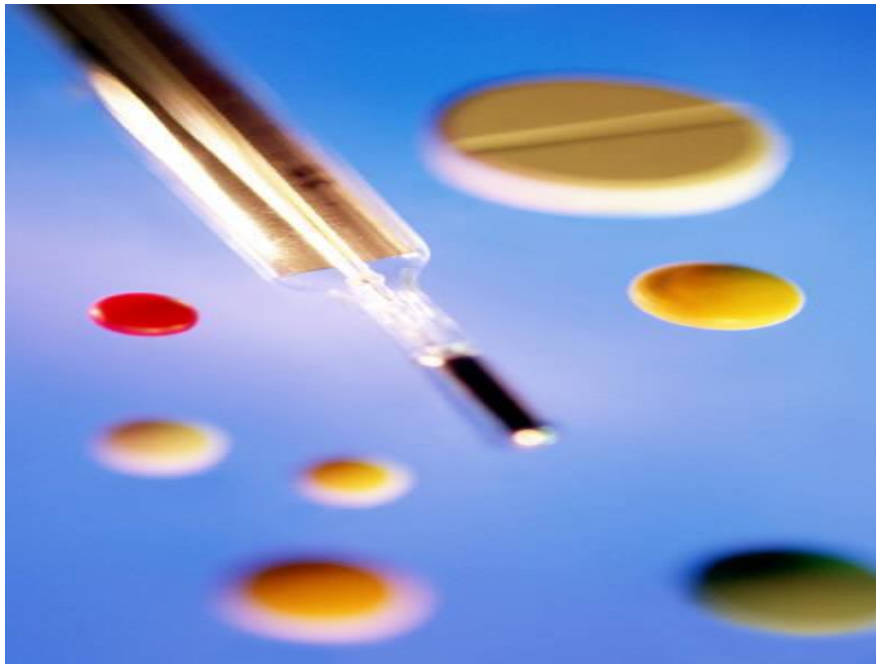
Fever in ICU



Dr. Osama A. Zayed

Hippocrates

recognized fever as
a beneficial sign
during infection

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 is defined as a body temperature of 38.3ºC or higher

The American College of Critical Care Medicine and the Infectious Diseases Society of America

Fever must be Documented on at least one measurement for 2 consecutive days.

Rabinstein Sandhu, J Neurol Neurosurg Psuchaiatry 2007

Fever --- why?

It complicates 26-44 % of all ICU admissions.
(Intensive care Med,2004,30:811-813)

90 % of patients with severe sepsis

while 50% of the new detected febrile episodes are of noninfectious origin **(Commichau C. et al 2003)**

Pathogenesis of fever

Fever is a normal adaptive brain response to infectious and noninfectious causes

Badjatia N Critical care med.2009 Jul;37(7 Suppl):S250-7.

Pathogenesis of fever

Endotoxin

Staphylococcal toxin

Viruses

IL1,IL6 and TNF

Pathogenesis of fever

The cytokine activates phospholipase A2, with liberation of arachidonic acid as substrate for the cyclo-oxygenase pathway.

leading to liberation of prostaglandin E2.

Pathogenesis of fever

Prostaglandin E2 diffuses across the BBB →

where it acts to raise the set point leading to decrease the rate firing of preoptic warm-sensitive neurons

Leading to activation of responses designed *to decrease* heat loss and *increase* heat production.

Pathogenesis of fever

Fever

It is a condition where the thermoregulatory system is intact but is operating at a higher set point

Accuracy of temperature measuring methods

Most accurate

Pulmonary artery thermistor
Urinary bladder catheter thermistor
Rectal probe

Other acceptable methods in order of accuracy

Oral probe
Infrared ear thermometry

Other methods less desirable

Axillary thermometer
Chemical dot

Naomi P, Crit Care Med 2008 Vol. 36, No. 4 •

Measuring Body Temperature

The gold standard is

the pulmonary artery Thermistor

Although

- **These are infrequently placed**
- **May give unreliable temperature readings if they are used for rapid volume administration.**

Approach to fever in the ICU

Patient

who **comes in with fever**

↓

Diagnosis of the Cause of fever is needed

Patient

with new onset fever

in the ICU

↓

What is causing this fever?

Approach to fever in the ICU

A) Patient who **comes in** with fever

Patient with an obvious focus of infection

Where is the focus?

Community acquired pneumonia
Acute CNS infection
Urinary tract infection
Abdominal focus of infection
Wound infection / Pus
Trauma with infection

Approach to fever in the ICU

B) Patient ***with new onset fever*** in the ICU

I) Non-infective causes

↓

What is causing this fever?

Non-infectious causes of fever

Drug fever

Transfusion reaction

Acalculous cholecyctitis

Thrombo-embolic diseases

Brain injury

Benign post-operative fever

1-Drug related fever

- *Hypersensitivity* reaction (eosinophilia)
- *Local inflammation* at the site of administration : Amphotericin B, erythromycin, KCl, sulfonamides,
- Drugs or their delivery systems may contain *pyrogens or microbial contaminants*

1-Drug related fever

To distinguish drug-induced fever noting that as few as **20%** of patients present with a rash.

It's often a diagnosis of exclusion, and one that should not be excluded itself until the patient has been off the drug for at least seven days

Jamie Newman
Hospital Medicine: From Admission to Discharge Hospital Medicine at Internal Medicine 2013

2- Febrile transfusion reactions

- Complicate about 0.5% of blood transfusions, more common *following platelet transfusion*

- due to *Antibodies against membrane* of transfused leukocytes and/or *antigens* platelets

- Usually *begin* within 30 min to 2 h after a blood-product transfusion

2- Febrile transfusion reactions

- 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

3- Acalculous cholecystitis

- 0.2 to 1.5% of patients in ICU
- RUQ abdominal pain, nausea, vomiting
- Gallbladder ischemia & Cholestasis with bile salt

  May progress to gangrene and perforation

4- Deep venous thrombosis and pulmonary embolism:

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

5- Brain injury

Fever is a secondary **brain injury** and may worsen neurological prognosis

The mechanism of the effect of fever may include:

increase in blood brain barrier permeability,

increase in excitatory amino acid release

increase in free radical production.

Audibert G, baunman A. Charpentier C . Deleterious role of hyperthermia in neurocritical care . Ann Fr Anesth Reanim 2009 Apr;28(4):345-51.

Approach to fever in the ICU

B) Patient ***with new onset fever*** in the ICU

II) **Infectious causes** ↓

Where is the focus?

Infectious causes of fever

- Ventilator associated pneumonia
- Catheter related blood stream infections
- Uro-sepsis
- Surgical wound infections

I

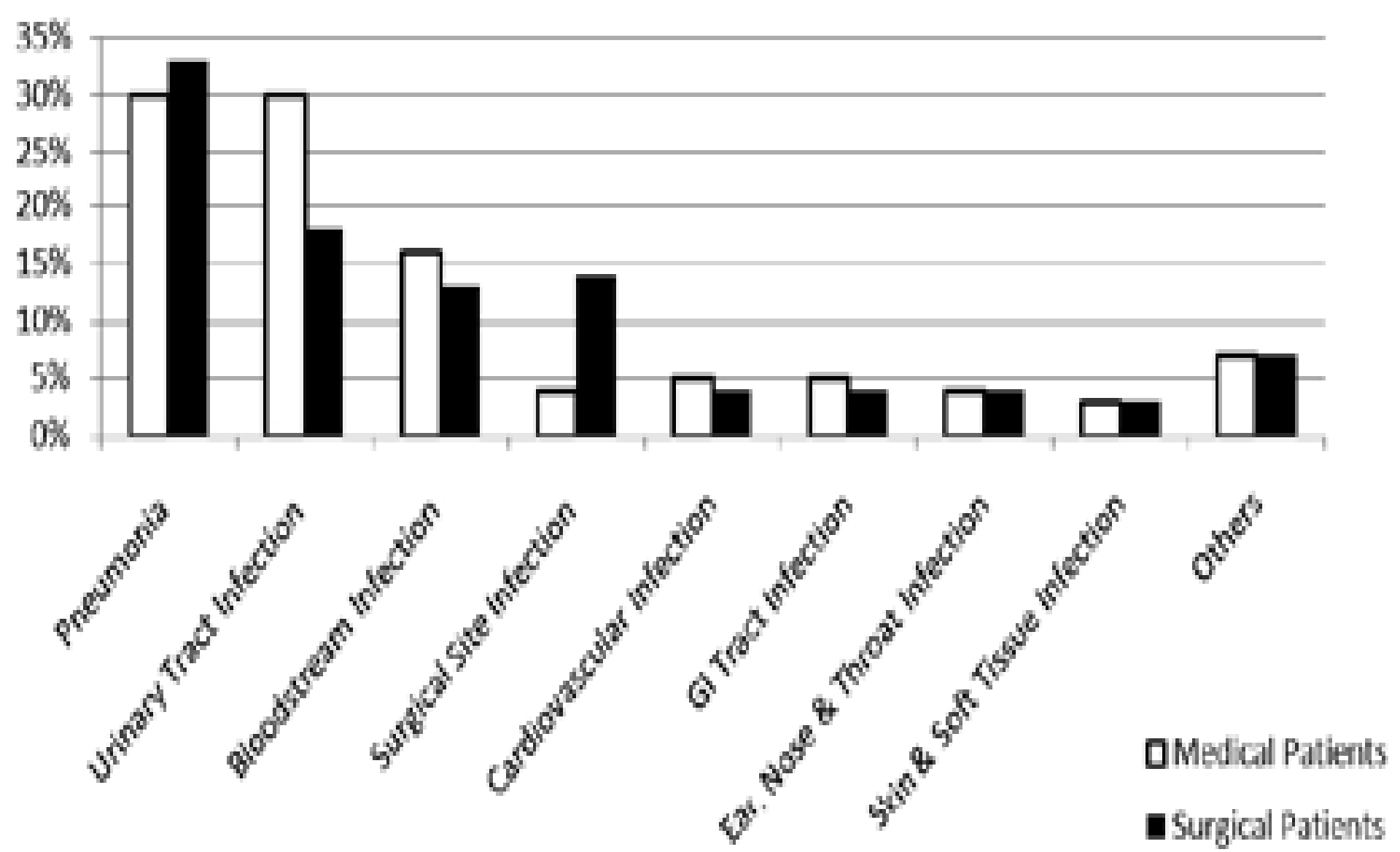
Infectious causes of fever

Intra-abdominal infections

Sinus infections

Fungal infections including candidemia(7%)

Diarrhea



Arulrhaj S, **Fever In ICU Medicine Update-2011**

The severity of fever
is not an indication
of presence or severity
of infection

Marik,PE. : fever in the ICU .Chest 2000,117:855-869

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

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

1- Ventilator Associated Pneumonia

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

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

2- Sinusitis

- Nasotracheal and nasogastric tubes are risk factors

- The incidence is increased in patients with *nasotracheal* tube for >1 wk

  Am J Respir Crit Care Med 1999; 159:695–701

- It represent **15-20 %** of patient with nasal tube

- Maxillary sinus – commonly involved

3- Catheter related blood stream infection

- **2-5 infections/ 1,000 catheter days**

- **Equal risk for arterial line and peripherally inserted central venous catheters**

3- Catheter related blood stream infection

- 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%,

- The mortality rate attributed to catheter-related *S. aureus* bacteremia (8.2%)

4- CNS infection

- Focal deficit
- Contiguous infection
- Neurosurgery
- Shunt drain

Infectious Vs non-infectious fever

A- Procalcitonin

Procalcitonin level elevations

SIRS- 0.6 to2.0 ng/mL

Severe sepsis – 2 to10 ng/mL

Septic -shock > 10 ng/mL

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

Infectious Vs non-infectious fever

B- Endotoxin levels

- Endotoxin activity assay (EAA)

- EAA had a **sensitivity** of 85.3% & a **specificity** of 44.0% for diagnosis of gram-negative infection

J Infect Dis 2004; 190:527–534

Is lowering temperature essential?

- Fever is an important clinical sign **for monitoring** response eg. Hepatotoxicity of acetaminophen (alcoholics &malnourished)

Arch Intern Med 2001, 161:121-123

Is lowering temperature essential?

Rise in temperature can be regarded as a cure, in that it is part of **the autonomic response to remove infection** and create a favorable environment for antibiotics

GardnerJ. Is fever after infection , Emerg Nurse 2012 Mar;19(10):20-5; quiz 27part of the illness or the cure?

Is lowering Temperature Essential?

Benefits of fever

Enhances parameters of immune function

Improves antibody production

Activates T-cells

Produces cytokines

Enhances neutrophil and macrophage function

Is lowering Temperature Essential?

Benefits of fever

Experimentally , A two fold increased risk of mortality was found with aspirin treatment in animal models of S pneumoniae infection

Jefferies S et al . Postgrad Med.J. 2012 Jan;88(1035):21-7.

Is lowering Temperature Essential?

But

Low doses of **ASA** of 100 mg/day trigger synthesis of lipoxins, which are anti-inflammatory

Patient with :

sepsis

acute lung injury ----- treated with ASA---- leading to lower mortality in ICU.

Antonelli M , intensive Care Med (2013)39:345-364A

Is lowering Temperature Essential?

Benefits of fever

Direct clinical evidence

In elderly patients with community-acquired pneumonia, a higher mortality rate was observed in patients who lacked fever (29%)

when compared with patients who developed a febrile response (4%)

The multicenter French Amar Cand study pointed out that fever >38.2°C was a protective factor in **invasive *Candida* infections in the ICU**

Is treatment of fever essential?

Benefits of fever

Why ?

Fever induces the production of **heat shock proteins** (**HSPs),** a class of proteins critical for cellular survival during stress.

HSPs act as molecular ***chaperones***, and they have an anti-inflammatory role.

Michael Ryan and Mitchell M Levy. *Critical Care* 2003, 7:221-225 Clinical review: Fever in intensive care unit patients

Is lowering Temperature Essential?

deleterious effects of fever

1. **An increase C.O.P**

2. **An increase O2 consumption (*increases by approximately 10% per degree Celsius)***

3. **An increase CO2 production**

Is treatment of fever essential?

deleterious effects of fever

4- Poorer neurological outcomes in patients with stroke and traumatic brain injury who manifest temperature

5- Fever poorly tolerated in patients with reduced cardio-respiratory reserve

Is lowering Temperature Essential?

Fever is associated with

***Unnecessary investigations and lead to in*appropriate antibiotic use.**

Increased length of stay in general ICU patients & increased cost of care

Crit Care Med 2008;36:1531-1535

ICU fever should be treated in:

1- **c**ardio-respiratory

2- **n**eurosurgical patients

3-temperature **e**xceeds 40 degrees C

Antipyretic therapy must be justified if fever exceeds its physiologic benefit

Fever

is not a sign of impending doom

BUT

it is a sign that requires attention

THANK YOU

Approach to fever in the ICU

A) Patient who **comes in** with fever

Acute

un-differentiated fever

↓

What is the cause

Fever with thrombocytopenia

Fever with hepato-renal dysfunction

Fever with pulmonary renal syndrome

Fever with altered sensorium

The most important Infectious causes are :

ventilator-associated pneumonia (83%)

intravascular catheter-related infections (87%).

Sinusitis

Richard et al : infect. Control hosp. epidemol 2000

The importance of catheter-related urinary tract infection (UTI) is harder to establish because of a lack of discrimination in the literature between bacteriuria (colonization) and genuine infection.

Noninfectious causes of fever in the intensive care unit

Important causes	Other causes
Acalculous cholecystitis	Acute respiratory distress syndrome (late)
Adrenal insufficiency	Burns
Benign post-operative fever	Drug overdose (eg, aspirin anticholinergic drugs)
Drug fever	Drug withdrawal
Pancreatitis	Gout
Thyroid storm	Heat stroke
Transfusion reaction	Intracranial hemorrhage
	Ischemic colitis
	Malignancy
	Malignant hyperthermia
	Myocardial infarction
	Neuroleptic malignant syndrome
	Pheochromocytoma
	Seizures
	Serotonin syndrome
	Thromboembolic disease
	Vasculitis

***After ischemic stroke*, hyperthermia during the first 72 hrs is associated with an increase in infarct size.**

Fever is not related to mortality but may increase morbidity.

Audibert G, baunman A. Charpentier C . Deleterious role of hyperthermia in neurocritical care . Ann Fr Anesth Reanim 2009 Apr;28(4):345-51.

Spectrum of ICU patient with Infectious

:

Bacteremia: presence of bacteria in the blood, as evidenced by blood cultures.

Septicemia: Presence of microbes or their toxins in blood1

SIRS: Two or more of the following conditions

1) Fever (Oral temperature > 38°C) or hypothermia (<36°C)
2) Tachypnea (>24 breaths/min)
3) Tachycardia (heart rate > 90 beats/min)
4) Leucocytosis (>12,000/microl), Leucopenia (<4,000/ microL), 10% bands.

May have an infections or noninfectious etiology.

Sepsis: SIRS that have a proven or suspected microbial etiology.

Spectrum of ICU patient with Infectious

Severe sepsis: ***Sepsis with one or more signs of*** organ dysfunction (such as metabolic acidosis, acute encephalopathy, oligouria, hypoxemia, or disseminated intravascular coagulation) or hypotension.

Septic shock: Sepsis with hypotension (arterial blood pressure of <90 mmHg systolic or 40 mmHg less than patient's normal blood pressure) that is unresponsive to

Spectrum of ICU patient with Infectious

***Refractory septic shock*: Septic shock that lasts for > 1** hr and does not respond to fluid or pressor administration.

***MODS*: Dysfunction of more than one organ, requiring** intervention to maintain hemostasis.

***Arulrhaj S,* Fever In ICU Medicine Update-2011**

1- Ventilator Associated Pneumonia

Definition of VAP:

1. New onset or progressively increasing infiltrates in CXR
2. Fever
3. Leucocytosis
4. Purulence tracheobronchial secretions

1-Drug related fever

- Stimulation of heat production e.g., thyroxine

  Limit heat dissipation e.g., atropine

  Alter thermoregulation e.g., phenothiazines,

- Antiparkinson drugs

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, Antiemitics (prochlorperazine), prokinetics (metclopromide), sedatives (promethazine)

- Withdrawal of levodopa/carbidopa, amantidine
- In the ICU, haloperidol is the most common offending drug

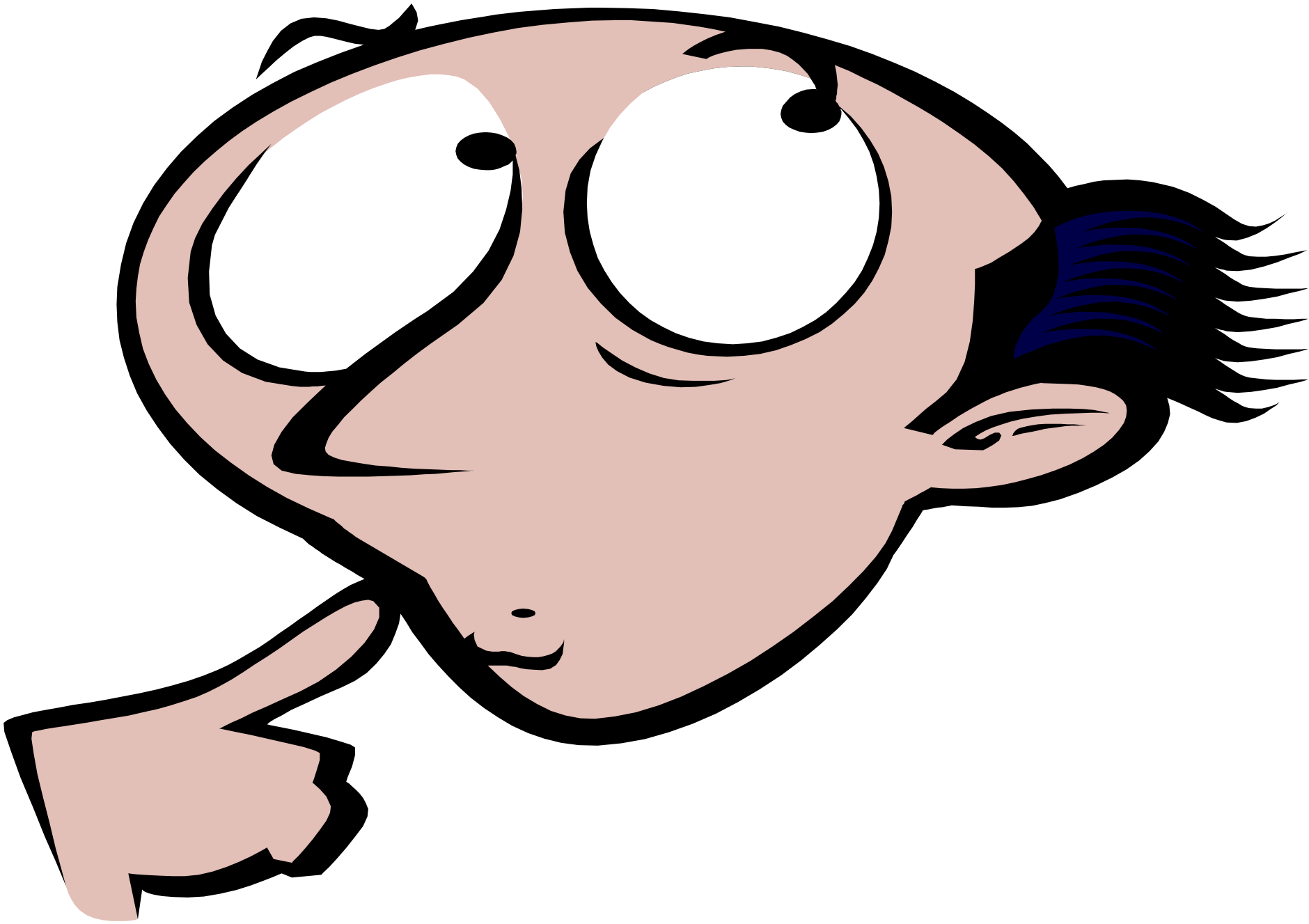
Is lowering Temperature Essential?

Benefits of fever

Direct clinical evidence

patients **without sepsis**, high fever is associated with mortality and **in sepsis** patients administration of NSAIDs or acetaminophen is independently associated with an increased 28-day mortality

Lee BH, Inui D, Suh GY, et al . *Critical Care*. 2012;16:R33



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

Crit Care Med 2008;36:1531-1535

Pathogenesis of fever

Exogenous pyrogens

Endotoxin

Staphylococcal toxin

Viruses

Endogenous pyrogens

IL1,IL6 and TNF

COX-2

Prostaglandin E2

Lymphocytes Decreased firing of heat sensitive neurons

Is treatment of fever essential?

Benefits of fever

Direct clinical evidence

In a selected population of ICU-infected patients, both hypothermia and fever increased morbidity and mortality rates, but patients with hypothermia had a higher mortality when compared with those who had fever (**80%** vs. **47**%

Launey,et al. Clinical review: Fever in septic ICU patients - friend or foe. *Critical Care* 2011, 15:222

Is treatment of fever essential?

Benefits of fever

Why ?

Fever induces the production of **heat shock proteins** (**HSPs),** a class of proteins critical for cellular survival during stress.

HSPs act as molecular chaperones, and they have an anti-inflammatory role.

by inhibiting the activation of NF-κβ, thus **decreasing** the levels of pro-inflammatory cytokines which **coupled with** improved survival of patient with fever and infection

Michael Ryan and Mitchell M Levy. *Critical Care* 2003, 7:221-225 Clinical review: Fever in intensive care unit patients

Is treatment of fever essential?

Benefits of fever

Direct clinical evidence

patients with Gram-negative bacilli bacteraemia reported significantly higher survival in patients who developed fever on the day of bacteraemia

Patients with spontaneous bacterial peritonitis reported reduced mortality when the body temperature was >38°C ..

Spectrum of ICU patient with Infectious

:

Bacteremia:

Septicemia:

SIRS:

Sepsis:

Refractory septic shock:

Severe sepsis:

Severe shock:

MODS:.

Arulrhaj S, **Fever In ICU Medicine Update-2011**

Non-infectious causes of fever

Adrenal insufficiency (spontaneous Hge)

ARDS (late)

Burns

pancreatitis

Thyroid storm

Gout

1- Ventilator Associated Pneumonia

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 // ARDS <240,// no ARDS

Score >6 is suggestive of VAP