67§
Cardiovascular system	65	63
Organ-system failure (% of patients)		
1 system	6	7
2 systems	36	25
3 systems	35	42
4 systems	21	21
5 systems	2	4
Site of infection (% of patients)		
Lung	46	48
Peritoneum	15	15
Urinary tract	10	10
Other or unknown	30	26

*Plus–minus values are means ±SD. APACHE II denotes Acute Physiology and Chronic Health Evaluation score, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, and ARDS acute respiratory distress syndrome. Because of rounding, percentages do not always total 100.

†To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for serum bilirubin to micromoles per liter, multiply by 17.1.

‡The various types of organ-system dysfunction are described more fully in the Methods section.

§$P=0.002$ for the comparison with the ibuprofen group. There were no significant differences between the groups with respect to any other characteristic.

- He concluded that patients with sepsis, treatment with ibuprofen
  - It is safe in such patients
  - Reduces levels of prostacyclin and thromboxane
  - Decreases fever, tachycardia, oxygen consumption, and lactic acidosis

  But
  - It does not prevent the development of shock or ARDS
  - It does not improve survival

SURGICAL INFECTIONS
Volume 6, Number 4, 2005

DOI: 1089/sur.2005.6.369

The Effect of Antipyretic Therapy upon Outcomes in Critically Ill Patients: A Randomized, Prospective Study

CARL I. SCHULMAN,[1] NICHOLAS NAMIAS,[1] JAMES DOHERTY,[1] RONALD J. MANNING,[1] PAMELA LI,[1] AHMED ELHADDAD,[1] DAVID LASKO,[1] JOSE AMORTEGUI,[1] CHRISTOPHER J. DY,[1] LUCIE DLUGASCH,[1] GIO BARACCO,[2] and STEPHEN M. COHN[1]

- Schulman et al, conducted a randomized, prospective clinical trial in the Trauma ICU of the Ryder Trauma Center (Miami, FL), 572 patients were screened and 82 met criteria for enrollment.
- Aggressive strategy
  - 650 mg acetaminophen every 6 hrs for fever > 38.5°C and a cooling blanket added if > 39.5°C)
  - Therapy was continued until fever resolution and was resumed for all subsequent febrile episodes.
- Permissive strategy
  - Treatment was reserved for fever > 40°C only
- The primary end point was development of culture-proven infection

- The inclusion criteria were
  - Admission to the ICU,
  - Age of 18 years,
  - Survival past the first 72 h of the ICU stay, an ICU stay longer than 72h
  - Temperature of 38.5°c.
- The exclusion criteria were
  - Acute brain injury (CT)
  - Malignant hyperthermia, heat stroke, neuroleptic malignant syndrome, hepatic cirrhosis, acute hepatic failure, or a history of stroke, seizure, or previous traumatic brain injury.

- The aggressive treatment group had
  - Higher rate of infections (131% vs. 85%)
  - Higher rate of antibiotic use (77% vs. 71% of days on therapy).
- The study had to be prematurely stopped because of safety concerns as interim analysis revealed an excess mortality rate of 7 of 44 (16%) in the aggressive group compared with 1 of 38 (3%) in the permissive group (*p0.06).*
- But its results may not be generalizable to a medical ICU .
- Its small sample size and it lack of a placebo-controlled, blinded design.

Deleterious Effects of fever

- Increase in cardiac output
- Increase oxygen consumption (10% per 1°C)

Manthous CA et al, *Am J Respir Crit Care Med 1995;151:10-14.*

- Increase carbon dioxide production
- Maternal fever associated with foetal malformations /or spontaneous abortion

Badawi N et al, *BMJ 1998;317:1554-8*.

- Poor neurological outcomes in patients with stroke and traumatic brain injury who manifest fever.

Ginsberg MD et al, *Stroke 1998;29:529-34.*

Marion DW et al, *Current Pharm Dis 2001;7:1533-6.*

Causes of Fever

- ICU Environment
  - Specialized Mattresses
  - Hot Lights
  - Air Conditioning
  - Cardiopulmonary Bypass
  - Peritoneal Lavage, Dialysis
  - Continuous Hemofiltration

Insler SR et al,*Anesthesiol Clin 2006; 24:823–837*

Sande FM et al, *Nephrol Dial Transplant 2006; 21:*1450–1451

Sande FM et al,*J Am Soc Nephrol 2005; 16:*1824–1831

Cont.

- Hyperthermic Syndrome
  - Environmental (heatstroke):
    - Classic
    - Exertional
  - Drug- induced:
    - Neuroleptic Malignant Syndrome,
    - Malignant Hyperthermia
    - Serotonin Syndrome
  - Endocrine :
    - Thyrotoxicosis
    - Pheochromocytoma
    - Adrenal Crisis

Hyperthermic Syndrome cont.

- Heatstroke:
  - > 40 °C, CNS Impairment & Multisystem Tissue Injury
  - Classic :
    - High external temperature that overwhelms the individual's thermoregulatory capacity to dissipate it.
    - Elderly, chronically ill, and debilitated persons
    - During heat waves
  - Exertional:
    - Excessive heat production such that thermal homeostasis cannot be achieved.
    - Young, otherwise healthy persons
    - Undergoing strenuous physical activity.
  - Complications:
    - Kidney & Liver Failure, DIC, Rhabdomyolysis, and Severe Metabolic Derangements

Bouchama A et al, *N Engl J Med 2002; 346:1978–1988*
Bouchama A et al, *Arch Intern Med* 2007; 167:2170–2176
Argaud L et al, *Arch Intern Med 2007; 167:2177–2183*

Hyperthermic Syndrome:Drug-indused

- Neuroleptic Malignant Syndrome

  (3 major or 2 major + 4 minor)

  - Major Criteria:
    - Insidious onset of hyperthermia
    - Muscle rigidity (Central)
    - Elevated CPK
  - Minor criteria:
    - Tachycardia
    - Tachypnea
    - Altered sensorium
    - Abnormal BP
    - Diaphoresis
    - Leukocytosis

- In the ICU, butyrophenones (haloperidole) is the most common offending drug
  - Other antipsychotic medications
    - phenothiazines, thioxanthenes
  - Antiemetic : prochlorperazine
  - Prokinetics : metclopromide
  - Sedatives : promethazine
  - Withdrawal of : levodopa/carbidopa, amantidine

- Management:
  - Withdrawal of offending drug
  - Dantrolene: 1mg/kg, max 10mg/kg (IV) f/b 4-8mg/kg divided in four x 1 to 3 days
  - Dopamine agonists
    - Bromocriptine (2.5- 5 mg TDS)
    - Amantidine (100 mg TDS)
  - Electroconvulsive therapy
  - Supportive care

HYPERTHERMIC SYNDROME:DRUG-INDUSED

- Malignant Hyperthermia
  - A genetically determined(AD) response mediated by a dysregulation of cytoplasmic calcium control in skeletal muscle
  - There are at least 6 genetic loci, most prominent is RYR1(ryanodine receptor gene)

    Litman R et al, JAMA 2005,293(23):2918-24
  - Often identified in OT room than in ICU, but onset can be delayed for as long as 24 hrs, if the patient is on steroids.
  - Triggered by succinylcholine and halothane mostly
    - Muscle rigidity - rapid onset
    - Hyperthermia
    - Acidosis
    - Elevated CPK

- Management:
  - Withdrawal of offending drug
  - Dantrolene: 1mg/kg, max 10mg/kg (IV)
  - Supportive Therapy directed to correct
    - Hyperthermia
    - Acidosis
    - Organ dysfunction

- Serotonin Syndrome
  - Patients using SSRI
  - It may be exacerbated with concomitant use of linezolid
  - Excessive stimulation of the 5-HT1A–receptor
    - Hyperthermia
    - Autonomic instability
    - Cognitive & Neuromuscular changes
  - Managements
    - stop the drug,
    - serotonin antagonist :cyproheptadine
    - supportive care

Caroff SN et al, Anaesth Intensive Care 1993; 21:477–478

Mason P et al, Medicine (Baltimore) 2000; 79:201–209

NON-INFECTIOUS CAUSES OF FEVER IN ICU

- Most noninfectious disorders usually do not lead to a fever >38.9°C (102°F)

Cunha BA et al, Crit Care Clin1998; 14:1–14

Non-infectious causes of fever in ICU

Body Part	Causes
Brain	Cerebral Infarction/Hemorrhage, Subarachnoid Hemorrhage.
Heart	Acute MI, Pericarditis
Pulmonary	Aspiration, Atelectasis, Chemical Pneumonitis Pulmonary Embolism, ARDS
Abdomen	Acalculous Cholecystitis, Ischemic Bowel, GI Bleeding, Pancreatitis, Hepatitis, Cirrhosis, Adrenal Insufficiency,
Vascular	DVT, Thrombophlebitis, Hematoma
Cutaneous	Decubitus Ulcers
Collagen vascular	SLE, Adult Still's disease, and others
Miscellaneous	Drug Fever, Reaction to Radiological Contrast, Fat Embolism, Neoplasms, Blood Transfusions, Transplant Rejection, Gout.

Noninfectious Fever

- Drug related fever
  - Hypersensitivity reaction
  - Local inflammation at the site of administration :
    - Amphotericin B,KCl, sulfonamides, and cytotoxic chemotherapies
  - Drugs or their delivery systems may contain pyrogens or microbial contaminants
  - Stimulation of heat production
    - thyroxine
  - Limit heat dissipation
    - Atropine, epinephrine
  - Alter thermoregulation
    - phenothiazines, antihistamines, antiparkinson drug

Drug fever

- Unexplained high spiking temperatures and shaking chills
- Usually in 2 week of drug administration
- May be associated with leukocytosis and eosinophilia, Skin rash
- Relative bradycardia, although commonly cited, is uncommon
- Rapid resolution of fever <72 hrs, but may take up to 7 days (if with rash).
- The diagnosis of drug-induced fever is usually established by temporal relationship of the fever to starting and stopping the drug.

Ann Intern Med 1987; 106:728–733

Am J Med Sci 1987; 294:275–286

Postgrad Med 1986; 80: 123–129

Common offenders	Atropine, Amphotericin B, Asparaginase, Barbiturates, Bleomycin, Methyldopa, Penicillins, Cephalosporins, Phenytoin, Procainamide, Quinidine, Salicylates, Sulfonamides (including sulfa-containing laxatives), Interferon
Uncommon offenders	Allopurinol, Azathioprine, Cimetidine, Hydralazine, Iodides, Isoniazid, Rifampin, Streptokinase, Imipenem, Vancomycin, Nifedipine, NSAIDs
Rare causes	Corticosteroids, Aminoglycosides, Macrolides, Tetracyclines, Clindamycin, Chloramphenicol, Vitamins

- Fever associated with drug withdrawal
  - Fever may occur several hours or days after admission to ICU
  - Patient will have
    - Fever
    - Tachycardia
    - Diaphoresis
    - Hyperreflexia
  - Offenders are
    - Alcohol
    - Opiates (including methadone)
    - Barbiturates
    - Benzodiazepines

FEBRILE TRANSFUSION REACTIONS

- Complicate about 0.5% of blood transfusions, more common following platelet transfusion
- Antibodies against membrane antigens of transfused leukocytes and/or platelets are responsible
- Usually begin within 30 min to 2 h after a blood-product transfusion
- The fever generally lasts between 2 to 24 h and may be preceded by chills
- An acute leukocytosis may lasting up to 12 h

Acalculous cholecystitis

- 0.2 to 1.5% of patients in ICU
- Non specific c/o
  - RUQ abdominal pain
  - nausea, vomiting
- Gallbladder Ischemia & Cholestasis with bile salt inspissations associated with parenteral nutrition and PEEP
- Secondary Bacterial invasion
- May progress to gangrene and perforation

- Investigation
  - USG abdomen
    - gall bladder distension, intraluminal lucencies, wall thickening >3 mm, pericholecystic fluid
  - CT abdomen
    - sensitive and specific
  - Hepatobiliary scintigraphy
    - provides functional information, high negative predictive value
- Management
  - Percutaneous cholecystostomy (procedure of choice)
  - Surgical drainage (as salvage procedure)

INFECTIOUS CAUSES OF FEVER IN ICU

- Peres Bota et al, reported fever (≥ 38.3°C) in 139 (28%) of 493 patients admitted to a large medical-surgical ICU in Brussels, Belgium
- The cause of fever was
  - Infection in 76 (55%)
  - Postoperative in 27 (19%)
  - Cerebral hemorrhage in 20 (14%)
  - Trauma in 5(3.6%), ARDS in 3 (2.2%), pancreatitis in 3 (2.2%), GI bleeding in 3 (2.2%), and MI in 2 (1.4%)

*Intensive Care Med 2004; 30:811–816*o

- Laupland KB et al, reported a large, retrospective cohort study evaluating the epidemiology of fever $\geq$ 38.3°C in adults (n=20,466) admitted to ICUs in Calgary, Canada, during 2000–2006
- The cumulative frequency (incidence density per 100 ICU days) of fever was 44% (24.3)
  - 43% (21.8) in medical,
  - 36%(17.2) in cardiac surgical,
  - 65% (38.2) in trauma/neurologic,
  - 45% (22.8) in other surgical patients.

*Crit Care Med 2008; 36:*1531–1535

- EPIC study: Single day prevalence of ICU acquired infection- 20%
  - VAP (46.9%)
  - UTI (17.6%)
  - Bacteremia (12%)

JAMA 1995; 274:639–644

- Malacarne et al, reported on the occurrence of infection among nearly 10,000 patients admitted to 71 ICUs in Italy (approximately 50% medical patients)
  - 12% community-acquired infections
  - 19% nosocomial infections (11% ICU acquired)

Crit Care Med 2008; 36:1105–1113

- Common sites of infection in otherwise immunocompetent medical ICU patients
  - Lower Respiratory Tract
  - Urinary Tract
  - Bloodstream
  - Sinus
  - Skin/Soft Tissue
  - Intra-abdominal/Gastrointestinal Tract (13–18).

*Lancet 2003; 361:*2068–2077

*Curr Opin Infect Dis 2006;*19:67–71

Crit Care 2005; 9:R60–R65

*Crit Care Med 2004; 32:*992–997

Ventilator Associated Pneumonia

- Pneumonia in a patient who has been on ventilator for >48 hours
- Risk of VAP highest early in the course of hospital stay
- 3%/day for first 5 days,
- 2%/day from 5 to 10 days &
- 1%/day thereafter
- Mortality in Pt with VAP twice than pts without VAP
- “Attributable mortality” has been estimated to be between 33 and 50%

- ACCP definition of VAP:
  - New onset or progressively increasing infiltrates in CXR and 2 out of 3
    - 1.Fever
    - 2. Leucocytosis
    - 3. Purulence tracheobronchial secretions

THE MODIFIED CLINICAL PULMONARY INFECTION SCORE

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
CXR	No infiltrate	Diffused	Localized
Temperature, °C	≥36.5 and ≤38.4	≥38.5 and ≤ 38.9	≥39 or ≤36
TLC, per mm^3	≥4,000 and ≤11,000	< 4,000 or > 11,000	< 4,000 or > 11,000 + band forms≥ 500
PaO_2/FiO_2	> 240 or ARDS		< 240 and no evidence of ARDS
Microbiology	Negative		Positive

The modified CPIS at baseline was calculated from the first five variables The CPIS gram and CPIS culture calculated from the CPIS baseline score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains (CPIS gram) or culture (CPIS culture) results was considered suggestive of pneumonia.

Am J Respir Crit Care Med Vol 168. pp 173–179, 2003

VAP - INVESTIGATIONS

- CXR in upright position
- LRT secretions for: Gram stain and Quantitative bacterial cultures

Methods	Quantitative culture	Sensitivity	Specificity
ETA	$\geq 10^5$CFU/ml	76±9%	75±28%
Bronchoscopy BAL PSB	 10^4-10^5CFU/ml $\geq 10^3$ CFU/ml	 73±18% 66±19%	 82±19% 90±15%
Blind Br Suction Blind mini BAL Blind PSB	$\geq 10^4$CFU/ ml $\geq 10^4$CFU/ml $\geq 10^3$ CFU/ml	74- 97% 63-100% 58-86%	74 -100% 66-96% 71-100%

Am J Respir Crit Care Med 2005;171:388–416

- As guided by clinical picture
  - KOH with calcofluor stain for fungus
  - ELISA or direct fluorescent antibody tests for respiratory viruses and P. Jiroveci
  - Acid-fast stain for mycobacteria.
  - Culture the specimen for fungi, mycobacteria, Legionella, and respiratory viruses

- Blood cultures
- Pleural fluid analysis
- As guided by clinical picture:
  - Antigenemia for CMV in non–human immunodeficiency virus infected patients, histoplasmosis, and cryptococcosis
  - PCR for CMV, varicella-zoster virus, human herpes virus-6, and adenovirus
  - Galactomannan and beta-D-glucan for aspergillosis and *Candida* may be useful as supportive evidence of infections
  - Urinary antigen tests for Legionella pneumophila type 1 and S. pneumoniae

SINUSITIS IN THE ICU

- It is a closed-space infection and may be clinically occult but, when it occurs, can have serious consequences
- Risk factor
  - Anatomic obstruction: transnasal intubation of the airway carrying a prevalence of sinusitis estimated to be 33% after 7 days of intubation.
- The etiological agents : colonizer of the naso-oropharynx
  - P. aeruginosa 60%
  - S. aureus and coagulase-negative staphylococci 33%
  - Fungi the remaining 5–10%

Acta AnaesthesiolScand 1994; 38:699–703

Am J Respir Crit Care Med 1994; 150:776–783

JAMA 1982; 247:639–641

Intensive Care Med 1988; 15:27–30

- Diagnostic Criteria > 7days (2 Major Or 1 Major+ 2 Minor)
  - Major Criteria
    - Cough
    - Purulent Nasal Discharge
  - Minor Criteria
    - Headache or Earache
    - Facial or Tooth Pain
    - Fever
    - Malodorous Breath
    - Sore Throat
    - Wheezing
- In intubated patients it may be impossible to elicit complaints of facial pain or headache and purulent nasal discharge is present in only 25% of proved cases of sinusitis

- So If clinical evaluation suggests that sinusitis may be a cause of fever,
  - Removal of all nasal tubes
  - CT scan of the facial sinuses
  - If the patient has not responded to empirical therapy, puncture and aspiration of the involved sinuses
- Aspirated fluid:
  - Gram-negative stain
  - Culture for aerobic and anaerobic bacteria and fungi

Crit Care Med 2008 Vol. 36, No. 4

DIARRHEA IN ICU PATIENTS

- Clostridium difficle- most common
  - Salmonella
  - Shigella
  - Campylobacter jejuni
  - Aeromonas
  - Yersinia
  - Escherichia coli
  - Entamoeba histolytica
  - Viruses

Community acquired organisms
Uncommon nosocomial infection

- Pseudomonas and Cl.septicum in neutropenic patients

- Symptoms usually begin during or shortly after antibiotic therapy but are occasionally delayed for several weeks
- Clinical spectrum
  - Colitis, Pseudomembranous Colitis, Toxic Megacolon
  - Neutrophilia and increased fecal leucocytes
- Send one stool sample
  - *C. difficile* common antigen, EIA for toxin A and B, or tissue culture assay
- A second specimen is not necessary if the common antigen test was negative
- If severe illness is present and rapid tests for *C. difficile are* negative o*r* unavailable, consider flexible sigmoidoscopy ,empirical therapy

Management

- Strict contact isolation
- Stop offending AMA
- Fluid & Electrolytes
- Tab Metronidazole 500 mg TDS/QID X 7-10 Days
- Tab Vancomycin 250 mg QID
- In case of Toxic Megacolon/ileus
  - IV Metronidazole
  - Retention enema Vancomycin

Gastroenterol Clin N Am 2006;35: 315–335

URINARY TRACT INFECTION

- Bacteriuria or candiduria defined as a quantitative culture of $>10^3$ CFU/mL

N Engl J Med 1984;311:560–564

- It has been reported in up to 30% of catheterized hospitalized patients
- Dysuria, urgency, pelvic or flank pain, fever or chills, that correlate well with significant bacteriuria in noncatheterized patients are rarely reported in ICU patients
- Catheter-associated bacteriuria or candiduria usually represents colonization, is rarely symptomatic, and is rarely the cause of fever or secondary bloodstream infection

- Bacteriuria should be treated if
  - Following urinary tract manipulation or surgery
  - In patients with kidney stones or urinary tract obstruction
  - Patients with neutropenia

Clin Infect Dis 2005; 40:1413–1421

Arch Intern Med 2000; 160:678–682

J Urol 1984; 132: 494–498

Postgrad Med J 1978; 54:668–671

- Urine sampling
  - Wear clean gloves whenever manipulating a urinary device
  - Clean the port with 70–90% alcohol before collecting the specimen
  - Aspirated the sample from the catheter sampling port
  - If the transport of urine will be delayed longer than 1 hr, the specimen should be refrigerated

CATHETER RELATED BLOOD STREAM INFECTION

- Seen in 5% of patients with indwelling vascular uncoated catheters
- The highest risk is with short-term, noncuffed central venous catheters, in the range of 2–5 per 1,000 catheter days, and is especially high with noncuffed temporary hemodialysis catheters
- In contrast, the risk of bloodstream infection with small, peripheral intravenous catheters is 0.1 cases per 1,000 catheter days
- The incidence of CRBSI increases with the length of time the catheter is in situ, the number of ports and increases with the number of manipulations
- The mortality rate attributed to catheter-related *S. aureus bacteremia (8.2%)* significantly exceeded the rates for other pathogens. (CONS – 0.7% only)

- Contaminated hubs are common portals of entry for organisms colonizing the endoluminal surface of the catheter
- Difficulty drawing or infusing through the catheter may point to the catheter as a source of infection
- The presence of inflammation, with or without purulence, at the insertion site, though absent in most cases

Crit Care Med 2003; 31:1318–1324
Am J Med 1991; 91(3B):197S–205S
Crit Care Med 2002; 30:2632–2635

Management

- Examine the patient at least daily for inflammation or purulence at the exit site or along the tunnel, signs of venous thrombosis or evidence of embolic phenomena
- Any expressed purulence from the insertion site should be Gram stained and cultured
- At least two blood cultures should be obtained one from peripherally by venipuncture and one from the suspected catheter
  - Quantitative culture (ten-fold or greater than peripheral culture)
  - Differential time to positivity (If both sets of cultures are positive for the same organism and the catheter sample becomes positive 120 mins earlier than the peripheral culture)
- Do not routinely culture all catheters removed from ICU patients

Fever Within 72 Hours of Surgery

- CXR is not mandatory during the initial 72 hrs postoperatively if fever is the only indication
- A urinalysis and culture are not mandatory in those with indwelling bladder catheters for < 72 hrs
- Surgical wounds should be examined daily for infection
- They should not be cultured if there is no symptom or sign suggesting infection
- High level of suspicion should be maintained for DVT, superficial thrombophlebitis, and pulmonary embolism, especially in patients who are at risk.

FUNGAL SEPSIS

- The CDC National Nosocomial Infection Study - 7% of all nosocomial infections were due to Candida species
- EPIC study - 17% of nosocomial ICU infections were due to fungi.
- Should be considered in patients with ICU stay >10 days and have received multiple courses of antibiotics
- The density of infection , number of positive cultures, isolation from non-contiguous sites, type of organism , and isolation from usually sterile fluids all predict the likelihood of severe systemic fungal infection.

Int J Antimicrob Agents 2000 Jul;15(2):83-90

- Candiduria is also controversial, although most would agree that it should be treated once (a) confirmed and (b) risk has been stratified appropriately.

  Mycoses 1999;42(4):285-9

- Newer tests that have been advocated for early diagnosis of systemic fungal infection include:
  - Sandwich ELISA for circulating galactomannan
  - Polymerase chain reaction.

CANDIDA SCORE

- In a large cohort of nonneutropenic critically illpatients in whom Candida colonization was prospectively assessed, a “Candida score” >2.5 accurately selected patients who would benefit from early antifungal treatment.

  Cristóbal León et al, Crit Care Med 2006; 34:730–737)

- Severe sepsis -2
- Total parenteral nutrition -1
- Surgery -1
- Multifocal colonisation -1
  - ET aspirate, urine, gastric aspirate
  - same or different species
  - atleast 2 weekly cultures

BLOOD CULTURES

- 3-4 sets of cultures from different veins or arterial sites preferably from distal port of CVC
- From intravenous devices but not from different lumens of same device
- Spread over time as chance of culture positivity is highest 1-2 hrs prior to fever spike but within 24 hrs of fever
- At least 1 sample before antibiotics
- Skin preparation with chlorhexidine and tincture of iodine (more than aqueous povidone iodine)
- 20-30 ml of blood each time
- Cleaning of injection port with 70% alcohol recommended for preventing contamination
  - True pathogen (multiple cultures are often positive)
  - Contaminant (only 1 of multiple cultures is positive for an organism commonly found on skin and lack of clinical correlation)

PROCALCITONIN

- Procalcitonin level elevations
  - SIRS 0.6 to2.0 ng/mL
  - Severe sepsis 2 to10 ng/mL
  - Septic shock ≥10 ng/mL
- Viral infections, recent surgery, and chronic inflammatory states are not associated with any increment
- Procalcitonin can be used as an adjunctive to microbiological tests for identifying infective diseases

IDSA guidelines. Crit Care Med 2008; 36:1330–1349

ENDOTOXIN LEVELS

- Kinetic luminometric antiassay (endotoxin activity assay)
- EA had a sensitivity of 85.3% and a specificity of 44.0% for the diagnosis of gram-negative infection
- High negative predictive value (98.6%) for Gram-negative Infection

J Infect Dis 2004; 190:527–534

CRP

- Originally named for its ability to bind the C polysaccharide of *Streptococcus pneumoniae*
- Its sequence is highly conserved and only one polymorphism is known.

Cao H et al, *J Hum Genet* 2000; 45:100–101

- CRP is mostly synthesized by hepatocytes in response to IL-6, IL-1 and TGF-ß.
- The plasma level of CRP rises within 6 hrs, double every 8 hrs and peak at 50 hrs

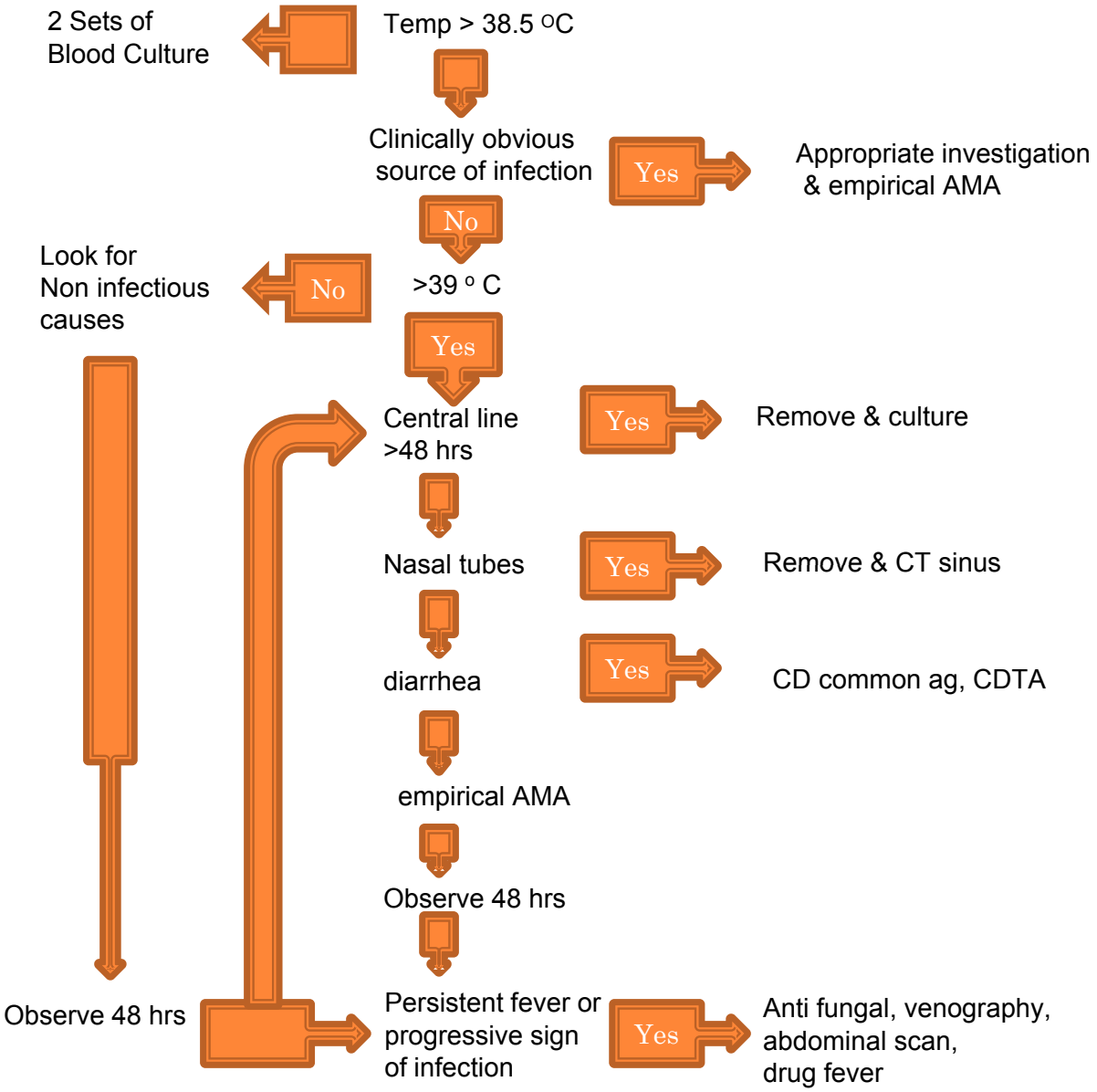
Young B et al, *Pathology 1991;*23:118–124

- Normal level in healthy adults < 10 mg/L.
- May rise up to a 1000-fold in response to an inflammatory stimulus

Immunol Today 1994; 15:81–88

Treatment of fever

- Relative risk-benefits should be evaluated in individual patient
- Treat with acetaminophen if:
  - Temperature > 39°C
  - CNS insult such as CVA
  - Poor cardiorespiratory reserve such as CHF, CAD
- External cooling useful in cases of hyperthermia rather than fever


2 Sets of
Blood Culture
Temp > 38.5 OC
Clinically obvious
source of infection
Yes
Appropriate investigation
& empirical AMA
No
Look for
Non infectious
causes
No
>39 o C
Yes
Central line
>48 hrs
Yes
Remove & culture
Nasal tubes
Yes
Remove & CT sinus
diarrhea
Yes
CD common ag, CDTA
empirical AMA
Observe 48 hrs
Observe 48 hrs
Persistent fever or
progressive sign
of infection
Yes
Anti fungal, venography,
abdominal scan,
drug fever