# Fever in ICU

DM Seminar

*Dr. Vamsi Krishna Mootha*

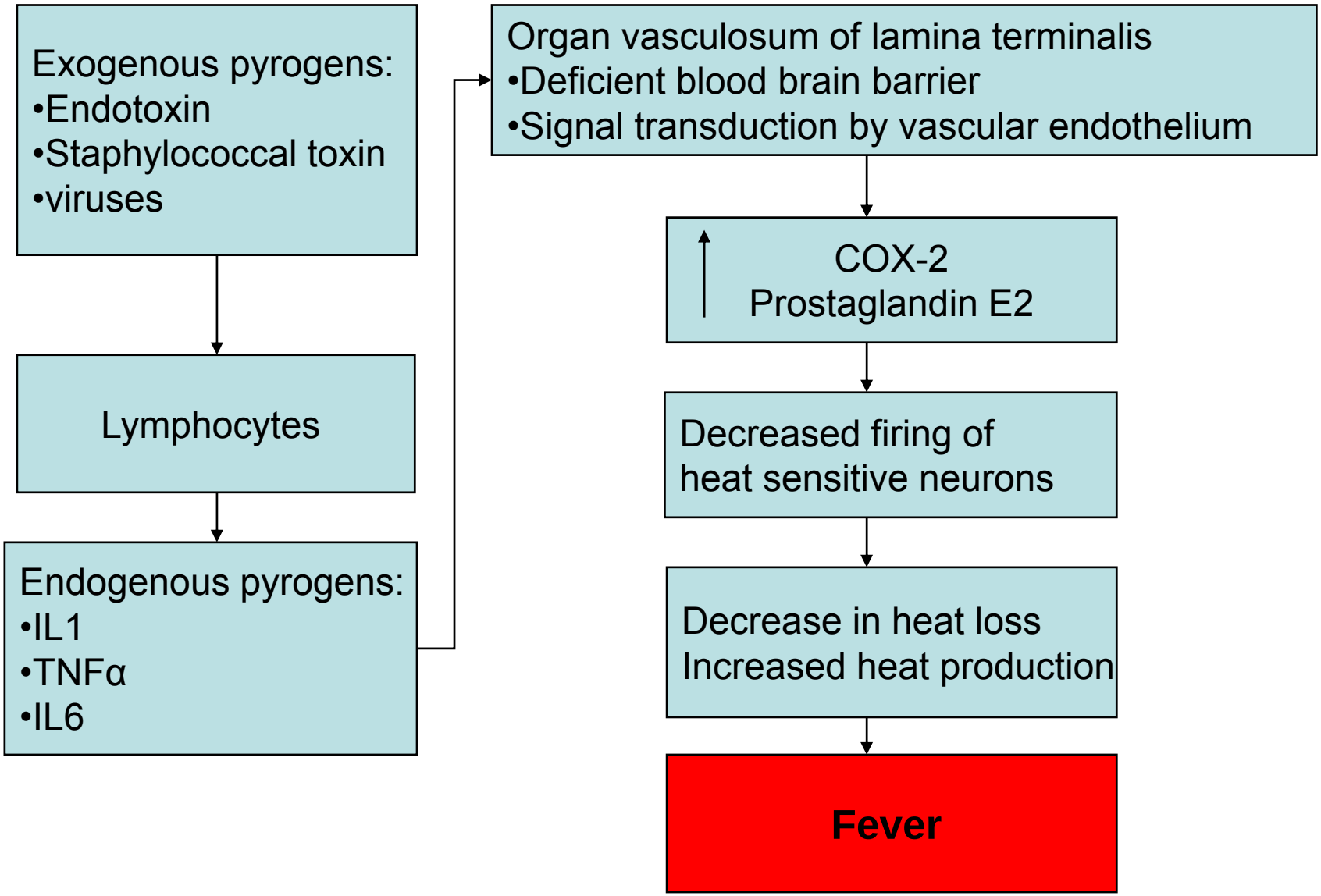
*Dept of Pulmonary medicine*

# 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*

# Pathogenesis



# Fever

- Normal body temperature is generally considered to be 37.0°C (98.6°F) with a circadian variation of between 0.5 to1.0°C

- The definition of fever is arbitrary depends on the purpose for which it is defined

- The Society of Critical Care Medicine and IDSA suggested that a temperature of above 38.3°C (101°F) should be considered a fever and should prompt a clinical assessment

# Fever in ICU

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

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

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

*^Crit Care Med 2008;36:1531-1535*

- Presence of high grade fever at admission or during ICU stay is associated with poor outcome

*Crit Care Med 2008;36:1531-1535*

# Fever in ICU

Apart from infections a variety of environmental factors can alter temperature:

- Specialized mattresses
- Hot lights
- Air conditioning
- Cardiopulmonary bypass
- Peritoneal lavage, dialysis, and continuous hemofiltration

A substantial proportion of infected patients may be euthermic or hypothermic:

- Elderly, patients with open abdominal wounds, burns
- Patients receiving ECMO, CRRT
- Patients with CHF, CRF, end-stage liver disease
- Patients taking anti-inflammatory or antipyretic drugs

*Even in the absence of fever other signs of SIRS and sepsis should prompt appropriate therapeutic and diagnostic steps*

# Measurement of temperature

| Method | Merits | Demerits /Limitations |
|---|---|---|
| Axillary temp. | | Underestimates core temp. |
| Sublingual temp. | | Food, drinks, respiratory devices |
| Infrared ear thermometry | | Inflammation or block of external ear interferes |
| Rectal temp. | Few tenths of °C above core temp | Rectal trauma<br>Cl.difficle transmission |
| Mixed venous blood from pulmonary artery | Optimal site for core temperature | Needs pulmonary artery catheter |
| Thermistor in urinary bladder | Represent core temperature | Costly<br>Requires monitor |
| Thermistor placed in distal esophagus | Represent core temperature | Position diff. to confirm<br>Uncomfortable<br>Risk of perforation |

# *Causes of fever in ICU*

# Non infectious causes

*Except drug fever and transfusion reactions, temperature rarely reaches 39°C (102°F)*

*Chest 2000;117;855-869*

# Drug related fever

- Hypersensitivity reaction
- Local inflammation at the site of administration : Amphotericin B, erythromycin, KCl, sulfonamides, and cytotoxic chemotherapies
- Drugs or their delivery systems may contain pyrogens or microbial contaminants
- Stimulation of heat production e.g., thyroxine
  Limit heat dissipation e.g., atropine
  Alter thermoregulation e.g., phenothiazines, antihistamines
  antiparkinson drugs

# Drug fever

- Unexplained high spiking temperatures and shaking chills
- Usually in 2nd week of drug administration
- May be associated with a with leukocytosis and eosinophilia
- Relative bradycardia, although commonly cited, is uncommon

  *Ann Intern Med 1987; 106:728–733*
- Associated skin rash
- Rapid resolution of fever <72 hrs (if no rash), may take up to 7 days

# Drug fever

| | |
|---|---|
| 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, Vitamin preparations |

# Neurolept malignant syndrome

- Idiosyncratic reaction to neuroleptic drugs (initiation or change of dose)
- It manifests as altered mentation , hyperthermia, muscle rigidity, rhabdomyolysis, and autonomic dysfunction
- Antipsychotic medications—phenothiazines, thioxanthenes, and butyrophenones
  Antiemitics (prochlorperazine), prokinetics (metclopromide), sedatives (promethazine)
  Withdrawal of levodopa/carbidopa, amantidine
- In the ICU, haloperidol is the most common offending drug
- CNS dopamine deficiency or D2 receptor antagonism in hypothalamus, resets temperature set point

# Neurolept malignant syndrome

Major criteria:
- Fever
- Muscle rigidity
- Elevated CPK

Minor criteria:
- Tachycardia
- Tachypnea
- Altered sensorium
- Abnormal BP
- Diaphoresis
- Leukocytosis

3 Major
2 major + 4 minor
} Diagnostic

Management:
- Withdrawal of offending drug
- Dantrolene
- Dopamine agonists
  Bromocriptine (2.5- 5 mg TDS)
  Amantidine (100 mg TDS)
  Levodopa/carbidopa
- Electroconvulsive therapy
- Supportive care

# 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 lasting up to 12 h occurs commonly

# Acalculous cholecystitis

- 0.2 to 1.5% of patients in ICU
- RUQ abdominal pain, nausea, vomiting } Non specific
- Laboratory investigations
- Gallbladder ischemia & Cholestasis with bile salt inpissation associated with parenteral nutrition and PEEP
- Bacterial invasion is a secondary process
- May progress to gangrene and perforation

# Acalculous cholecystitis

- 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
- Percutaneous cholecystostomy is procedure of choice
- Surgical drainage as salvage procedure

# Non infectious fever

Deep venous thrombosis and pulmonary embolism:

- DVT and PE can be associated with fever (up to 50%)

- But fever does not warrant routine initial investigation for DVT because of poor predictive power of fever

# Infectious complications

EPIC study:

Single day prevalence of ICU acquired infection- 20%

VAP (46.9%)
UTI (17.6%)
Bacteremia (12%)

*JAMA 1995; 274:639–644*

# Ventilator Associated Pneumonia

Pneumonia in a patient who has been on ventilator for >48 hours

Risk of 3%/day during the first 5 days of ventilation, 2%/day during Days 5 to 10 of ventilation, and 1%/day after that

“Attributable mortality” has been estimated to be between 33 and 50%

ACCP definition of VAP:

1. New onset or progressively increasing infiltrates in CXR (sine quo non)
2. Fever
3. Leucocytosis
4. Purulence tracheobronchial secretions

} 2 out of 3

# Clinical pulmonary infection score (CPIS)

| | 0 | 1 | 2 |
|---|---|---|---|
| Temperature | 36.5-38.4 | 38.4-39 | >39,<36 |
| Leucocyte count | 4000-11000 | <4000,>11000 | >500 band forms |
| CXR | Normal | Diffuse infiltrates | Localized shadows |
| Secretions | Minimal | Moderate | Profuse |
| ET aspirate culture | Sterile | | Positive |
| PaO2/FiO2 | >240 or ARDS | | <240, no ARDS |

Score >6 is suggestive of VAP

# VAP - investigations

CXR in upright position

LRT secretions for:

- Gram stain and Quantitative bacterial cultures

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

# VAP - investigations

- 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*.

Always pathological :

- *Legionella*
- *Chlamydia*
- *M. tuberculosis*
- *Rhodococcus equi*
- Influenza virus
- Respiratory syncytial virus
- Parainfluenza virus
- *Strongyloides*,
- *Toxoplasma gondii*
- *P. jiroveci*
- *Histoplasma capsulatum*
- *Coccidioides Immitis*
- *Blastomyces dermatitidis*
- *Cryptococcus neoformans*

Rarely causative organism:

- Enterococci viridans
- Streptococci
- CONS
- *Candida*

Potential pathogens :
(Quantitative cultures needed)

- *Pseudomonas aeruginosa*
- Enterobacteriaceae
- *S. pneumoniae*
- *S. Aureus*
- *Haemophilus influenzae*

# Sinusitis

- Nasotracheal and nasogastric tubes are risk factors
- 85% in patients with nasotracheal tube for >1 wk

  *Am J Respir Crit Care Med 1999; 159:695–701*
- Maxillary sinus – commonly involved
  frequently associated with ethmoid and sphenoid sinusitis
- Major criteria (cough, purulent nasal discharge) and minor criteria (headache or earache, facial or tooth pain, fever, malodorous breath, sore throat,wheezing) are less senitive or difficult to elicit
- CT imaging is required ( X rays not sufficient)
  Opacification or fluid levels are suggestive

# Sinusitis

Diagnosis necessitates drainage of sinus presence of pus and isolation of organism in culture only 38% of patients with radiological evidence

Microbiology:

- Pseudomonas -60%
- Staphylococcus aureus and CONS – 33%

Treatment:

- Removal of all nasal tubes
- Needle drainage (maxillary sinus)
- Surgical drainage (ethmoid and sphenoid sinuses)
- Antibiotics

# 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

# *Clostridium difficle* colitis

- 20% of all hospitalized patients become “infected” with *C difficile,* of whom only about a third develop diarrhea
- Use of Clindamycin, 3rd generation cephalosporins and flouroquinolones are risk factors
- Other risk factors: Severity of underlying illness, use of PPI, GI surgery, elderly patient, prolonged hospital stay, stay in the ICU and tube feeding
- Toxin A causes fluid secretion and intestinal inflammation when injected into the rodent intestine and is a chemo-attractant for neutrophils in vitro. Toxins A and B activate the release of cytokines from monocytes

# *Clostridium difficile* colitis

- Symptoms usually begin during or shortly after antibiotic therapy but are occasionally delayed for several weeks
- Clinical spectrum includes colitis, pseudomembranous colitis, toxic megacolon
- Neutrophilia and increased fecal leucocytes
- Stool assay for toxin A and B by ELISA is recommended
- Those with high clinical probability and negative ELISA can be further assessed with cytotoxicity assay (gold standard), sigmoidoscopy, CT scan of abdomen (for thickened colonic wall)

# Management

1. Stop the offending antibiotic if possible (grade B).
2. Provide adequate fluid and electrolyte repletion.
3. Do not use antimotility agents.
4. If specific treatment is required, then use metronidazole, 500 mg orally every 6 to 8 hours for 7 to 10 days. Oral vancomycin at a dosage of 125 to 250 mg orally every 6 hours is a second-line alternative agent (grade A).
5. If the patient cannot tolerate oral medication, then metronidazole may be given intravenously, but switching to oral therapy is recommended after the patient is able to do so. In the case of ileus or toxic megacolon, the recommended treatment is intravenous metronidazole or vancomycin retention enemas (500 mg mixed in 100 mL of normal saline).
6. Vancomycin should be avoided unless metronidazole appears ineffective, the patient is pregnant or allergic to metronidazole, or true resistance is demonstrated.
7. In all cases, strict contact isolation of the patient is essential in controlling the spread of the disease to other patients (grade A).

Gastroenterol Clin N Am 2006;35: 315–335

# Urinary tract infection

- Bacteriuria or candiduria defined as a quantitative culture of >1000 CFU/mL, 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

- It is unclear how many catheterized patients bacteriuria actually have UTI.

- Criteria have not been developed for differentiating asymptomatic colonization of the urinary tract from symptomatic infection

# Urinary tract infection

Bacteriuria should, however, be treated

- Following urinary tract manipulation or surgery
- In patients with kidney stones or urinary tract obstruction
- Patients with neutropenia

Surveillance for and treatment of isolated bacteruria in most ICU patients is currently not recommended.

# Catheter related blood stream infection

- Seen in 5% of patients with indwelling vascular uncoated catheters
- 2-5 infections/ 1,000 catheter days
- Equal risk for arterial line and peripherally inserted central venous catheters
- 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
- Case-fatality rate is 14%, and 19% of these deaths were attributed to the CRBSI
- The mortality rate attributed to catheter-related *S. aureus* bacteremia (8.2%) significantly exceeded the rates for other pathogens. (CONS – 0.7% only)

# Catheter related blood stream infection

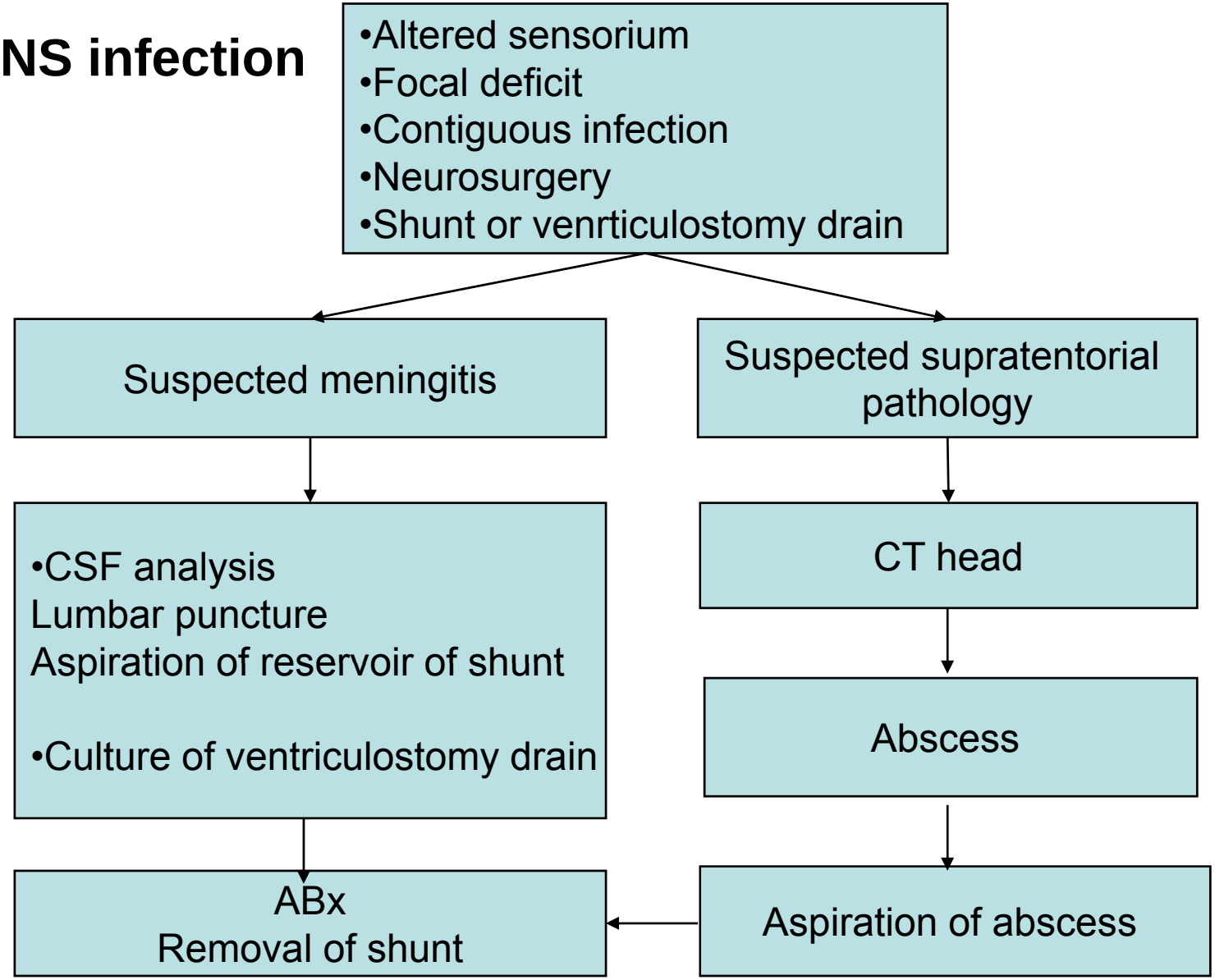
Pointers to CRBSI:

- Fever, sepsis
- Inflammation with or without purulent discharge at exit site
- Difficulty in aspirating or flushing from CVC

Only 25-45% of cases of sepsis in patients with CVC have CRBSI

Routine culture of CVC tip in absence of sepsis is not recommended as 20% of catheters are colonised with pathogenic bacteria

# CNS infection



# 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 except 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 sedentary, have lower limb immobility, have a malignant neoplasm, or are taking an oral contraceptive

# 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

# *Investigating a febrile patient*

# Investigating a febrile patient

| Test | Comment |
|---|---|
| Blood cultures | Bacteremia (catheter related and others) |
| CVC tip culture | For CRBSI |
| Chest X ray | For VAP |
| ET/NBAL/BAL quantitative culture | Will guide adjusting empiric antibiotics |
| CT PNS | Needs to be followed by drainage and cultures |
| CT abdomen | For abdominal sepsis> acalculous cholecystitis |
| USG abdomen | For acalculous cholecystitis > abdominal sepsis |
| Cl.difficle toxin assay | Less sensitive than cytotoxic assay |
| Fungal cultures | Prolonged ICU stay, multiple ABx, TPN |
| Microbiological, Serological test for viral, fungal and bacteria | As epidemiological features guide |

# 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

# Blood cultures

- Appropriately collected cultures discern whether an organism found in blood culture represents

1. True pathogen (multiple cultures are often positive)
2. Contaminant (only 1 of multiple cultures is positive for an organism commonly found on skin and lack of clinical correlation)
3. Bacteremia/fungemia from an infected catheter

- Culture for routine surveillance and monitoring is not recommended

- Repeat cultures for patients with worsening status and those with staphylococcal or fungal sepsis (for monitoring response)

# Infectious Vs non-infectious fever

Procalcitonin :

- Best cut-off values in the diagnosis of sepsis were 0.47 ng/mL for Procalcitonin

*Minerva Anestesiol. 2006;72:69-80*

- PCT was 1.58 ng/ml in patients with sepsis, 0.38 ng/ml in the SIRS patients ($P < 0.05$), and 0.14 ng/ml in patients with no SIRS ($P < 0.05$).

*Crit Care. 2004;8:R234-42*

- The median plasma PCT concentrations in nonseptic (systemic inflammatory response syndrome) and septic (sepsis, severe sepsis, or septic shock) patient days were 0.4 and 3.65 ng/mL ($p < .0001$),

*Crit Care Med. 2003 Jun;31(6):1737-41*

# Infectious Vs non-infectious fever

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*

# Infectious Vs non-infectious fever

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*

- Procalcitonin can be used as an adjunctive to microbiological tests for identifying infective diseases

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

# Empirical antibiotics

- When clinical evaluation suggests that infection is the cause of fever, empirical antimicrobial therapy should be instituted as soon as possible after cultures are obtained, especially if the patient is seriously ill or deteriorating

- Initial empirical antibiotic therapy should be directed against likely pathogens, as suggested by the suspected source of infection, the patient risk for infection by multidrug-resistant pathogens, and local knowledge of antimicrobial susceptibility pattern

# Antifungal

Candida score: >2.5 should receive antifungal Tt

- 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)

*Is treatment of fever essential?*

# Is fever a beneficial host response?

- Fever is a metabolically expensive response preserved over millennia of evolution
- Artificial pyrexia used to treat neuro-syphilis
- But no controlled studies in humans on effect of treatment of fever (physical methods and COX 2 inhibitors)

# Clinical evidence

- In 218 patients who had gram-negative bacteremia, fever correlated positively with survival

  *Arch Intern Med 1971, 127:120-128*

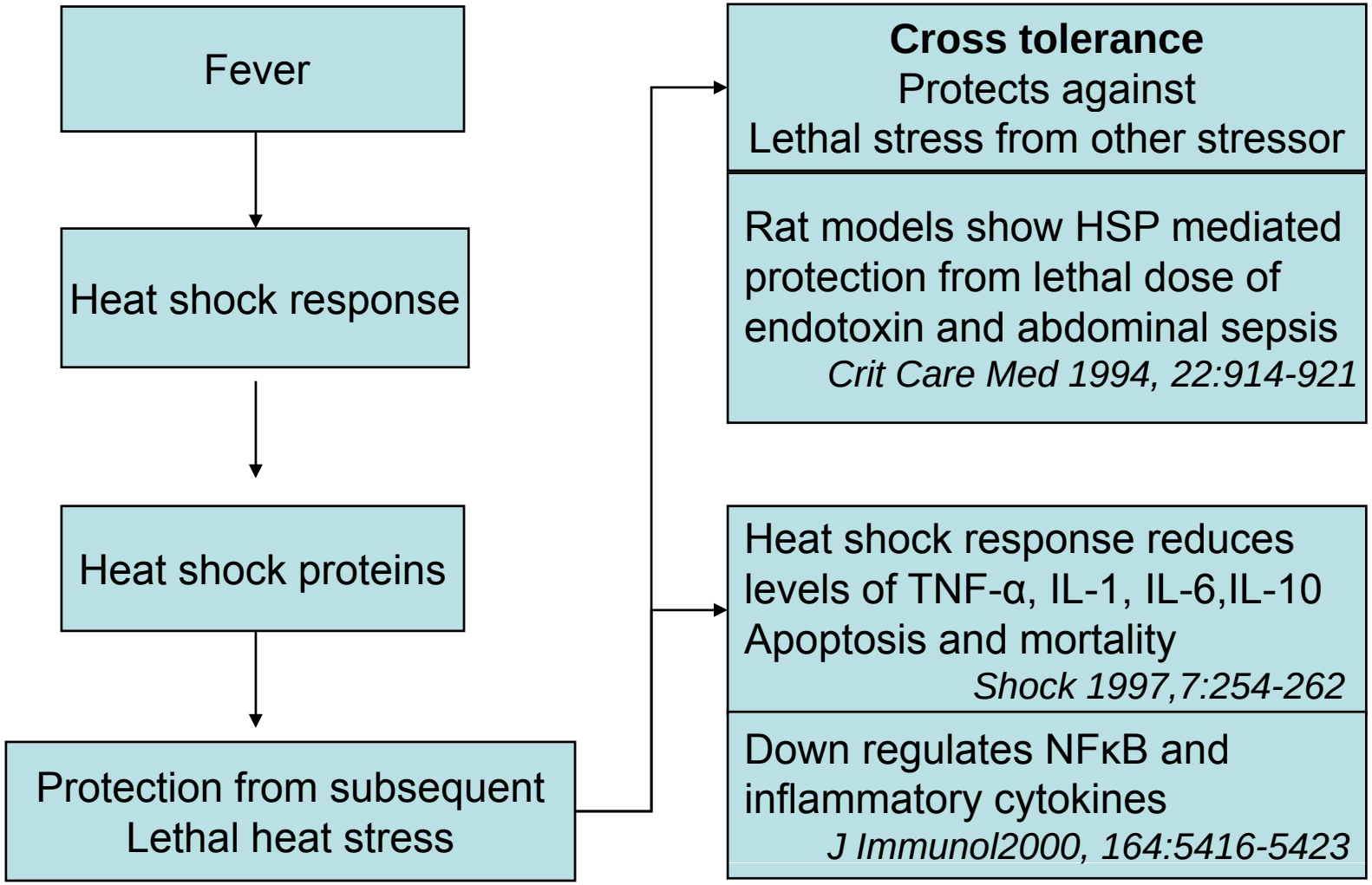
- Failure to mount a febrile response within the first 24 hours was associated with increased mortality with gram negative bacteremia

  *Am J Med 1980, 68:344-355*

- Survival in SBP correlated with temperature >38°C

  *Am J Med 1978; 64:592–598*

# Protective effects of fever



# Is fever deleterious?

Fever is associated with increase in

- Cardiac output
- Oxygen consumption
- Carbon dioxide production
- Energy expenditure increases

These changes may be poorly tolerated in patients with limited Cardio-respiratory reserve.

In patients who have suffered CVA or traumatic head injury, fever induces secondary injury

# Should fever be treated ?

- Fever is an important clinical sign for monitoring response

- Hepatotoxicity of acetaminophen (alcoholics and malnourished)

- External cooling with cold sponging and hypothermia blankets can

1. Can cause rebound fever
2. Increase metabolic demands
3. Propensity to induce cutaneous vasoconstriction, shivering, sympathetic activation and discomfort

- No difference in the comfort level of patient who had fever treated versus control

*Arch Intern Med 2001, 161:121-123*

# 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

# Take home message

- Appropriately obtained temperature >38.3° should prompt clinician to take appropriate diagnostic tests
- Fever has no one to one relation with infection
- Consider infectious and non-infectious causes
- Appropriate microbiological and imaging studies
- Empirical antibiotics within 1 hr of identifying sepsis
- Treatment of fever is recommended if deemed essential