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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
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

- 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
• 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
· Ear thermometers measure radiant heat energy from tympanic membrane, ear canal, frequently inaccurate
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 \(\uparrow\) heat production from muscles
- If heat conservation mechanisms raise blood temperature enough, shivering not required
- \(\uparrow\) heat production from liver
• 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
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
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

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics, including antihistamines</td>
</tr>
<tr>
<td>Antiparkinsonian drugs</td>
</tr>
<tr>
<td>Diuretics</td>
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<tr>
<td>Phenothiazines</td>
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<tr>
<td>Amphetamines</td>
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<tr>
<td>Monoamine oxidase (MAO) inhibitors</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Phencyclidine</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>LSD</td>
</tr>
</tbody>
</table>
Some Causes of Nonexertional Hyperthermia

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

- Endocrinopathy
  - Thyrotoxicosis
  - Pheochromocytoma

Source Undetermined
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
  - phencyclididine
  - 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
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)
• 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.
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'-monophosphosphate (cAMP, which is neurotransmitter)
- Activates neuronal endings from the thermoregulatory center
Working Up a Febrile Patient
“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?
“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 1\textsuperscript{st} and 3\textsuperscript{rd} days (e.g. Plasmodium vivax)
• Quartan fever: on 1\textsuperscript{st} and 4\textsuperscript{th} (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

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Critical Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Pneumonia with respiratory failure</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Cavernous sinus thrombosis</td>
</tr>
<tr>
<td>Systemic</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Meningococcus</td>
</tr>
</tbody>
</table>
## Generating a Differential

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Emergent Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Peritonsillar abscess</td>
</tr>
<tr>
<td></td>
<td>Retropharyngeal abscess</td>
</tr>
<tr>
<td></td>
<td>Epiglottitis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Endocarditis</td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
</tr>
</tbody>
</table>
# Generating a Differential

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Emergent Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Appendicitis, Cholecystitis, Diverticulitis, Intraabdominal abscess</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pyelonephritis, Tuboovarian abscess, Pelvic inflammatory disease</td>
</tr>
</tbody>
</table>
### Generating a Differential

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Emergent Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Encephalitis</td>
</tr>
<tr>
<td></td>
<td>Brain Abscess</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Cellulitis</td>
</tr>
<tr>
<td></td>
<td>Infected decubitus ulcer</td>
</tr>
<tr>
<td></td>
<td>Soft tissue abscess</td>
</tr>
</tbody>
</table>
### Generating a Differential

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Nonemergent Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Otitis media</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Colitis / enteritis</td>
</tr>
</tbody>
</table>

- Otitis media
- Sinusitis
- Pharyngitis
- Bronchitis
- Influenza
- Tuberculosis
- Colitis / enteritis
### Generating a Differential

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Nonemergent Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary</td>
<td>Cystitis</td>
</tr>
<tr>
<td></td>
<td>Epididymitis</td>
</tr>
<tr>
<td></td>
<td>Prostatitis</td>
</tr>
</tbody>
</table>

Source Undetermined
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

Initial history and physical examination

Stable vital signs, no serious symptoms

- Obvious source of fever
  - Treat focal bacterial infection with oral antibiotics, antipyretics

- No obvious source of fever
  - Supportive care antipyretics, antiemetics rehydration

Unstable vital signs, serious symptoms (stiff neck, mental status changes, petechial rash)

- Monitor, IV access, respiratory support, appropriate cultures, appropriate antibiotics, ancillary testing as indicated
Algorithm: Elderly or Chronically Ill

Unstable vital signs? Toxic appearance? Serious symptoms? (e.g., mental status changes, stiff neck, shock, respiratory distress)

Yes

Chest x-ray, UA, urine culture, blood culture, assess need for LP, appropriate antibiotics, admit to special care unit

No

Identify source of fever?

Yes

Treat source of infection. Many require admission

No

Chest PA and lateral film, CBC with differential, indwelling devices may need to be removed and/or cultured, consider LP, most require admission with cultures and empiric antibiotics, consider noninfectious causes

Many require admission
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

- 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
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

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

Source Undetermined
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
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!
<table>
<thead>
<tr>
<th>Acetaminophen</th>
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<tbody>
<tr>
<td>- Abenol</td>
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<tr>
<td>- Aceta</td>
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<tr>
<td>- Actamin</td>
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<tr>
<td>- Aminofen</td>
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<td>- Anacin-3</td>
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<td>- Apacet</td>
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<td>- APAP</td>
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<td>- Atasol</td>
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<td>- Banesin</td>
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<td>- Dapa</td>
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<td>- Datril</td>
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<td>- Exdol</td>
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<td>- Feverall</td>
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<td>- Redutemp</td>
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<td>- Ridenol</td>
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<tr>
<td>- Robigesic</td>
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<td>- Rounox</td>
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<tr>
<td>- Snaplets-FR</td>
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<tr>
<td>- Suppap</td>
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<tr>
<td>- Tapanol</td>
</tr>
<tr>
<td>- Tempra</td>
</tr>
<tr>
<td>- Tylenol, etc</td>
</tr>
</tbody>
</table>
Acetaminophen

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

Ben Mills (Wikipedia)
Aspirin
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
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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Analgesia</th>
<th>Anti-Inflammatory</th>
<th>Antipyretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>0.7</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>8</td>
<td>7</td>
<td>0.4</td>
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<tr>
<td>Naproxen</td>
<td>13</td>
<td>56</td>
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<tr>
<td>Aspirin</td>
<td>228</td>
<td>162</td>
<td>18</td>
</tr>
</tbody>
</table>
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 a potent immunosuppressant.
- Treating fever does not slow the resolution of common viral and bacterial infections.
- Reducing fever with antipyretics reduces headache, myalgias, and 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
• 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 externally
- 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