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Alterations in Body Temperature: The Adult Patient with a Fever

Joe Lex, MD, FAAEM
Temple University Hospital
22 April 2010

Objectives

- Differentiate fever from hyperthermia
- Explain what causes a fever
- Describe an appropriate fever work-up
- Recognize life-threatening causes of fever, both infectious and non-infectious

Objectives

- Explain reasons to either treat or not treat fever
- Describe appropriate methods of treating fever
- Explain how acetaminophen and aspirin reduce fever
- Describe treatment for NMS

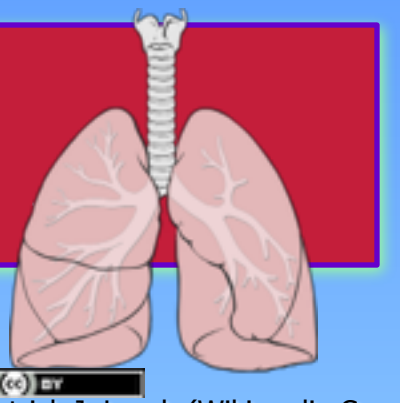
Fever

- 6% of adult visits
- 20 – 40% of pediatric visits
- Benign self-limited diseases
- 10% to 15% of >65 years old
  - 70 – 90% hospitalized
  - 7 – 9% die within one month

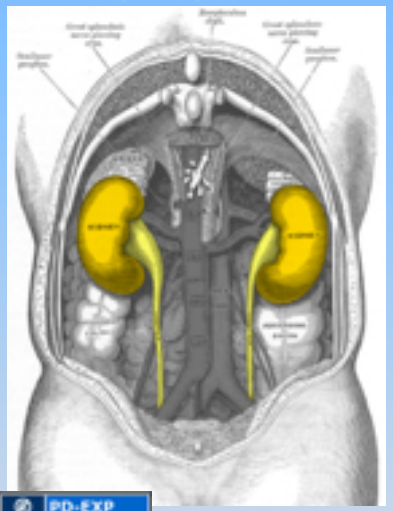
Fever

Three body systems account for more than 80% of infections

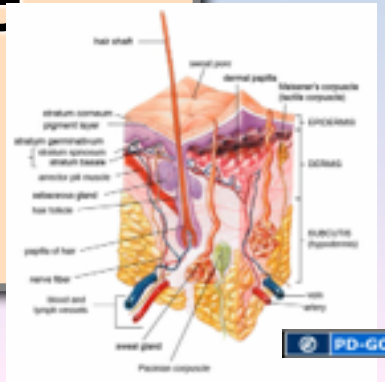
- Respiratory tract
- Urinary tract
- Skin and soft tissue



Patrick J. Lynch (Wikimedia Commons)



Gray's Anatomy (Wikimedia Commons)



US-Gov (Wikipedia)

Hypothalamus

Neurons in preoptic anterior and posterior hypothalamus receive signals…

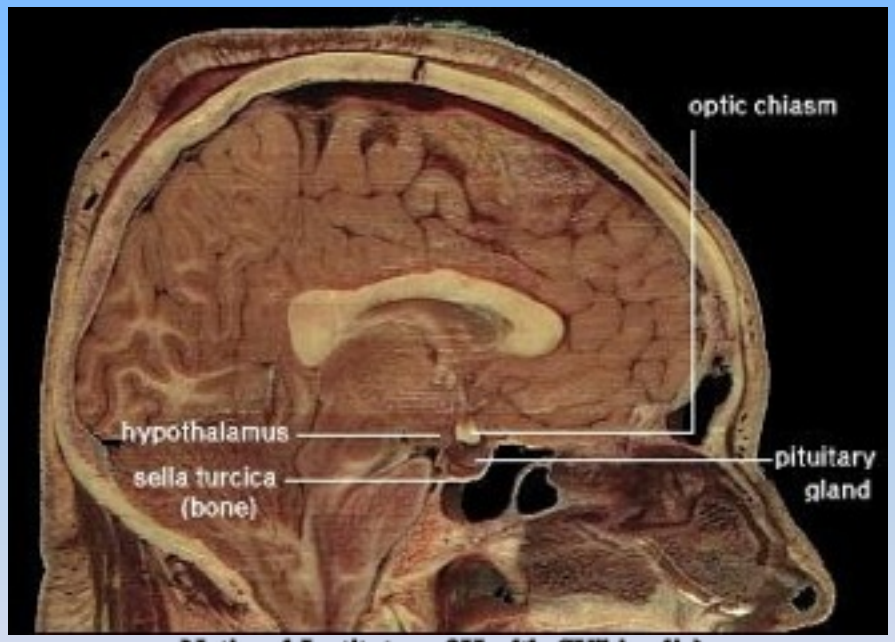
…from peripheral nerves that reflect warmth / cold receptors

…from temperature of blood bathing the region

Hypothalamus

- Signals integrated by thermo-regulatory center to maintain normal temperature
- In neutral environment, human metabolism produces more heat than necessary to maintain core body temperature at 37°C

Hypothalamus



PD-GOV National Institutes of Health (Wikipedia)

- Hypothalamus controls temperature by causing heat loss

Hypothalamus

- Normal body temperature maintained despite environment
- Hypothalamic thermoregulatory center balances heat production from metabolic activity in muscle and liver with heat dissipation from skin and lungs

Normal Temperature

- In healthy 18 to 40 year-olds, mean oral temperature 36.8° ± 0.4°C (98.2° ± 0.7°F)
- Lowest 6 a.m., highest 4 - 6 p.m.
- Maximum normal oral:
  - 37.2°C (98.9°F) at 6 a.m.
  - 37.7°C (99.9°F) at 4 p.m.

Fever

- Fever: morning temperature >37.2°C (98.9°F) or evening temperature >37.7°C (99.9°F)
- Normal daily variation: 0.5°C (0.9°F)
- If recovering from virus, can be 1.0°C

Location, Location, Location

- Rectal temperature higher than oral by about 0.4°C (0.7°F)
- Distal esophageal best core temperature
- Freshly-voided urine also accurate

Location, Location, Location

- Ear thermometers measure radiant heat energy from tympanic membrane, ear canal, frequently inaccurate

 jim846 (Flickr)

Physiologic Elevation

- Women: morning temperature lower in 2 weeks before ovulation, then rises about 0.6°C (1°F) with ovulation and stays there until menses
- Body temperature also elevated in postprandial state

Physiologic Elevation

- Daily temperature variation fixed in early childhood
- Elderly have reduced ability to develop fever, may have modest fever even in severe infections

Fever vs. Hyperthermia

Fever vs. Hyperthermia

- Fever: ↑ body temperature that exceeds normal daily variation
- Occurs in conjunction with ↑ in hypothalamic set point
- Like resetting home thermostat to a higher level in order to raise ambient room temperature

Fever vs. Hyperthermia

- Hypothalamic set point raised ➔ activates vasomotor center neurons ➔ vasoconstriction first noted in hands and feet
- Blood shunted from periphery ➔ ⬇ heat loss from skin ➔ feels cold

Fever vs. Hyperthermia

- Shivering ↑ heat production from muscles
- If heat conservation mechanisms raise blood temperature enough, shivering not required
- ↑ heat production from liver

Fever vs. Hyperthermia

- In humans, behavioral instinct (e.g., putting on more clothing or bedding) leads to reduction of exposed surfaces ➔ helps raise body temperature

Fever vs. Hyperthermia

- Heat production (shivering, ↑ metabolic activity) and heat conservation (vasoconstriction) continue until temperature of blood bathing hypothalamic neurons matches new thermostat setting

Fever vs. Hyperthermia

- Hypothalamus maintains febrile level by same mechanisms operative in afebrile state
- When reset downward ➔ heat lost through vasodilation and sweating

Lamiot (Wikimedia Commons)

Fever vs. Hyperthermia

- Fever >41.5°C (106.7°F) ➔ hyperpyrexia
- Can develop in severe infections
- Most common in patients with CNS hemorrhages
- Preantibiotic era: fever due to infection rarely >106°F

Fever vs. Hyperthermia

- "Hypothalamic fever" caused by abnormal hypothalamic function
- Most patients with hypothalamic damage have subnormal body temperature

Fever vs. Hyperthermia

Hyperthermia is characterized by a normothermic setting of thermoregulatory center in conjunction with uncontrolled increase in body temperature that exceeds the body's ability to lose heat

Fever vs. Hyperthermia

- Exogenous heat exposure or endogenous heat production
- Over-insulating clothing ↑ core temperature
- Work or exercise in hot environment ➔ heat production > peripheral heat loss

Fever vs. Hyperthermia

- Thermoregulatory failure with warm environment ➔ exertional or nonexertional (classic) heat stroke

1. SWEAT
2. FAINT
3. DIE

HEAT KILLS

Fever vs. Hyperthermia

- Classic heat stroke: elderly during heat waves
  - Chicago: July 1995, 465 deaths certified as heat related
  - Europe: Summer 2003, estimated 17,000 additional deaths

Some Causes of Nonexertional Hyperthermia

- Anticholinergics, including antihistamines
- Antiparkinsonian drugs
- Diuretics
- Phenothiazines
- Amphetamines
- Monoamine oxidase (MAO) inhibitors
- Cocaine
- Phencyclidine
- Tricyclic antidepressants
- LSD

Some Causes of Nonexertional Hyperthermia

- Malignant hyperthermia:
  - Genetically unstable sarcoplasmic reticulum
  - Massive calcium release after inhalational anesthetic or succinylcholine
- Endocrinopathy
  - Thyrotoxicosis
  - Pheochromo-cytoma

Neuroleptic Malignant Syndrome

- Muscle rigidity, autonomic dysregulation, hyperthermia
- Inhibition of central dopamine receptors in hypothalamus ➔ heat generation and ⬇ heat dissipation ⬆

Neuroleptic Malignant Syndrome

- Phenothiazines (Thorazine®, Compazine®, Mellaril®)
- Butyrophenones (Haldol®)
- Thiothixene (Navane®)

- Dibenzoxazepines (Loxitane®)
- Dibenzodiazepines (Clozaril®)
- Indoles (Moban®)
- Metoclopramide (Reglan®)

…and many others

Drug-Induced Hyperthermia

- Prescription psychotropic drugs
  - monoamine oxidase inhibitors,
  - tricyclic antidepressants
  - amphetamines
- Illicit drugs
  - phencyclidine
  - lysergic acid diethylamide (LSD)
  - cocaine

Malignant Hyperthermia

- Inherited abnormality of skeletal-muscle sarcoplasmic reticulum
- Halothane or succinylcholine causes rapid ↑ intracellular Ca^{++}
- ↑ temperature, ↑ muscle metabolism, rigidity, acidosis, rhabdomyolysis, cardiovascular instability

Fever vs. Hyperthermia

- Hyperthermia can be rapidly fatal
- No rapid way to differentiate from fever
- Physical aspects may be a clue
  - History of drug that blocks sweat
  - Skin hot and dry
  - No response to antipyretics

Pyrogen

- Any substance that causes fever
- Exogenous: microbial products or toxins, whole microorganisms
  - Classic: lipopolysaccharide endotoxin from all Gram-negatives
  - Enterotoxin from Staphylococcus aureus and group A and B strep toxins (superantigens)

Pyrogenic Cytokines

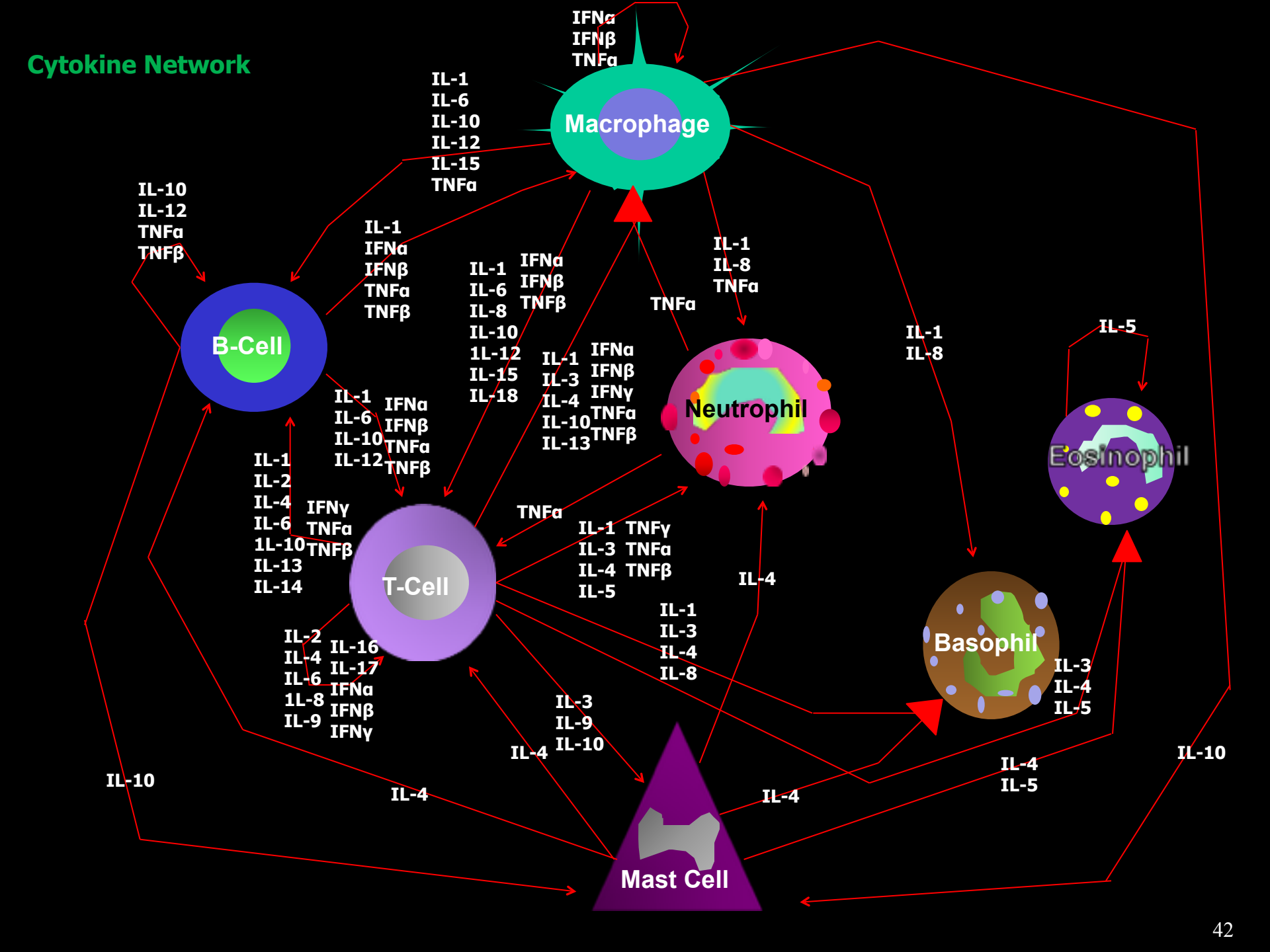
- Cytokines: small proteins that regulate immune, inflammatory, and hematopoietic processes
- Endogenous pyrogens IL-1, IL-6, tumor necrosis factor (TNF), ciliary neurotropic factor (CNTF), and interferon (IFN) all known to cause fever

Pyrogenic Cytokines

- Induced exogenous pyrogens, mostly from bacterial or fungal sources
- Viruses induce pyrogenic cytokines by infecting cells

Pyrogenic Cytokines

- Inflammation, trauma, tissue necrosis, and antigen-antibody complexes cause production of IL-1, TNF, and IL-6, which trigger hypothalamus to raise set point to febrile levels
- Cellular sources: monocytes, neutrophils, lymphocytes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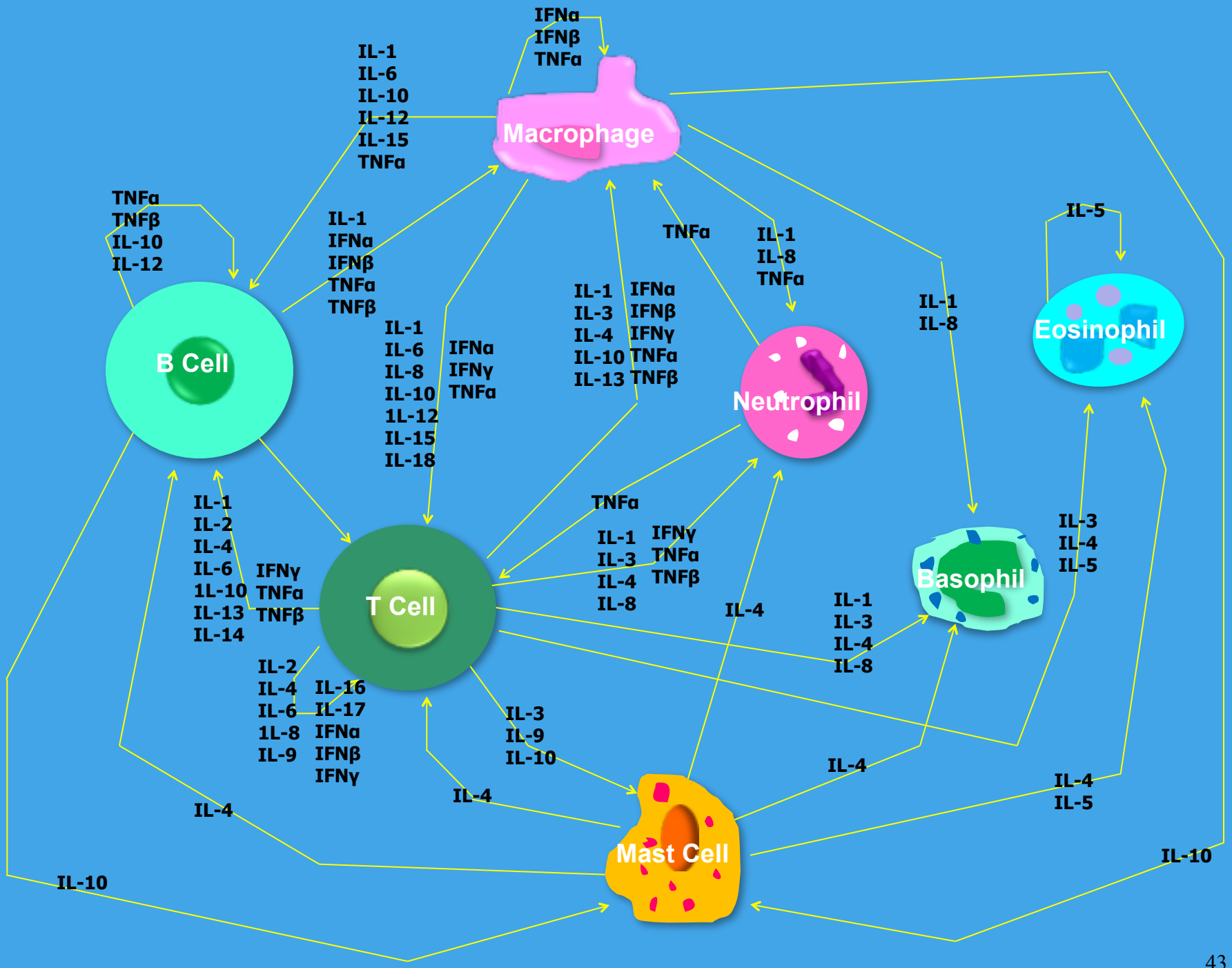
Mast Cell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Mast Cell
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How to Make a Fever

- IL-1, IL-6, and TNF released into systemic circulation
- Induce central and peripheral synthesis of PGE2
  - Peripheral PGE2 causes nonspecific myalgias, arthralgias
  - Central PGE2 raises hypothalamic set point

How to Make a Fever

- PGE2 not a neurotransmitter
- Triggers receptor on glial cells ➔ rapid release of cyclic adenosine 5'-monophosphate (cAMP, which is neurotransmitter)
- Activates neuronal endings from the thermoregulatory center

Working Up a Febrile Patient

Taking a History

"It is in the diagnosis of a febrile illness that the science and art of medicine come together. In no other clinical situation is a meticulous history more important…"

William Osler?

Harvey Cushing?

18th edition Harrison's

Taking a History

"Painstaking attention must be paid to the chronology of symptoms in relation to the use of prescription drugs (including drugs or herbs taken without a physician's supervision) or treatments such as surgical or dental procedures…"

Taking a History

- Occupational history: exposure to…

…animals?

…toxic fumes?

…potential infectious agents?

- Other febrile individuals at home, work, or school?
- Prosthetic materials?
- Implanted devices?

Taking a History

- Travel history, including military service
- Unusual hobbies
- Sexual orientation
  - Practices
  - Precautions

- Dietary
  - raw or poorly cooked meat
  - raw fish
  - unpasteurized milk or cheese
- Household pets

Taking a History

- Tobacco, marijuana, intravenous drugs, alcohol
- Trauma
- Animal bites
- Tick or other insect bites

- Prior transfusion
- Immunizations
- Drug allergies or hypersensitivity

Taking a History

Family history

- Tuberculosis,
- Other febrile or infectious diseases
- Arthritis / collagen vascular disease

Unusual familial symptomatology:

- Deafness
- Urticaria
- Fevers and polyserositis
- Bone pain
- Anemia

Taking a History

Ethnic origin

- Hemoglobinopathies: more common in African-American
- Familial Mediterranean fever: more common in Turks, Arabs, Armenians, Sephardic Jews

Fever Pattern

- Usual times of peak and trough may be reversed in typhoid fever and disseminated tuberculosis
- Temperature-pulse dissociation (relative bradycardia) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever

Fever Pattern

- Normothermia, hypothermia despite infection: newborns, elderly, patients with chronic renal failure, and patients taking glucocorticoids
- Hypothermia observed in septic shock

Fever Pattern

- Relapsing fevers: separated by intervals of normal temperature
- Tertian fever: paroxysms on 1st and 3rd days (e.g. Plasmodium vivax)
- Quartan fever: on 1st and 4th (Plasmodium malariae)

Fever Pattern

- Borrelia infections and rat-bite fever: several days of fever followed by a several afebrile days, then relapse of fever days
- Pel-Ebstein fever: 3 to 10 days fever followed by afebrile 3 to 10 days
  - Hodgkin's disease, lymphomas

Fever Pattern

- Cyclic neutropenia: fevers every 21 days accompany neutropenia
- Familial Mediterranean fever: no periodicity

Physical Examination

- All vital signs are relevant
- Temperature may be oral or rectal, but consistent site used
  - Axillary temperatures unreliable
- Daily physical examination until diagnosis certain and anticipated response achieved

Physical Examination

- Special attention to skin, lymph nodes, eyes, nail beds, cardiovascular system, chest, abdomen, musculoskeletal system, and nervous system.
- Rectal examination imperative

Physical Examination

- Penis, prostate, scrotum, and testes; retract foreskin
- Pelvic examination: pelvic inflammatory disease, tubo-ovarian abscess

Generating a Differential

Organ system	Critical Diagnosis
Respiratory	Pneumonia with respiratory failure
Gastrointestinal	Peritonitis
Neurologic	Meningitis Cavernous sinus thrombosis
Systemic	Sepsis Meningococcus

Generating a Differential

Organ system	Emergent Diagnosis
Respiratory	Bacterial pneumonia Peritonsillar abscess Retropharyngeal abscess Epiglottitis
Cardiovascular	Endocarditis Pericarditis

Generating a Differential

Organ system	Emergent Diagnosis
Gastrointestinal	Appendicitis Cholecystitis Diverticulitis Intraabdominal abscess
Genitourinary	Pyelonephritis Tuboovarian abscess Pelvic inflammatory disease

Generating a Differential

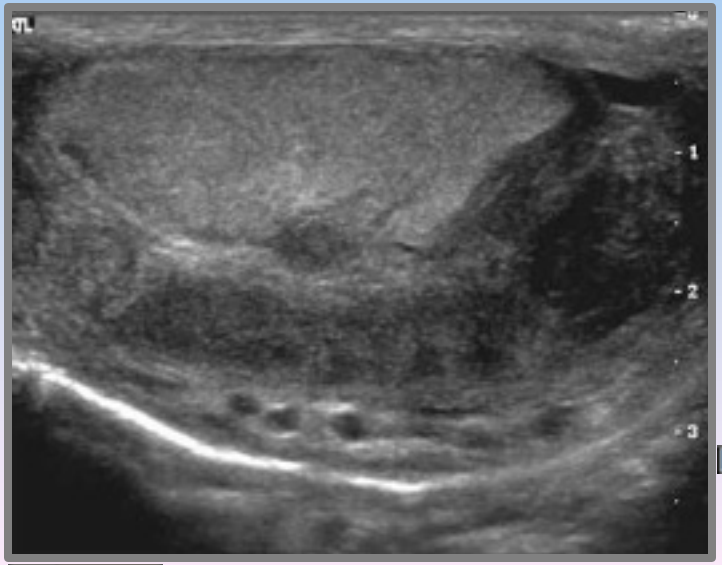
Organ system	Emergent Diagnosis
Neurologic	Encephalitis Brain Abscess
Soft tissue	Cellulitis Infected decubitus ulcer Soft tissue abscess

Generating a Differential

Organ system	Nonemergent Diagnosis
Respiratory	Otitis media Sinusitis Pharyngitis Bronchitis Influenza Tuberculosis
Gastrointestinal	Colitis / enteritis

Generating a Differential

Organ system	Nonemergent Diagnosis
Genitourinary	Cystitis Epididymitis Prostatitis



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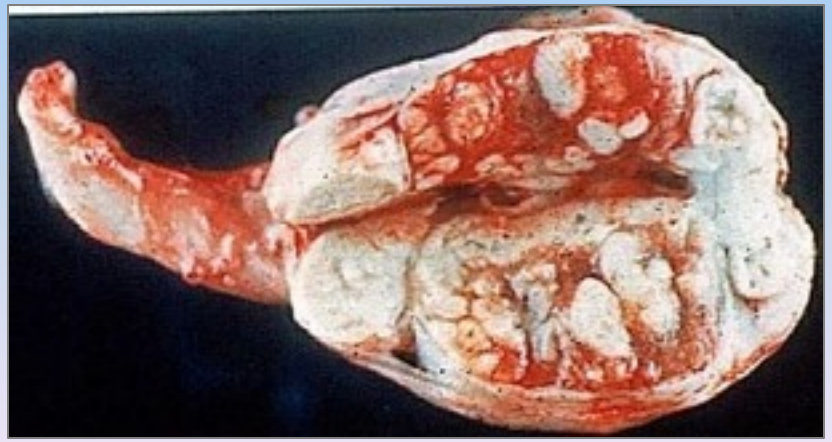

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Noninfectious – Critical

- Acute myocardial infarction
- Pulmonary embolus or infarct
- Intracranial hemorrhage
- Cerebrovascular accident
- Neuroleptic-malignant syndrome
- Thyroid storm
- Acute adrenal insufficiency
- Transfusion reaction
- Pulmonary edema

Noninfectious – Emergent

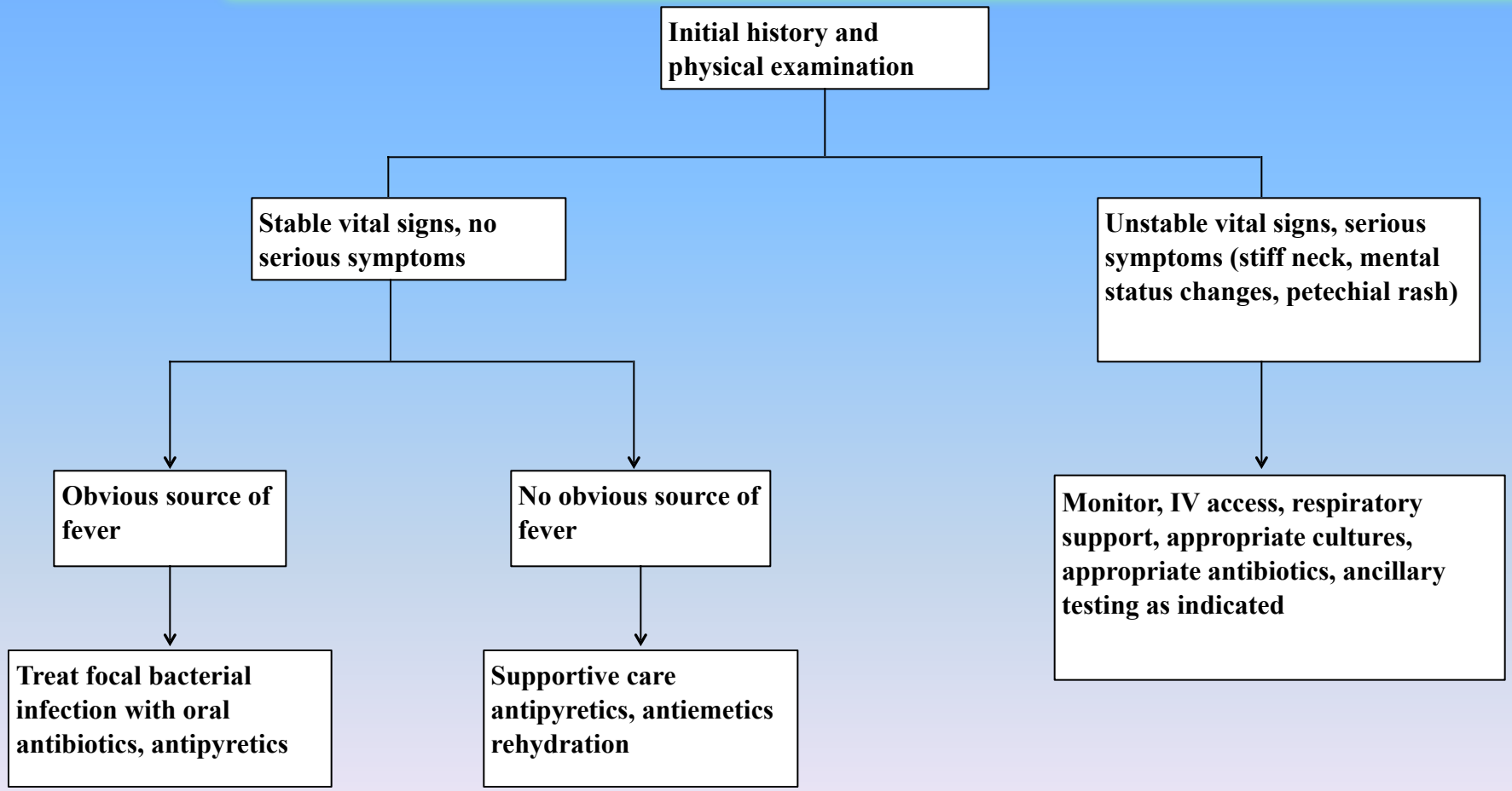
- Congestive heart failure
- Dehydration
- Recent seizure
- Sickle-cell disease

- Transplant rejection
- Pancreatitis
- Deep venous thrombosis

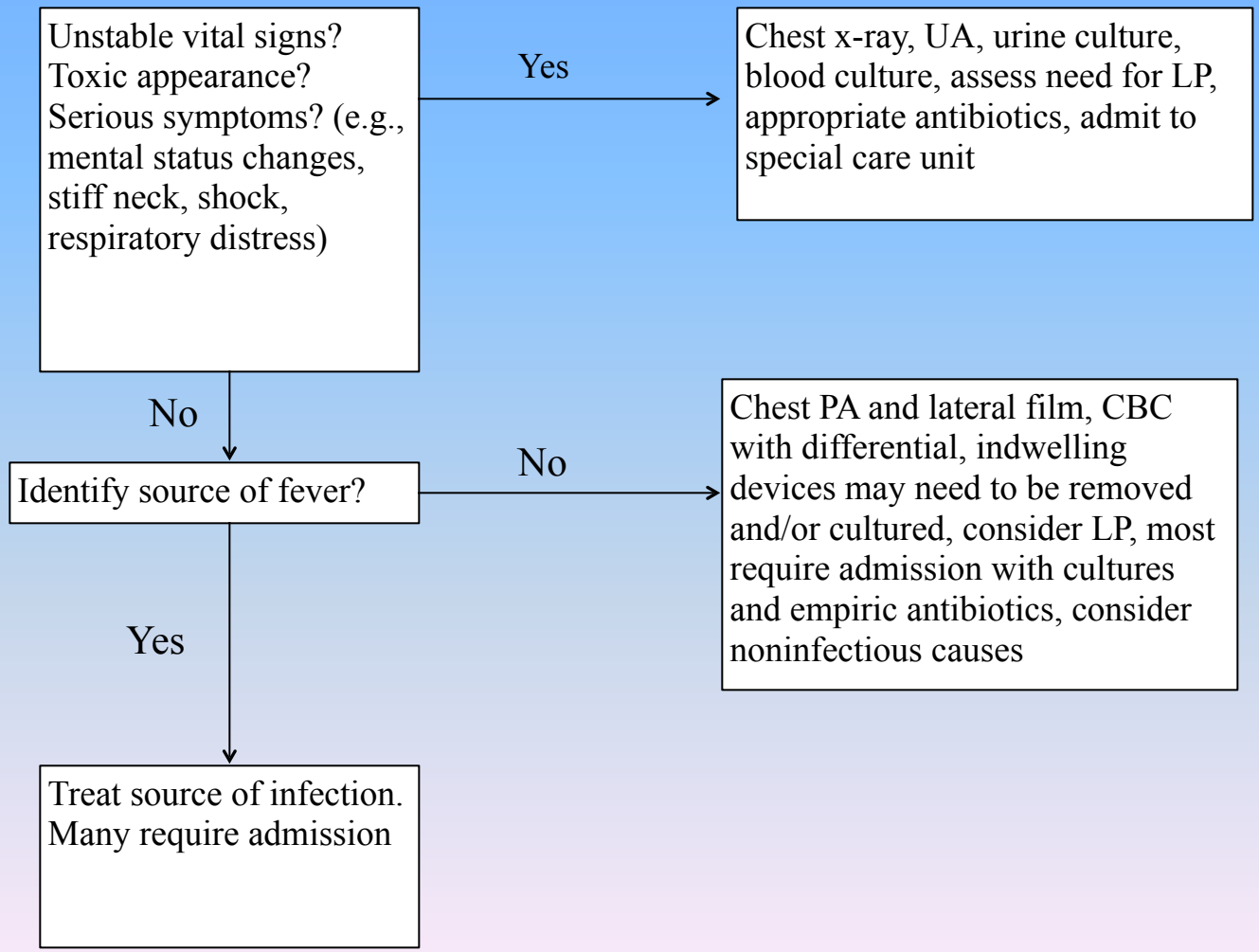
Noninfectious – Nonemergent

- Drug fever
- Malignancy
- Gout
- Sarcoidosis
- Crohn's disease
- Postmyocardiotomy syndrome

Algorithm: Young and Healthy



Algorithm: Elderly or Chronically Ill



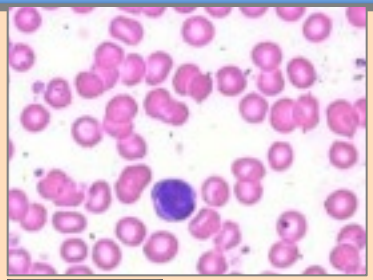
Laboratory Studies

- Many diagnostic possibilities
- If history, epidemiology, or physical examination suggests more than simple viral illness or streptococcal pharyngitis, then laboratory testing is indicated

Laboratory Studies

- Tempo and complexity of work-up depends on pace of illness, diagnostic considerations, immune status of host
- If findings focal, laboratory examination can be focused
- If fever undifferentiated, more studies warranted

Complete Blood Count

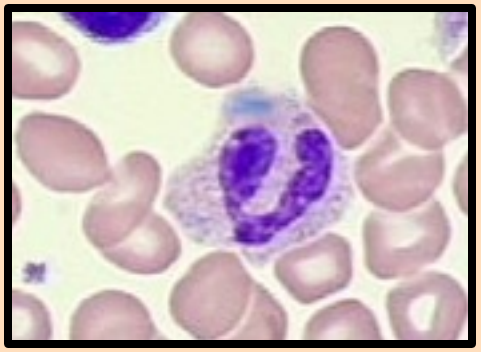


Source Undetermined

- Highly insensitive
- Highly nonspecific
- Most valuable use: ensure adequate immune response (polymorphonuclear neutrophil leukocyte count) in elderly or those with immune compromise

Complete Blood Count

- Manual or automatic differential sensitive to identification of eosinophils, band forms, toxic granulations, and Döhle bodies
- Last three associated with bacterial infections



PD-INEL Source Undetermined

Other CBC Clues

- If febrile illness prolonged, examine smear for malarial or babesial pathogens (where appropriate) as well as classic morphologic features
- Erythrocyte sedimentation rate
- C-reactive protein

Fever and Neutropenia

- Viral infection, particularly parvovirus B19
- Drug reaction
- Systemic lupus erythematosus
- Typhoid
- Brucellosis

- Infiltrative diseases of bone marrow:
  - Lymphoma
  - Leukemia
  - Tuberculosis
  - Histoplasmosis

Fever and Lymphocytosis

- Typhoid
- Brucellosis
- Tuberculosis
- Viral disease

PD-INEL Source Undetermined

Atypical lymphs

- EBV, CMV, HIV
- Dengue
- Rubella
- Varicella
- Measles
- Viral hepatitis.
- Serum sickness

Fever and Other WBCs

Monocytosis

- Typhoid
- Tuberculosis
- Brucellosis
- Lymphoma

Eosinophilia

- Hypersensitivity drug reactions
- Hodgkin's
- Adrenal insufficiency
- Metazoan infections

Other Labs – Possible

- Urinalysis with examination of urine sediment
- Any abnormal fluid accumulation (pleural, peritoneal, joint) needs exam in undiagnosed fever
- Stool for fecal leukocytes, ova, or parasites may be indicated

Other Labs – Possible

- BMP recommended
- Liver function tests if other organ cause not obvious
- Blood, urine, and abnormal fluid collections culture
- Additional labs added as work-up progresses

Other Labs – Possible

- Smears and cultures of throat, urethra, anus, cervix, and vagina
- Sputum for Gram's stain, acid-fast bacillus staining, culture
- CSF if meningismus, severe headache, mental status change

Radiography

- Chest x-ray part of evaluation for significant febrile illness

PD-INEL Source Undetermined

PD-INEL Source Undetermined

Resolution

- Most patients recover without treatment or history, physical examination, and initial studies lead to diagnosis
- Fever 2 to 3 weeks, examination and laboratory tests unrevealing ➔ provisional diagnosis FUO

Treating a Fever

Antipyretics

Antipyretics

- By reducing fever with antipyretic, assume no diagnostic benefit gained by allowing fever to persist
- Daily highs and lows of normal temperature exaggerated in most fevers

Antipyretics

- PGE2 synthesis depends on enzyme cyclooxygenase (COX)
- COX substrate is arachidonic acid released from cell membrane
- Release of arachidonic acid is rate-limiting step
- COX inhibitors: antipyretics

Antipyretics

- Potency correlated with inhibition of brain COX
- Acetaminophen
  - Poor peripheral COX inhibition
  - Poor anti-inflammatory
  - Oxidized in brain by cytochrome p450 ➔ potent COX inhibitor

Acetaminophen

- Discovered 1889 by Karl Morner (8 years before aspirin)
- Principal active metabolite of phenacetin and acetanilid
- As effective as phenacetin, but less toxic
- APC=aspirin/phenacetin/caffeine
- Widespread use after 1949

Acetaminophen

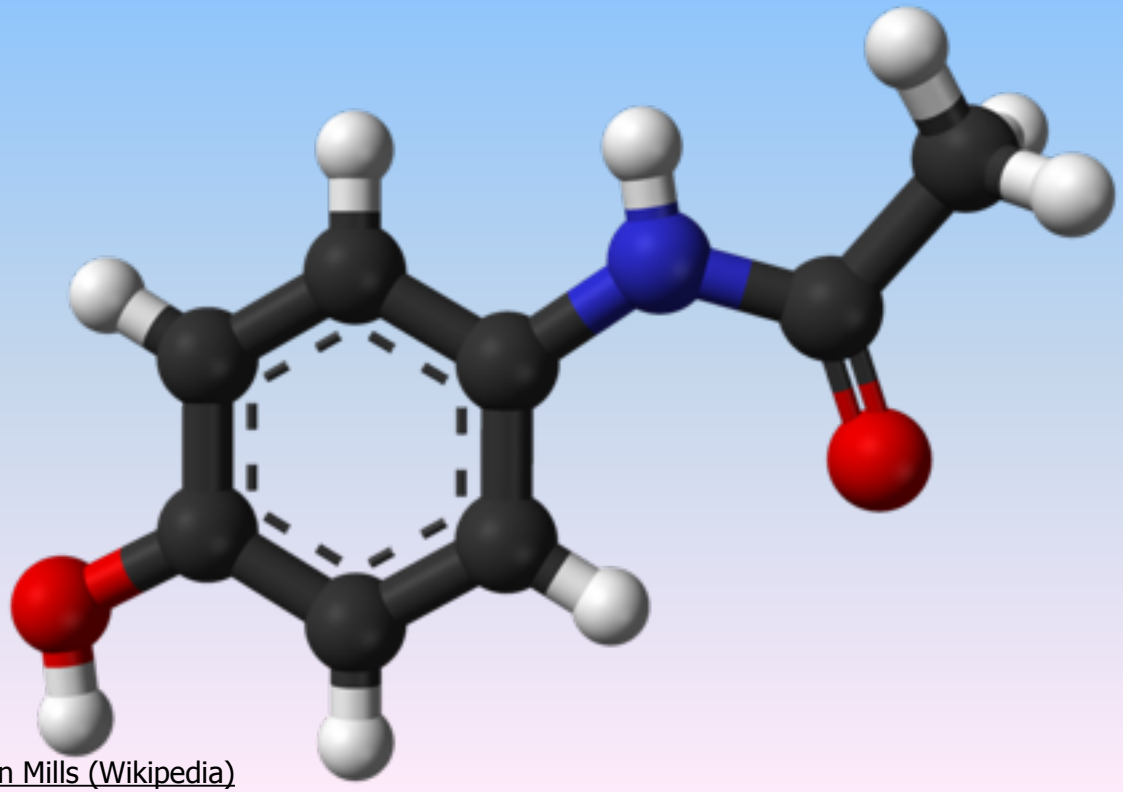
- McNeil Laboratories first sold in 1955 (Tylenol Children's Elixir)
- Package looked like fire truck!

Acetaminophen

- Abenol
- Aceta
- Actamin
- Aminofen
- Anacin-3
- Apacet
- APAP
- Atasol
- Banesin
- Dapa
- Datril
- Exdol
- Feverall
- Genapap
- Genebs
- Halenol
- Liquiprin
- Meda Cap
- Neopap
- Oraphen
- Panadol
- Phenaphen
- Redutemp
- Ridenol
- Robigesic
- Rounox
- Snaplets-FR
- Suppap
- Tapanol
- Tempra
- Tylenol, etc

Acetaminophen

- APAP = N-acetyl-para-aminophenol
- Britain: Paracetamol



Aspirin

 Mosesofmason (Wikipedia)

 Bayer AG (Wikipedia)

Aspirin

- Hippocrates: willow tree leaves for eye diseases and childbirth
- Leviticus: "boughs of goodly trees, … willows of the brook"
- Dioscorides (AD1): "…leaves of willow…excellent formentation for ye Gout…"

Aspirin

- AD 60 Caius Plinius Secundus: poplar bark for sciatica
- 1763 Reverend Edward Stone: willow bark as remedy for agues
- Standard treatments until 1800s
  - Pain: opium
  - Fever: Peruvian cinchona bark

Aspirin

- 1828 Johann Büchner: salicin
- 1838 Raffaele Piria derived salicylaldehyde from salicin, then converted to salicylic acid
- 1874 Heyden Chemical Company produced commercial salicylic acid

Aspirin

- August, 1897: Felix Hoffman, working for Frederick Bayer, synthesized acetylsalicylic acid (ASA)

Aspirin

- A few weeks later, Hoffman synthesized diacetylmorphine
- Initial subjects felt "heroic"
- Bayer sold commercially: "Heroin"
- Aspirin required prescription, heroin sold over the counter

PD-EXP New York Times (Wikipedia)

PD-EXP Mpv_51 (Wikipedia)

Antipyretics

- Oral aspirin and acetaminophen equally effective in reducing fever in humans
- Nonsteroidal anti-inflammatory agents (NSAIDs) also excellent antipyretics

Antipyretics

- Chronic high-dose aspirin or NSAID therapy in arthritis does not reduce normal core body temperature
- Thus, PGE2 appears to play no role in normal thermoregulation

Antipyretics

- Glucocorticoids act at two levels
  - Reduce PGE2 synthesis by inhibiting activity of phospholipase A2, which is needed to release arachidonic acid from the cell membrane
  - Block transcription of mRNA for the pyrogenic cytokines

Antipyretics

- Drugs that interfere with vasoconstriction (phenothiazines) or block muscle contractions can also lower fever
- Not true antipyretics: reduce core temperature independent of hypothalamic control

Comparing Antipyretics

	Analgesia	Anti-Inflammatory	Antipyretic
Ketorolac	0.7	2	0.9
Indomethacin	3	4	21
Diclofenac	8	7	0.4
Naproxen	13	56	0.5
Ibuprofen	45	10	7
Piroxicam	100	3	1.7
Tenoxicam	100	5	1.7
Aspirin	228	162	18

Reasons to Treat

- Fever increases oxygen demand
- Every ↑ of 1°C over 37°C ➔ 13% ↑ in O_2 consumption
- Fever can aggravate preexisting cardiac, cerebrovascular, or pulmonary insufficiency

Reasons to Treat

- Fever ↑ mental changes in patients with organic brain disease
- Fever ↑ oxygen consumption
- Fever ↑ metabolic demands
- Fever ↑ protein breakdown
- Fever ↑ gluconeogenesis

Reasons to Treat

- Peripheral PGE2 production is potent immunosuppressant
- Treating fever does not slow resolution of common viral and bacterial infections
- Reducing fever with antipyretics reduces headache, myalgias, arthralgias

Reasons to Not Treat

- Moderate elevations of body temperature may increase chemotaxis, decrease microbial replication, and improve lymphocyte function
- Fever directly inhibits growth of certain bacteria and viruses

Reasons to Not Treat

- No proof that treating fever with antipyretics has beneficial effect on outcome or prevents complications

…but no evidence that fever facilitates recovery from infection

Treating Fever

- Objectives: reduce elevated hypothalamic set point and facilitate heat loss

Treating Fever

- Acetaminophen is preferred antipyretic
- Oral aspirin and NSAIDs reduce fever, but can affect platelets and gastrointestinal tract
- Children: aspirin increases risk of Reye's syndrome

Treating Fever

If patient unable to take oral:

- Parenteral preparation of NSAID
- Rectal suppository preparations of antipyretics
- Rectal dose: 30-45 mg/kg

Rectal Acetaminophen

- Antipyretic plasma concentration range: 10 – 20 µg/ml
- 45 mg/kg rectal APAP → mean peak concentration <15 µg/ml more than 3 hours after insertion
- Rectal absorption unpredictable
- 2 to 4 hours to peak concentrations
- Bioavailability 30 – 50% oral

Treating Fever

- In hyperpyrexia, cooling blankets facilitate temperature reduction
- Don’t use without oral antipyretic
- When your house is too hot, do you turn down the thermostat, or hose down the roof with cold water?

Special Cases

Malignant Hyperthermia

- Stop anesthesia, succinylcholine
- Cool externallly
- Dantrolene sodium: 1 – 2.5 mg/ kg of body weight
- Procainamide to prevent ventricular fibrillation

Treating NMS

- Supportive care
- Discontinue offending medication
- Treat agitation, hyperactivity, rigidity with IV benzodiazepines
- If refractory, RSI and neuromuscular blockade with nondepolarizing agent (e.g., pancuronium, atracurium)

Treating NMS

- Manage hyperthermia: IV fluids, active external cooling
- Treat rhabdomyolysis
- Dopamine antagonists (bromocriptine, amantadine): no consistent benefit, response requires at least 24 hours, linked to stroke, seizure, MI, etc

Treating NMS

- Dantrolene inhibits calcium release from sarcoplasmic reticulum
- No proven benefit
- Muscular rigidity of NMS due to brain abnormality, not muscle
- No advantage over neuro-muscular blockade, benzos

Conclusion

- Fever is symptom, not a disease
- Careful history and physical will reveal source of most fevers
- Recognize life-threats early
- Make decision about benefits of treating fever before doing so
- Acetaminophen is drug of choice