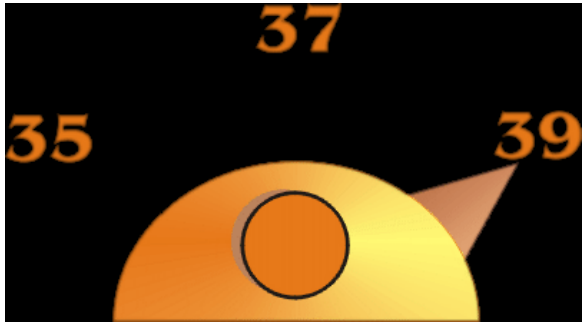
Approach to Fever

Prof. G. Zuliani

Types of body temperature elevation

Physiological elevation:



- before menstruation
- severe exercise
- severe stress

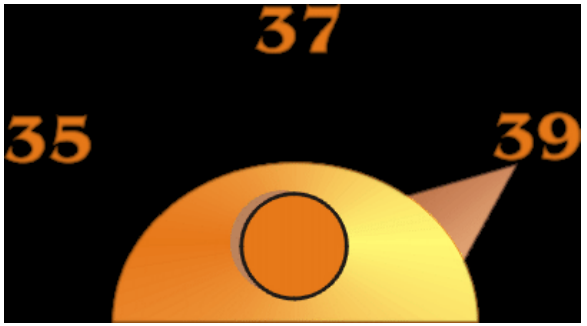
Pathological elevation:

- Fever (e.g. Infection diseases)
- Hyperthermia (e.g. heatstroke)

DEFINITION OF FEVER

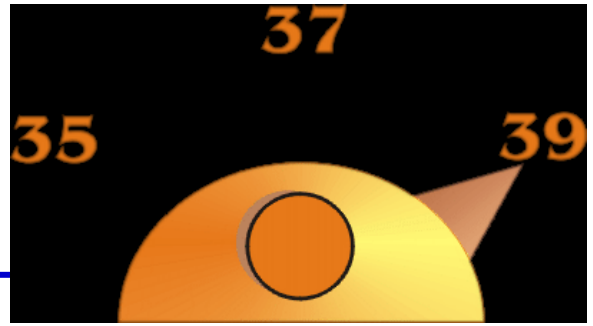
Fever is a complicated pathological process characterized by a regulated elevation of core body temperature that exceeds the normal daily variation (>0.5℃), in which *pyrogens cause a temporary upward resetting of the hypothalamic thermostatic set-point.*

Clinical features of fever



- Body temperature:
  - Naturally varies with circadian rhythm
    - **1.1°C** (lower in the morning, higher in the afternoon)
- Fever threshold:
  - Varies: most agree **38°C** warrant evaluation
  - Higher temperatures are associated with higher incidence of bacteremia

PHYSIOLOGY OF FEVER



Exogenous pyrogen (activated leukocytes)

Endogenous pyrogen

↓ → **Acute Phase Response**

- **Preoptic area of anterior hypothalamus increase of set point =>**
  - Brain cortex
  - Vasoconstriction → heat conservation
  - Muscle contraction → heat production

} **FEVER**

Infection, toxins, injury, inflammation

Immune Response Mediators

IL-1, IL-2, TFN, IFN

↓

Leukocytes

Monocytes, neutrophils, lymphocytes

Endothelium, glial cells, mesenchymal cells

↓

Pyrogenic Cytokines

IL-1, TNF, IFN

gp130 receptor ligands

↓

Hypothalamic Endothelium

Production of PGE2

Rise in cAMP (acts as neurotransmitter)

↓

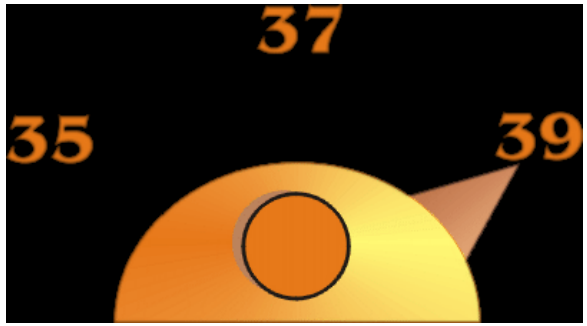
Elevated Set-Point

Activation of vasomotor centre neurons

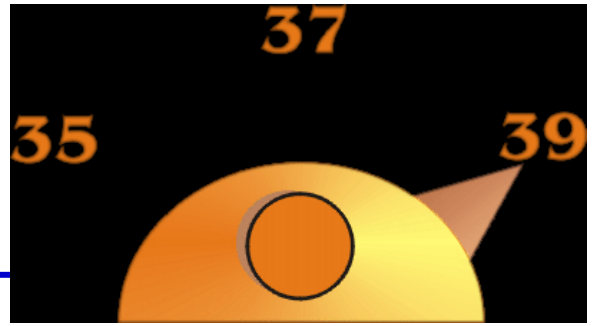
Peripheral vasoconstriction and heat production

↓

FEVER



Bacterial Pyrogens



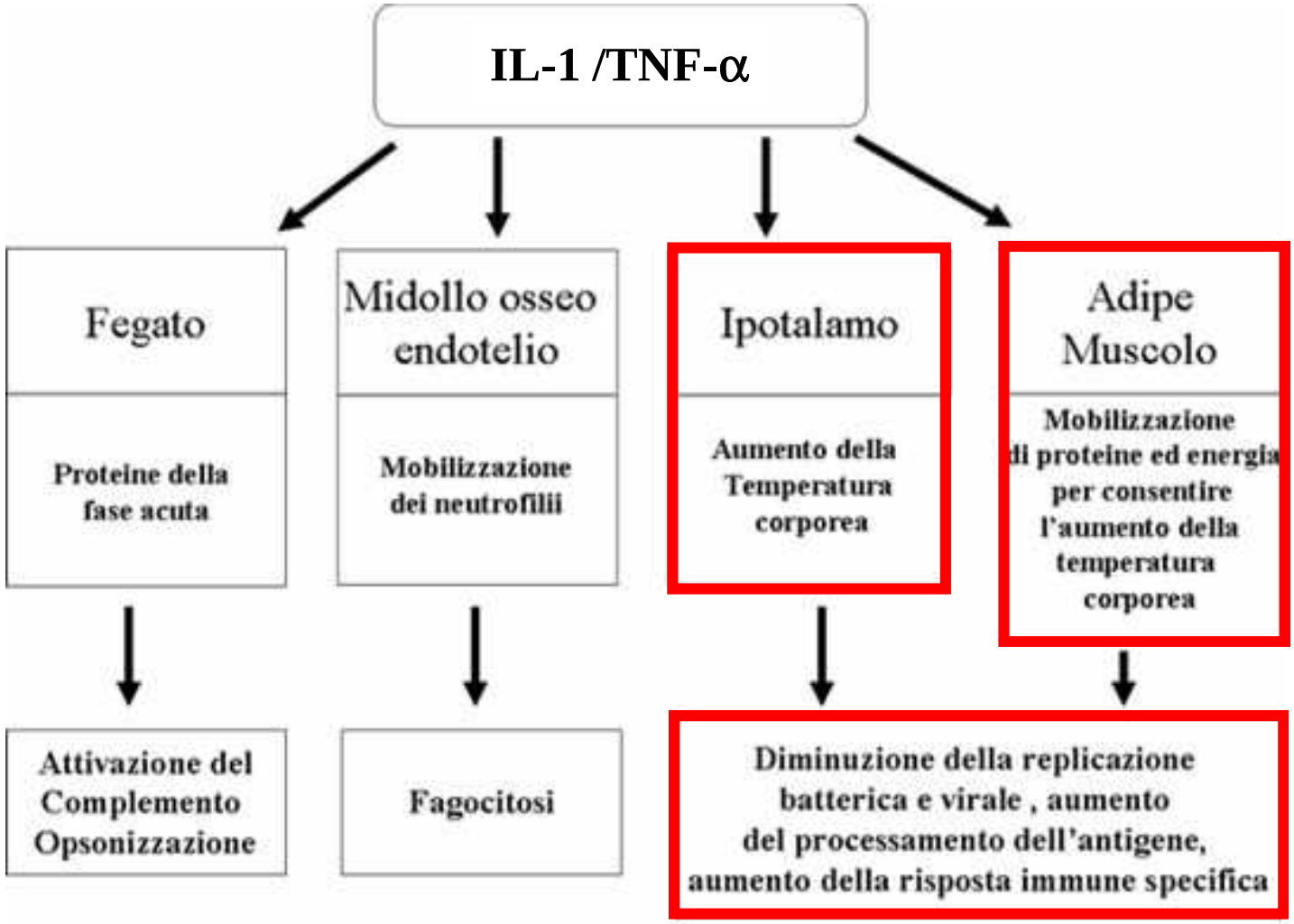
- ***Lipopolysaccharide (LPS) endotoxin***

  Endotoxin binds to LPS-binding protein and is transferred to CD14 on macrophages, which stimulates the release of TNF-α
- ***Staphylococcus aureus* enterotoxins**
- ***S. aureus* toxic shock syndrome toxin *(TSST)***

  Both *Staphylococcus* toxins are super-antigens and activate T cells leading to the release of interleukin (IL)-1, IL-2, TNF-α and TNF-β, and IFN-γin large amounts
- ***Group A and B streptococcal toxins***

Exotoxins induce human mononuclear cells to synthesize **TNF-α, IL-1, and IL-6**

Pathophysiology of fever



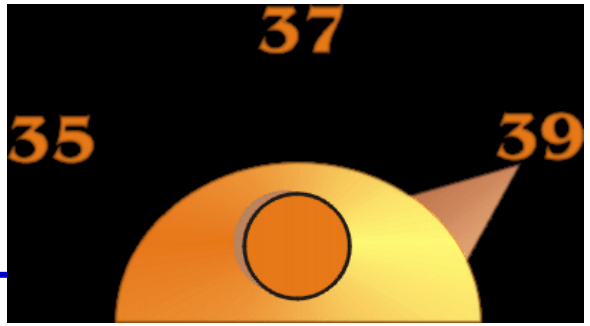
ACUTE PHASE RESPONSE

- Metabolic changes
  - Negative nitrogen balance
  - Loss of body weight
- Altered synthesis of hormones
- Hematologic alterations
  - Leukocytosis
  - Thrombocytosis
  - Anemia

Acute Phase Reactants

- **C reactive protein (increased)**
- **Serum amyloid A (increased)**
- **Fibrinogen (increased)**
- **Fibronectin (increased)**
- **Haptoglobin (increased)**
- **Ceruloplasmin (increased)**
- **Ferritin (increased)**
- **Albumin (decreased)**
- **Transferrin (decreased)**
- **Total cholesterol (decreased)**
- **HDL-C (decreased)**

Wunderlich's Maxim



- After analyzing > 1million axillary temperatures from ~ 25.000 patients (!) Wunderlich identified **37.0°C (36.2-37.5)** as the mean temperature in healthy adults.

- Temperature readings >38.0°C were deemed as "suspicious/probably febrile".

Wunderlich C. *Das Verhalten der Eiaenwarme in Krankenheiten*. Leipzig, Germany: Otto Wigard;1868.
Mackowiak, et al., JAMA 1992;268:1578

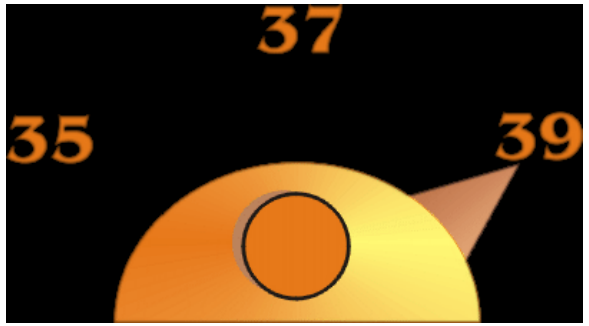
Normal Body Temperature

- For healthy individuals 18-40 years of age, the mean oral temperature is **36.8° ± 0.4°C** ***Lower levels occur at 6 AM and higher levels at 4 to 6 PM***
- The maximum normal oral temperature is 37.2°C at 6 AM and 37.7°C at 4 P.M.

- These values define the **99th percentile** for healthy individuals.

Mackowiak, et al., JAMA 1992;268:1578

FEVER CLASSIFICATION



BY SEVERITY

- **Febbricola: non supera i 38°C**
- **Febbre lieve: temperatura tra 38-38,5°C**
- **Febbre moderata: 38,5-39°C**
- **Febbre elevata: 39-40°C**
- **Iperpiressia: > 40°C**

- **(Ipertermia: > 41°C)**

FEVER CLASSIFICATION

BY PATTERN

CONTINUA: le fluttuazioni quotidiane di temperatura sono <1°C e la febbre persiste nel tempo

REMITTENTE: le fluttuazioni quotidiane (almeno due) sono >1°C ma non tornano mai ai valori basali (caratteristica della maggioranza delle malattie febbrili)

INTERMITTENTE: la febbre sale e scende durante il giorno per tornare alla normalità verso il mattino. Se le escursioni di temperatura sono molto alte si parla di febbre settica. La febbre intermittente è caratteristica delle malattie neoplastiche.

RICORRENTE: episodi febbrili intervallati da periodi di tempo più o meno lunghi in cui la temperatura corporea torna ai valori normali (tipico di alcune malattie come: malaria, la brucellosi e l'infezione da borrelia).

FEVER CLASSIFICATION

BY PATTERN

Fever continues

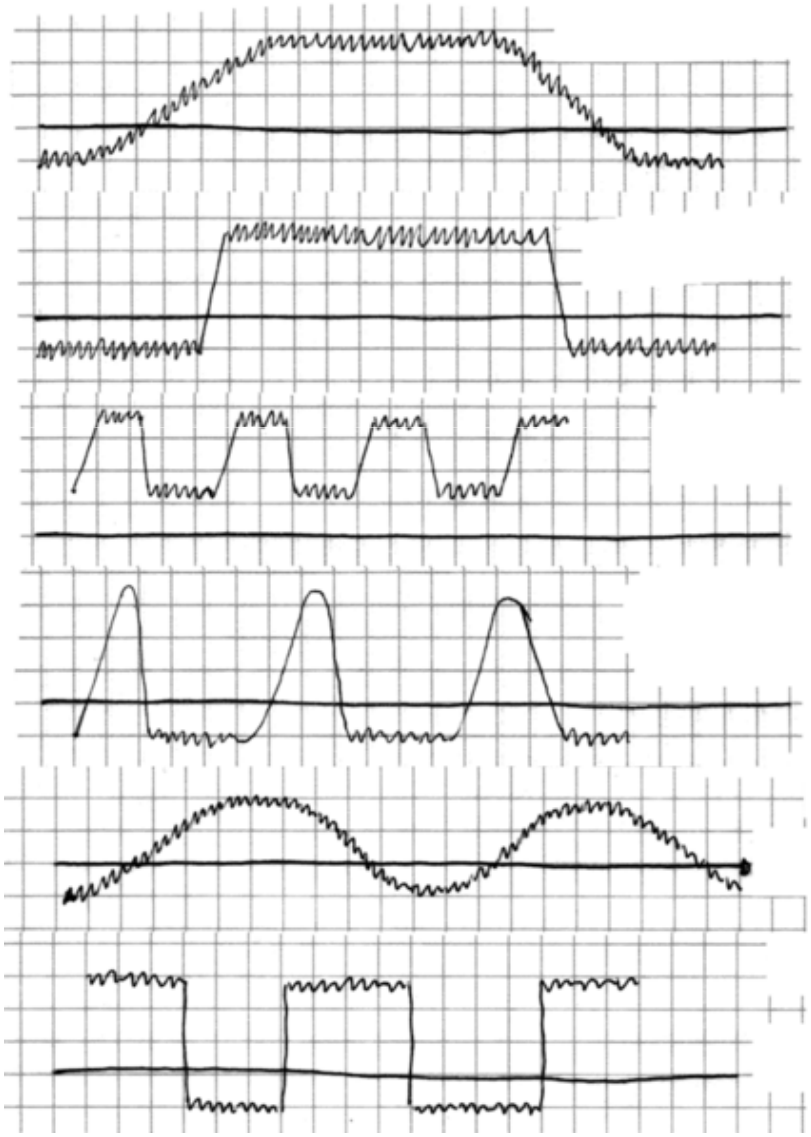
Fever continues to abrupt onset and remission

Fever remittent

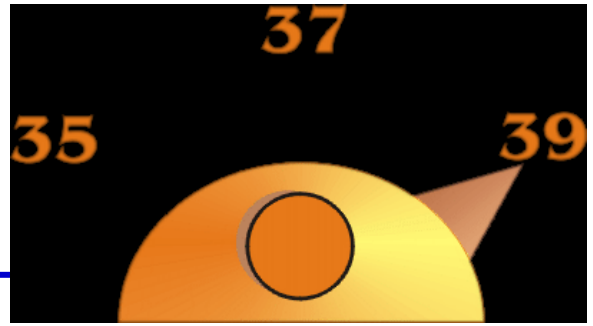
Intermittent fever

Undulant fever

Relapsing fever



Manifestations of fever



Effervescence period

Heat production ↑

- shivering, brown adipose tissue, basal metabolic rate

Heat loss ↓

- feeling of being cold, skin is cold and pale (vasoconstriction), piloerection, goose flesh

Persistent febrile period

Heat equipoise at a higher level:

shivering ceases, sensation of warmth, cutaneous vasodilation occurs, skin becomes warm and flushed

Defervescence period

Heat loss ↑

heat production↓: sweating, sensation of warmth, etc.

Functional changes in fever

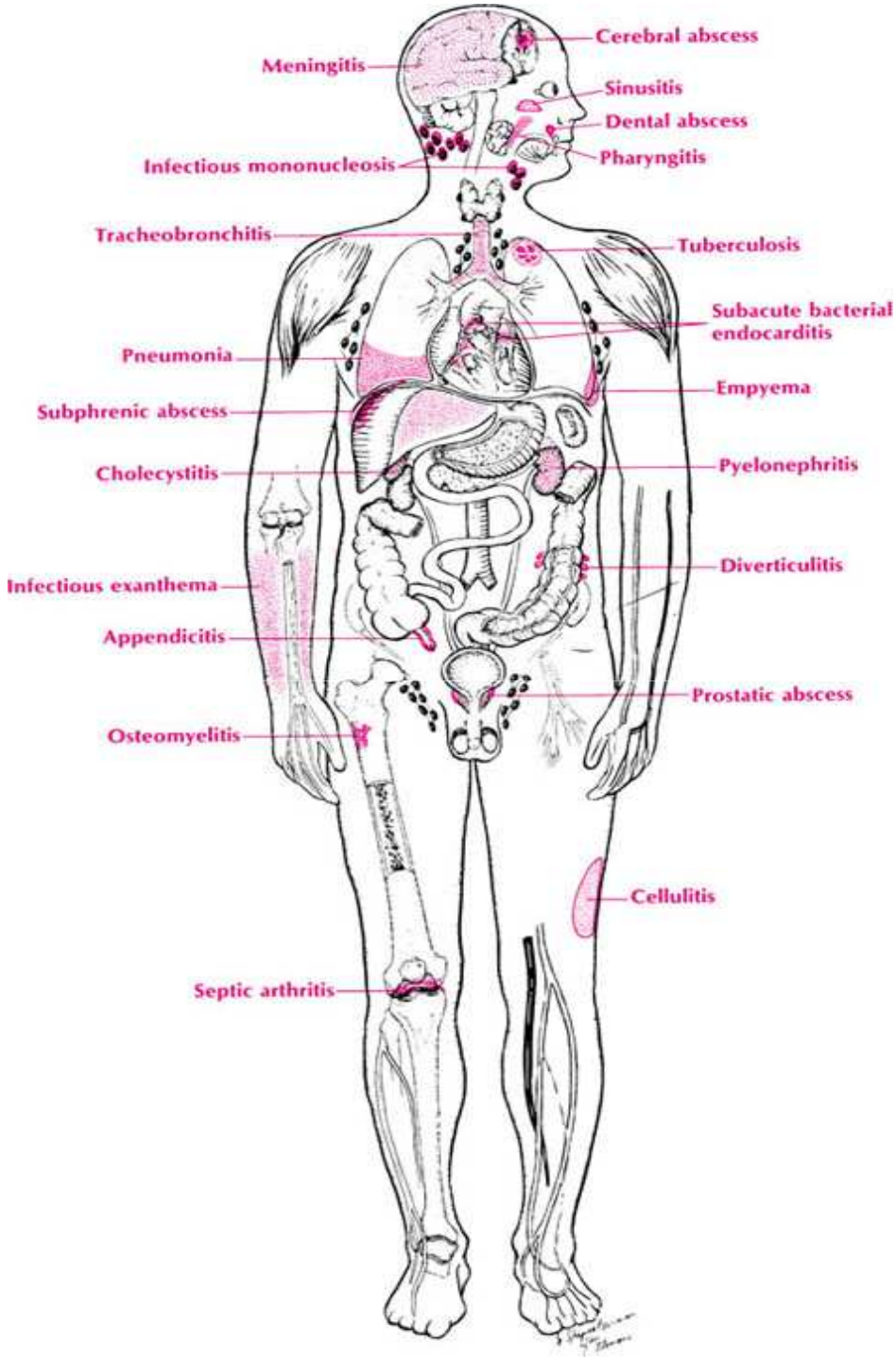
Functional changes

- Central nervous system: ***sleepiness***, excitability ↑
- Cardiovascular system: ***beat rate ↑, cardiac output ↑ (1°C = 10-20 beats/min)***
- Respiratory system: ***respiratory rate ↑***, hyperventilation
- Digestive system: suppressed ↓
- Immune system: activities ↑

Changes of metabolism

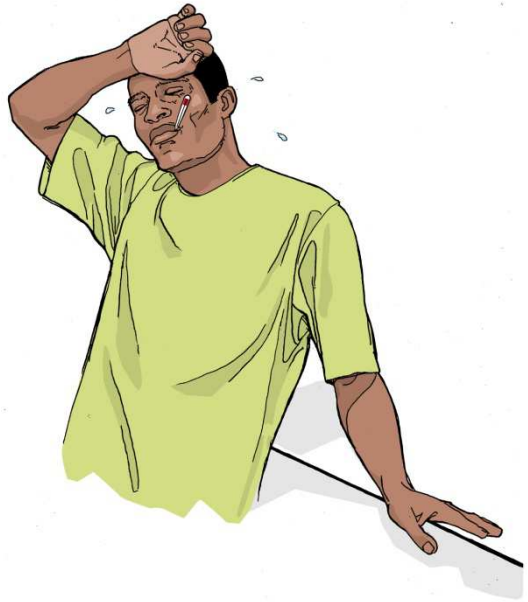
- Generally, ***the basal metabolic rate increases 10% with 1°C elevation in body temperature.***
- Consumption and ***catabolism of nutrients*** increase during fever: Carbohydrates, Lipid, Protein, Walter, Salts, Vitamines

CAUSES OF INFECTIOUS FEVER

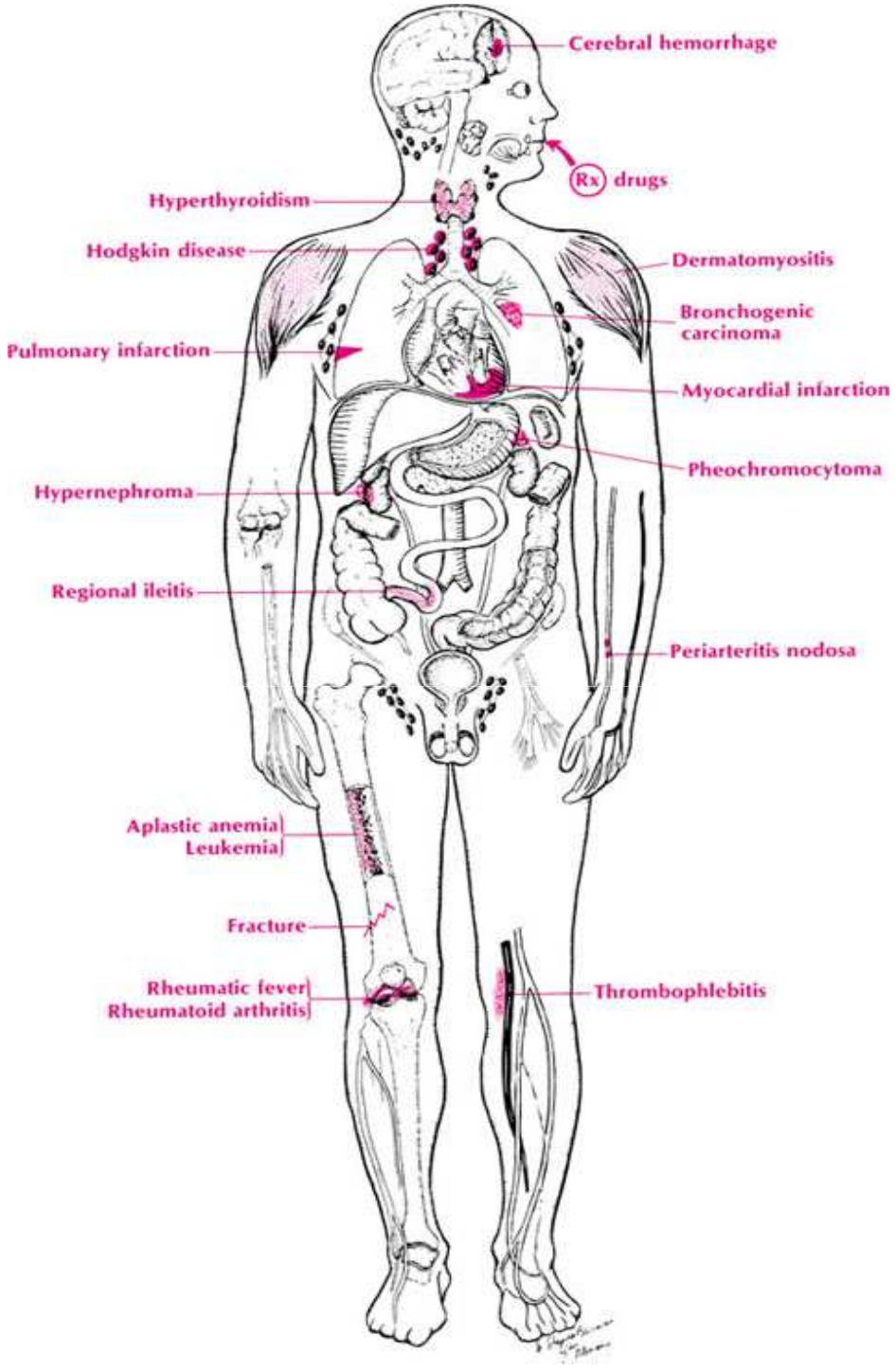


NON INFECTIOUS FEVER

- Stroke
- Pulmonary embolism
- Myocardial infarction
- Hyperthyroidism
- Lymphoma
- Pheochromocytoma
- Kydney cancer
- Lung cancer
- Dermatomyosites
- Vasculitis
- Rheumatoid arthritis
- Chron disease
- Phlebitis
- Alcohol abstinence
- Hematoma
- GI bleeding



CAUSES OF NON INFECTIOUS FEVER



HYPERTHERMIA

- **Hyperthermia *is an elevation of body temperature due to failure of thermoregulation.*** Hyperthermia occurs when the body produces or absorbs more heat than it can dissipate. When the elevated body temperatures are sufficiently high, hyperthermia is a ***Medical Emergency*** and requires immediate treatment to prevent disability or death.

- Hyperthermia differs from fever in the mechanism that causes the elevated body temperatures: ***fever is caused by a change in the body's temperature set-point, hyperthermia is NOT.***

CAUSES OF HYPERTHERMIA SYNDROME

- Heat stroke: excess exercise, hot climate
- Drug induced: Cocaine, Amphetamine, MAO-inhibitors, Anticholinergics
- Neuroleptic malignant syndrome: Phenothiazines, Butyrophenones
- Malignant hyperthermia: Inhalational anesthetics
- Endocrinopathy: tireotoxicosis, pheochromocytoma

DIAGNOSIS OF HYPERTHERMIA

- History
- Antipyretics are not effective !
- Skin is hot but dry

Comparison between hyperthermia and fever

Hyperthermia	Fever
Arising from changes within the body or by changes in environment	Resulting from Pyrogens
Set-point remains unchanged or damaged, or effectors organs fails	Ability to regulate set-point remains intact, but is turned up at a high level functionally
Body temperature may rise to a very high level	Rise of body temperature has an upper limit
Treatment with water-alcohol bathing	Treatment with antipyretics and measures and drugs to eliminate the causes

APPROACH TO FEVER

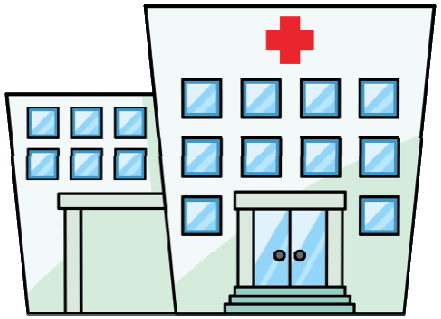
- Physical Examination:
  - Vital Signs (HR, BP, RR, SAT.O2)
  - ENT (Ear, Nose and Throat)
  - Lungs and Heart
  - Skin Lesions, Mucous Membrane
  - Lymphadenopathies
  - Eyes
  - Neurological Examination
  - Abdominal Region (hepatomegaly, splenomegaly)
  - Musculoskeletal

Initial Laboratory Evaluations in UNEXPLAINED PROLONGED FEVER

- CBC
- Chest XR
- Urine analysis, culture
- Two Blood Culture in 30 minutes interval, from 2 different sites
- *In selected patients:*
- Test for Borrelia, Malaria, West Nile fever
- Widal-Wright
- Liver Function Tests

INDICATIONS FOR HOSPITALISATION IN PATIENT WITH FEBRILE ILLNESS

1. Persons who are *clinically unstable* or are at risk for *rapid deterioration* (multimorbidity, fragility)
2. Presence of known *major alterations of immunity*
3. Need for *IV antimicrobials or other fluids*
4. *Advanced age*



SIRS - SEPSIS

Systemic Inflammatory Response Syndrome - SIRS

- **Definition:** ***SIRS is a serious condition related to systemic inflammation, organ dysfunction, and organ failure***. It is a subset of *"cytokine storm"*, in which there is abnormal regulation of various cytokines.

SIRS CRITERIA:

1. **Temp >38ºC** or <36ºC
2. Heart Rate >90 bpm
3. Respiratory Rate >20/m or pCO2 <32
4. WBC >12.000 or <4.000 mm3

Systemic Inflammatory Response Syndrome - SIRS

The causes of SIRS are broadly classified as infectious or non-infectious. Causes of SIRS include:

- Trauma
- Burns
- Pancreatitis
- Ischemia
- Haemorrhage

- Other causes include:
- Complications of surgery
- Adrenal insufficiency
- Pulmonary embolism
- Anaphylaxis
- Drug overdose

Sepsis and septic shock

SEPSIS ***is life-threatening organ dysfunction caused by a dysregulated host response to an infection***.
For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment **(SOFA)** ***score of 2 or more*** (score=0 if the condition is absent) which is associated with an in-hospital **mortality greater than 10%.**

SEPTIC SHOCK is a ***subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone.***
Patients with septic shock can be clinically identified by: 1. a *vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater* and 2. *serum lactate level greater than 2 mmol/L (>18 mg/dL)* in the absence of hypovolemia. This combination is associated with hospital **mortality greater than 40%.**

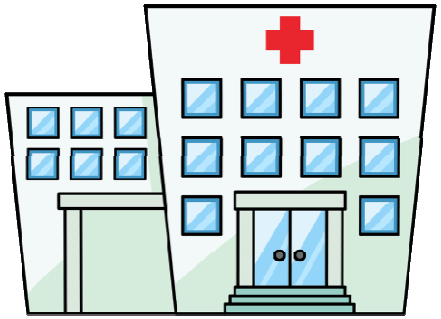
Sepsis: SOFA SCORE

	Organ system	1	2	3	4
1	**Respiratory** PaO_2/FiO_2, (mmHg)	<400	<300	<200	<100
2	**Hematologic** Platelets/ nl	<150	<100	<50	<20
3	**Hepatic** Bilirubin, mg/dl (µmol/l)	1,2–1,9 (20–32)	2,0–5,9 (33–101)	6,0–11,9 (102–204)	>12,0 (>204)
4	**Cardiovascular** Hypotension	MAP[2)] <70 mmHG	Dopamine ≤ 5[1)] or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0,1[1)] or Norepinephrine ≤0,1[1)]	Dopamine >15 epinephrine > 0 or norepinehrine 0,1
5	**Neurologic** Glasgow Coma Score	13–14	10–12	6–9	<6
6	**Renal** Creatinine, mg/dl (µmol/l) urine output	1,2–1,9 (110–170)	2,0–3,4 (171–299)	3,5–4,9 (300–440) <500 ml/day	>5,0 (>440) <200 ml/day

Nosocomial Fevers

- Hospital-acquired fevers occur in 2 to 15% of all medical inpatients

- Nosocomial fevers even more common in the Intensive Care Units (ICU)



Causes of Fever in the ICU

- SEPSIS
- Intravenous-line infections
- Nosocomial pneumonia
- Intra-abdominal infections
- Urinary catheter-associated infection
- Drug fever
- Post-operative fever
- Neurosurgical causes

Intravenous-line Infections

- Prevalence: 5% in ICU patients in a University study
- Bloodstream infection is a serious catheter-related complication: case fatality rate ~10-20%
- Look for local signs of infection: present in < 50%
- Remove line if no other source and T > 39°C

Cobb DK. NEJM

Nosocomial Pneumonia

- **Hospital-acquired pneumonia (HAP)** or **nosocomial pneumonia** refers to any pneumonia contracted by a patient in a hospital >48–72 hours after being admitted
- Signs are:
  - fever
  - leukocytosis
  - purulent tracheal secretions
  - new or worsening infiltrates on CXR

Intra-abdominal Infections

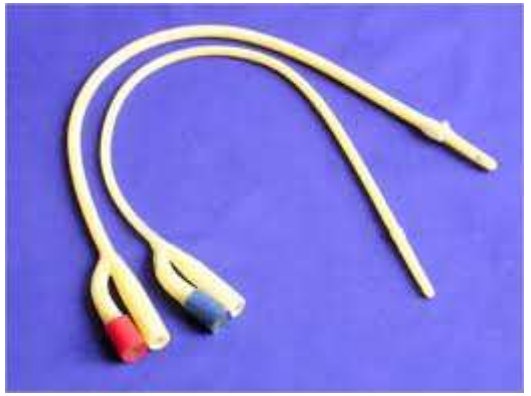
- Suspect an intra-abdominal abscess in patients with prolonged post-operative fever after ***abdominal surgery***
- Acalculous cholecystitis and subsequent biliary sepsis may complicate post-operative period

Intra-abdominal Infections

- Suspect antibiotic-associated colitis due to **Clostridium difficile** in patients on broad-spectrum antibiotics
- Fever and leukocytosis may be present prior to diarrhea or abdominal symptoms !
- Splenic or hepatic **abscesses** may complicate other intra-abdominal infections (cholecystitis, appendicitis) causing prolonged fevers

Catheter-Associated Bacteriuria

- Foley catheters
  - Result in acquisition of bacteriuria
  - Most often represents ***colonization***, not infection
  - Pyuria may accompanies CAB, mimicking a UTI



Catheter-Associated Bacteriuria

- Foley + fever + bacteriuria:
  - does not necessarily mean urosepsis
  - unless there is partial or total obstruction or pre-existing renal disease
- Asymptomatic CAB:
  - in normal hosts need NOT be treated
  - in compromised hosts and chronically immunosuppressed must be treated promptly

Drug Fever

- Lab tests show:
  - leukocytosis with left shift
  - eosinophilia (low-grade)
  - eosinophils on peripheral smear (common)
  - elevated ESR
  - mildly elevated ALP, AST, ALT

Common Causes of Drug Fever

Antibiotic Induced Fever

- Erythromycin
- Isoniazid
- Penicillin
- Nitrofurantoin
- Procainamide
- Quinidine

Cardiovascular Medication Induced Fever

- Atropine
- Captopril
- Clofibrate
- Hydralazine
- Hydrochlorothiazide
- Methyldopa
- Nifedipine

Miscellaneous Medications Inducing Fever

- Allopurinol
- Antihistamines
- Aspirin
- Cimetidine
- Heparin
- Meperidine
- Phenytoin

Post-operative Fever

- Fever is common post-operatively
- Many episodes are *non-infectious*
- Probably due to intra-operative tissue trauma with subsequent release of endogenous pyrogens into the bloodstream
- Garibaldi found that 72% of fevers within the 48 h after surgery were *non-infectious*
- Wound, urinary tract, and respiratory infections usually occur later than 48 h

Garibaldi RA. Infect Control

Causes of very High Fever (>41ºC)

Central Fevers

- intracranial: hemorrhage, large head trauma, infection, and malignancy
- especially if the midbrain or hypothalamus are affected

- Infusion-related sepsis (contaminated infusion)
- Rarely: bacterial infection
- Drug fever (usually 39-41°C)

Malignant Hyperthermia

Malignant hyperthermia

- Rare genetic disorder, probably autosomal dominant
- Incidence about 1:15.000 in kids; less in adults
- ***Hyper-catabolic reaction to anesthetic drugs***
- ***Sustained muscle contraction ➔ excess heat***
- Treated with **dantrolene**; mortality ~7%

Malignant Hyperthermia

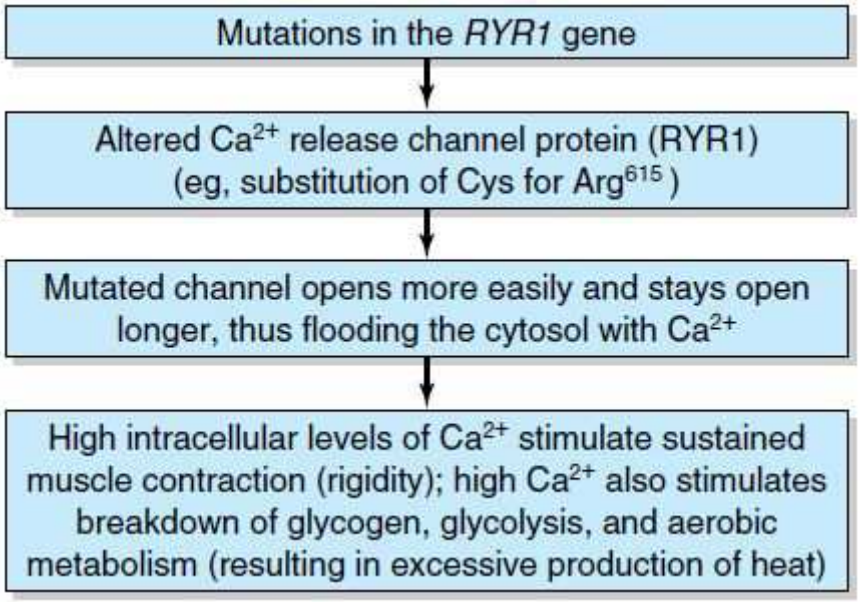


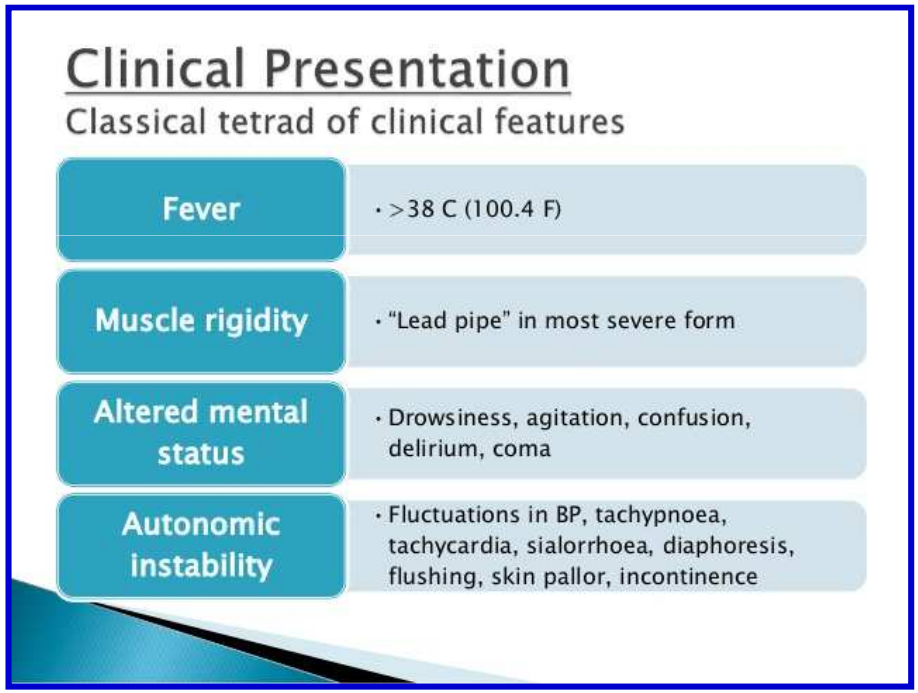
Table. Clinical Signs of Malignant Hyperthermia

EARLY SIGNS	LATE SIGNS
Increased end tidal carbon dioxide ($ETCO_2$)	Cardiac arrest
Skeletal muscle rigidity	Disseminated intravascular coagulation
Muscle spasm	Myoglobinuria
Tachycardia	Elevated creatine phosphokinase
Metabolic and respiratory acidosis	Elevated temperature
Tachypnea	Hypocalcemia or hypercalcemia
Sweating	Mottled cyanosis

Sources: Neacsu A. Malignant hyperthermia. *Nurs Stand* 2006 Mar 22;20(28):51-7; McNeil B. Malignant hyperthermia. *Br J Perioper Nurs* 2005 Sep;15(9):376-7, 379-82; Ali SZ, Taguchi A, Rosenberg H. Malignant hyperthermia. *Best Pract Res Clin Anaesthesiol* 2003 Dec;17(4):519-33.

Malignant Hyperthermia

Malignant Neuroleptic Syndrome



– Dantrolene or bromocriptine (dopamine agonist) seem to be effective in (uncontrolled) studies

Fever in specific patients

- Fever in the Neutropenic patients
- Fever in the Diabetic patients
- Fever in the Alcoholic patients
- Fever in intravenous drug users
- Fever in the HIV infected patients
- Fever in the patients with splenectomy

Fever in the alcoholic patients

- Alcohol withdrawal
- Delirium tremens
- Hepatitis
- Pancreatitis
- Subarachnoid hemorrhage
- Pneumonia (aspiration)
- TBC
- Spontaneous bacterial peritonitis (cirrhosis)
- Sepsis

Fever in the intravenous drug users

- Cellulites at injection sites
- Septic pulmonary emboli
- Pyrogenic reaction
- Viral hepatitis
- Infective endocarditis (right side valves)
- Pneumonia
- HIV
- Tetanus
- TBC

Fever of Unknown Origin

In English:

FUO (Fever of Unknown Origin)

FUO cause ?

The commonest cause of FUO is:

a) A common disease presenting in an atypical way
b) A rare disease presenting in atypical way
c) A common disease presenting typically
d) A rare disease presenting typically

FUO cause

The commonest cause of FUO is:

a) A common disease presenting in an atypical way
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c) A common disease presenting typically
d) A rare disease presenting typically

FUO classification

Classification of Fever of Unknown Origin (FUO)

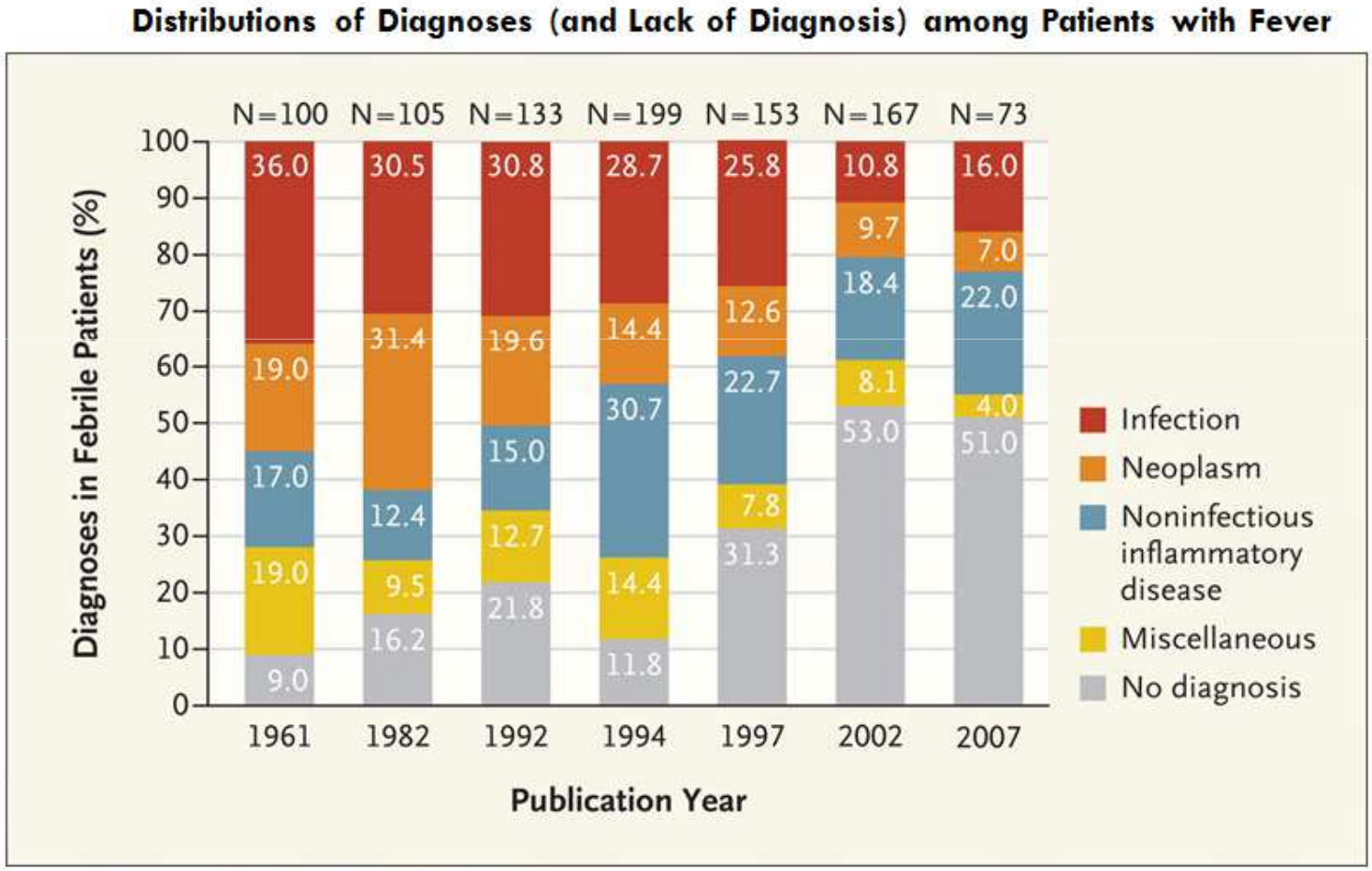
Category of FUO	*Definition*	*Common etiologies*
Classic	Temperature >38.3°C (100.9°F) Duration of >3 weeks Evaluation of at least 3 outpatient visits or 3 days in hospital	Infection, malignancy, collagen vascular disease
Nosocomial	Temperature >38.3°C Patient hospitalized ≥24 hours but no fever or incubating on admission Evaluation of at least 3 days	*Clostridium difficile* enterocolitis, drug-induced, pulmonary embolism, septic thrombophlebitis, sinusitis
Immune deficient (neutropenic)	Temperature >38.3°C Neutrophil count ≤500 per mm^3 Evaluation of at least 3 days	Opportunistic bacterial infections, aspergillosis, candidiasis, herpes virus
HIV-associated	Temperature >38.3°C Duration of >4 weeks for outpatients, >3 days for inpatients HIV infection confirmed	Cytomegalovirus, *Mycobacterium avium-intracellulare* complex, *Pneumocystis carinii* pneumonia, drug-induced,Kaposi's sarcoma, lymphoma

Classic FUO

Definition:

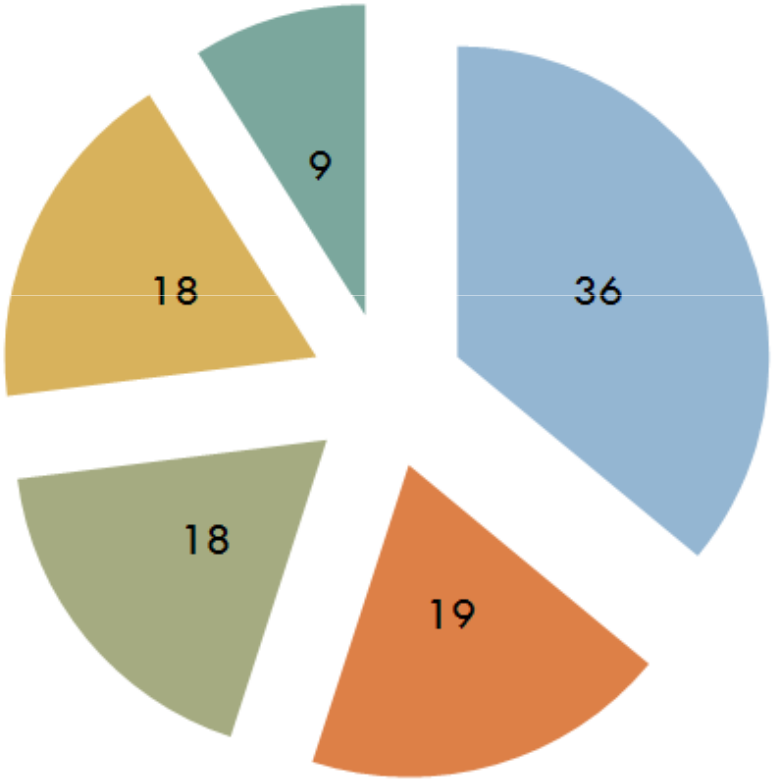
1. Fever of 38.3°C or higher on several occasions
2. Fever of more than 3 weeks duration
3. Diagnosis uncertain, despite appropriate investigations after at least 3 outpatient visits or at least 1 week in hospital

Classic FUO epidemiologic trend



Horowitz HW. N Engl J Med 2013;368:197-199.

Classic FUO epidemiology



Etiology of FUO in 1961 Petersdorf and Beeson Case Series

Most Common Infections:
(in order of frequency)

- Mycobacterial disease
- Rheumatic fever
- Endocarditis
- Abdominal abscess

Common Etiologies of Fever of Unknown Origin

Infections
Tuberculosis (especially extrapulmonary)
Abdominal abscesses
Pelvic abscesses
Dental abscesses
Endocarditis
Osteomyelitis
Sinusitis
Cytomegalovirus
Epstein-Barr virus
Human immunodeficiency virus
Lyme disease
Prostatitis
Sinusitis

Malignancies
Chronic leukemia
Lymphoma
Metastatic cancers
Renal cell carcinoma
Colon carcinoma
Hepatoma
Myelodysplastic syndromes
Pancreatic carcinoma
Sarcomas

Autoimmune conditions
Adult Still's disease
Polymyalgia rheumatica
Temporal arteritis
Rheumatoid arthritis
Rheumatoid fever
Inflammatory bowel disease
Reiter's syndrome
Systemic lupus erythematosus
Vasculitides

Miscellaneous
Drug-induced fever
Complications from cirrhosis
Factitious fever
Hepatitis (alcoholic, granulomatous, or lupoid)
Deep venous thrombosis
Sarcoidosis

Malignancies commonly associated with FUO

- Hodgkin’s disease
- Non-hodgkin’s lymphoma
- Leukemia
- Renal cell carcinoma
- Hepatoma
- Colon carcinoma

Miscellaneous causes of FUO

- Drug fever
- Factitious fever
- Familial Mediterranean Fever
- Recurrent pulmonary emboli
- Subacute thyroiditis

Drug induced fever

Agents Commonly Associated with Drug-Induced Fever

Allopurinol (Zyloprim)
Captopril (Capoten)
Cimetidine (Tagamet)
Clofibrate (Atromid-S)
Erythromycin
Heparin
Hydralazine (Apresoline)
Hydrochlorothiazide (Esidrix)
Isoniazid
Meperidine (Demerol)
Methyldopa (Aldomet)
Nifedipine (Procardia)
Nitrofurantoin (Furadantin)
Penicillin
Phenytoin (Dilantin)
Procainamide (Pronestyl)
Quinidine

FACTITIOUS FEVER

- This diagnosis should be considered in any FUO, especially in:
  - More often young women
  - Persons with medical training
  - If the patients is clinically well
  - Disparity between temperature and pulse
  - Absence of the normal diurnal pattern

Aetiology of fever of unknown origin in Elderly vs Young patients

Etiology	Elderly (n = 204)	Young (n = 152)
Infection	72 (35)	33 (21)
Viral	1 (.05)	8 (5)
Tuberculosis	20 (10)	4 (3)
Abscess	25 (12)	6 (4)
Endocarditis	14 (7)	2 (1)
Other	12 (6)	13 (9)
Multisystem disease[a]	57 (28)	27 (17)
Tumor	38 (19)	8 (5)

NOTE. Data are no. (%) of patients. This table is adapted from the comparative study in [41].

[a] In descending order of frequency [41]: temporal arteritis, polymyalgia rheumatica, Wegener's granulomatosis, polyarteritis nodosa, rheumatoid arthritis, and sarcoidosis.

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Minimal Initial Diagnostic Workup in FUO

- **Comprehensive history !**
- **Physical examination !**

- **CBC + Routine blood chemistry**
- **Chest radiography**
- **Urine analysis and microscopy**
- **Urine cultures**
- Blood (x 3)
- Blood film reviewed by hematopathologist
- Antinuclear antibodies, rheumatoid factor
- CMV IgM antibodies
- HIV antibody
- Hepatitis serology (if abnormal Liver FTs)

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History in FUO

- Contact with other people with similar symptoms
- Sexual history
- Exposure to pets and other animals
- Recent travel
- Family history
- Work environment
- Past medical history and list of medications
  - Include OTC drugs

Diagnostic Imaging in FUO

Diagnostic Imaging in Patients with FUO

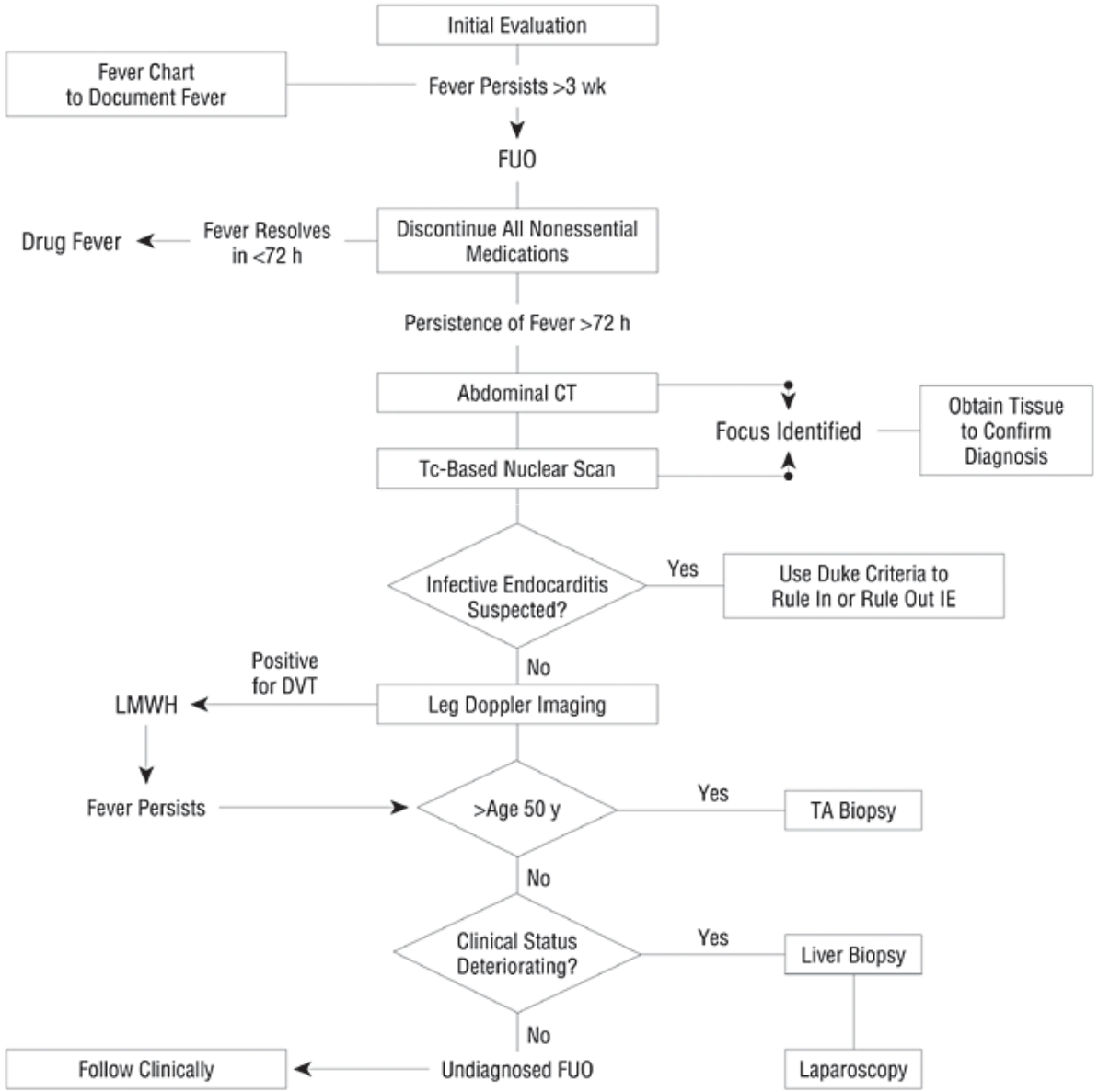
Imaging	*Possible diagnoses*
Chest radiograph	Tuberculosis, malignancy, *Pneumocystis carinii* pneumonia
CT of abdomen or pelvis with contrast agent	Abscess, malignancy
Gallium 67 scan	Infection, malignancy
Indium-labeled leukocytes	Occult septicemia
Technetium Tc 99m	Acute infection and inflammation of bones and soft tissue
MRI of brain	Malignancy, autoimmune conditions
PET scan	Malignancy, inflammation
Transthoracic or transesophageal echocardiography	Bacterial endocarditis
Venous Doppler study	Venous thrombosis

FUO = fever of unknown origin; CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

Invasive procedures in FUO

- Biopsies:
  - Bone marrow
  - Skin lesion
  - Lymph nodes
  - Liver
  - Temporal artery

Proposed Approach to FUO



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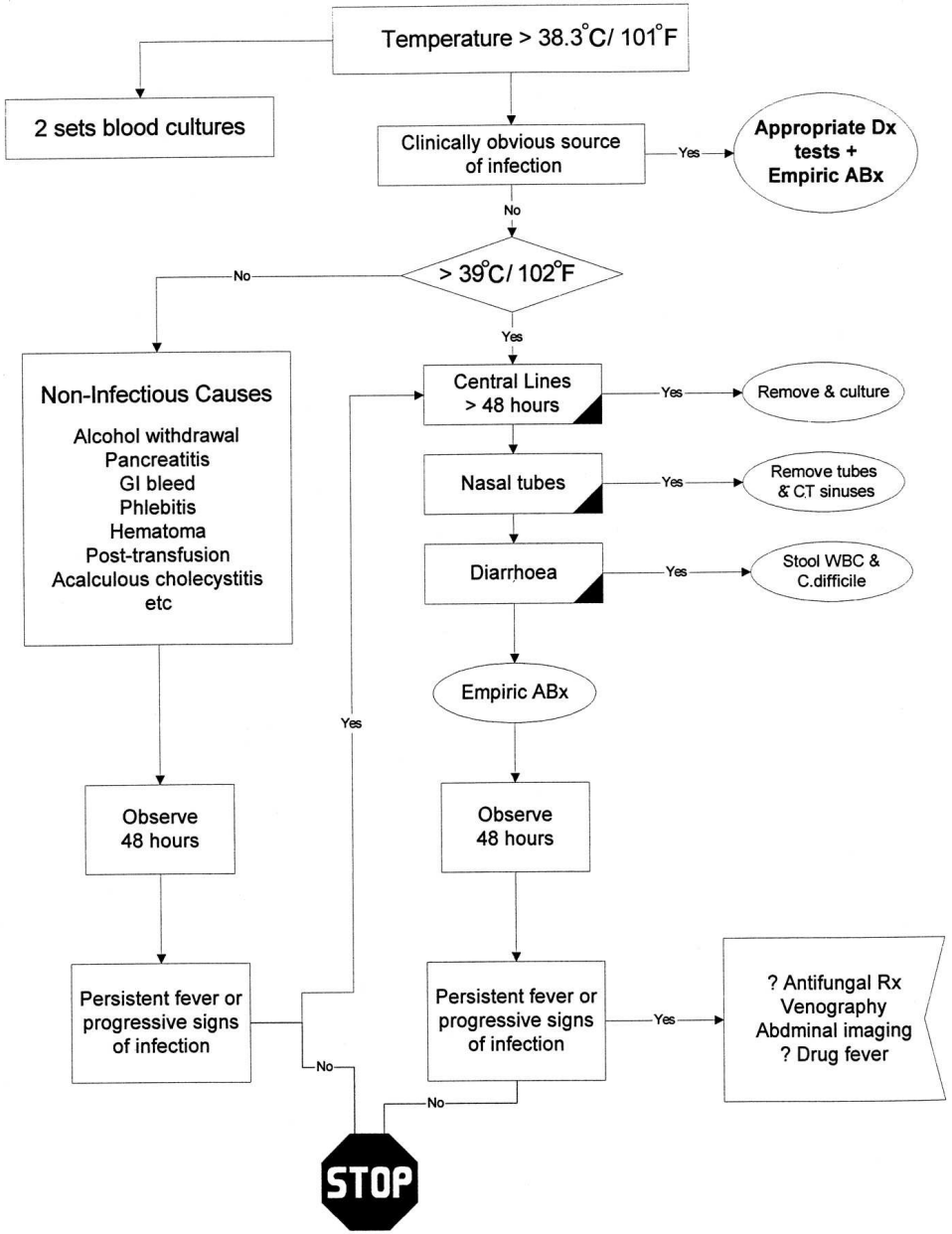
Approach to Fever in the ICU

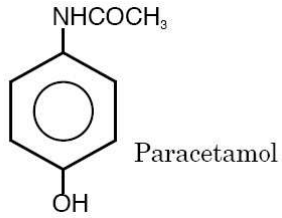


Marik, P. E. Chest

Treatment of Fever

- Antipyretics can be given if a patient (particularly a child or an elderly) is really uncomfortable.
- These include: ***Acetaminophen (Paracetamol), Aspirin, and Propionic acid derivatives***
- Aspirin should not be given to a child or adolescent with a fever since this drug has been linked to an increased risk of ***Reye's syndrome*** (affecting liver and brain with rapid development of life-threatening neurological symptoms)
- Bathing a patient in cool water can also help to alleviate a high fever.

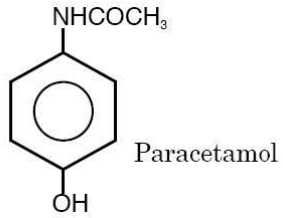
PARACETAMOL



Paracetamol

- Is a non-prescription drug commonly used as an aspirin substitute because it does not cause nausea, vomiting, or GI bleeding, and it does not interfere with blood clotting.
- It is equal to aspirin in analgesic and antipyretic effects, but *it lacks anti-inflammatory activity*.
- Acetaminophen is well absorbed with oral administration and peak plasma concentrations are reached within 30-120 minutes.
- Duration of action: 3 to 4 hours.

PARACETAMOL



Paracetamol

		Routes and Dosage Ranges		
Generic/Trade Name	**Indications for Use**	Adults	Children	**Comments**
Acetaminophen (Tylenol, others)	Pain Fever	PO 325–650 mg q4–6h, or 1000 mg three or four times per day; maximum 4 g/d	PO 10 mg/kg or according to age as follows: 0–3 mo, 40 mg; 4–11 mo, 80 mg; 1–2 y, 120 mg; 2–3 y, 160 mg; 4–5 y, 240 mg; 6–8 y, 320 mg; 9–10 y, 400 mg; 11 y, 480 mg. Doses may be given q4–6h to a maximum of 5 doses in 24 h.	**Warning:** Overdoses may cause fatal liver damage. Maximum recommended dose for adults is 4 g/d, from all sources. Parents and caregivers should ask pediatricians about the amounts of acetaminophen children may take safely.
		Rectal suppository 650 mg q4–6h, maximum of 6 in 24 h	Rectal suppository: age under 3 y, consult physician; age 3–6 y, 120 mg q4–6h, maximum, 720 mg in 24 h; age 6–12 y, 325 mg q4–6h, maximum 2.6 g in 24 h	

ASPIRIN

- Aspirin is the prototype of the *analgesic–antipyretic–anti-inflammatory* drugs and the most commonly used salicylate.
- It is effective in pain of low to moderate intensity, involving the skin, muscles, joints, and other connective tissue.
- It is useful in inflammatory disorders, such as arthritis, but many people prefer drugs that cause less gastric irritation.

ASPIRIN

- Regular aspirin tablets are well absorbed after oral administration
- Their action starts within 15-30 minutes, peaks in 1 to 2 hours, and lasts 4 to 6 hours.
- Taking aspirin with food slows absorption, but also decreases gastric irritation.
- Absorption of enteric-coated aspirin and rectal suppositories is slower and less complete.

ASPIRIN

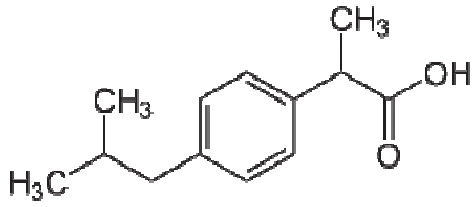
Aspirin	Pain, fever Osteoarthritis (OA), rheumatoid arthritis (RA) Prophylaxis of myocardial infarction (MI), transient ischemic attacks (TIAs) and stroke in men Rheumatic fever	*Pain, fever:* PO 325–650 mg q4h PRN; usual single dose, 650 mg *OA, RA:* PO 2–6 g/d in divided doses *Prophylaxis of MI, TIA, and stroke:* PO 81–325 mg/d	*Pain, fever:* PO 10–15 mg/kg q4h, up to 60–80 mg/kg/d. *Recommended doses for weight:* 24–35 lb (10.6–15.9 kg), 162 mg; 36–47 lb (16–21.4 kg), 243 mg; 48–59 lb (21.5–26.8 kg), 324 mg;	Therapeutic serum level of salicylate is 100–300 mcg/mL for treatment of arthritis and rheumatic fever; toxicity occurs at levels above 300 mcg/mL.

Propionic acid derivatives

- **Ibuprofen, Ketoprofen, Naproxen**

- Also available OTC
- These drugs are usually better tolerated than aspirin, they are much more expensive and may cause all the adverse effects associated with aspirin and other prostaglandin inhibitors

Ibuprofen



- Ibuprofen is well absorbed with oral administration.
- Its action starts in about 30 minutes, peaks in 1-2 hours, and lasts 4 to 6 hours.
- The drug is highly bound (about 99%) to plasma proteins and has a half-life of about 2 hours.
- It is metabolized in the liver and excreted through the kidneys.
- It is available by prescription and OTC, in tablets, capsules, oral suspension, and oral drops, for use by adults and children.

Treatment of Fever

- Acetaminophen can cause liver damage
- Ibuprofen is a relative of aspirin that can cause gastrointestinal upset and bleeding.

Total daily dosage should not exced:

- Paracetamol above 4 doses of 1000 mg each
- Ibuprofen above 2400 mg

Treatment of Fever

- Some OTC products contain an analgesic/antipyretic as a single ingredient, while others combine an analgesic/antipyretic with a nasal decongestant, an antihistamine, or a cough suppressant.
- Products listed in the ***headaches, body aches, fever, and flu-like symptoms category*** contain analgesics/antipyretics either alone or in combination with other ingredients to treat cold/flu/allergy symptoms.