Fever, I never knew ya!

Andrew Morris

March 20, 2002 13:30-15:00

Medicine Residents' Half-Day

Hamilton Health Sciences
EXEMPLARY CARE • ACADEMIC EXCELLENCE

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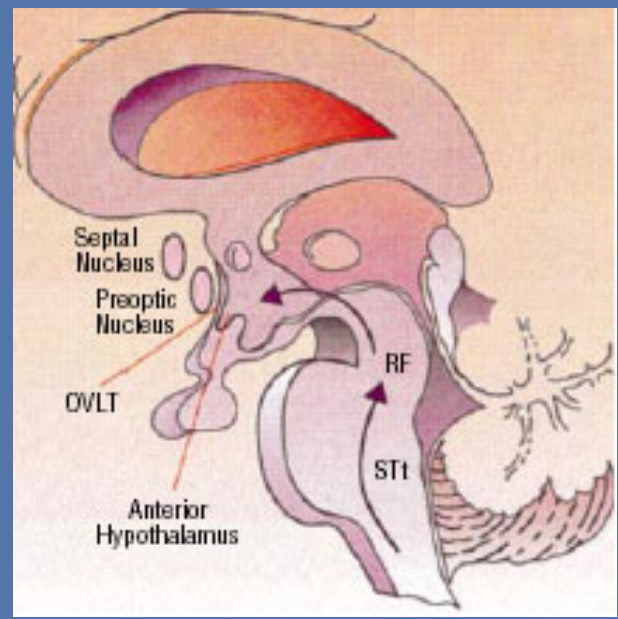
HEALTH SCIENCES

Q: What is fever?

- Wunderlich, after measuring over 1 million axillary temperatures, concluded that 38.0ºC was the upper limit of normal.
- he also said that 37.0ºC was normal
- recent evaluation of Wunderlich's thermometer showed it to be 1.2-2.2ºC higher than what we accept

Q: What is fever?
Mechanisms

- A: ***Fever is a pyrogen-mediated rise in body temperature above normal (i.e. different from hyperthermia)***
- the preoptic region plays a pivotal role in a multi-faceted neural regulation of temperature (see right)
- both endogenous and exogenous pyrogens can induce fever
- exogenous pyrogens
  - primarily come from microbes
  - usually induce endogenous pyrogens



Sagittal view of the brain and upper spinal cord showing the multisynaptic pathway of skin and spinal thermoreceptors through the spinothalamic tract (STt) and reticular formation (RF) to the anterior hypothalamus, preoptic region, and the septum. OVLT indicates organum vasculosum laminae terminalis.

Arch Intern Med 1998;**158**:1870-1881

Pyrogenic Cytokine	Aliases	Cell Source	Expression: Up-regulated by	Expression: Down-regulated by	Effect on Other Pyrogenic Cytokines	Biological Activities
IL-1	Endogenous pyrogen Leukocyte endogenous pyrogen Lymphocyte-activating factor Mononuclear factor Catabolin Osteoclast-activating factor Hematopoietin-1 Melanoma growth inhibition factor Tumor inhibitory factor-2	Astrocytes Endothelial cells Keratinocytes Monocytes Macrophages Dendrites Fibroblasts	TNF IFN-γ GM-CSF Zymosan LPS IL-1 C5a Leukotrienes PMA	IL-4 IL-6 IL-10 TGF-β Corticosteroids PGE_2 Retinoic acid	↑ IL-6 ↑ TNF ↑ IL-1	IL-2 and IL-2R induction Thymocyte costimulation Fibroblast activation Induce acute phase response T-cell activation Costimulation of B-cell proliferation and differentiation Augment CTL, LAK induction Induce endothelial adhesion molecules Enhance phagocyte microbial killing Accelerate wound healing
TNF-α	Cachectin	Monocytes Macrophages Eosinophils Neutrophils Lymphocytes Astrocytes Endothelial cells Mast cells Kupffer cells NK cells Certain tumors	Bacteria Viruses Fungi Protozoa LPS Staph TSSTI IL-1 IL-2 TNF IFNs GM-CSF PAF Substance P Anti-TCR Tumor cells PMA	Corticosteroids Cyclosporine PGE_2 IL-4 IL-6 IL-10 TGF-β Vitamin D_3	↑ TNF ↑ IL-1 ↑ IL-6	Septic shock Enhance phagocyte microbial killing Tumor necrosis Cachexia Anorexia Endothelial and epithelial MHC, adhesion molecule induction Osteoclast activation B-cell differentiation CTL induction
IL-6	Interferon beta-2 B-cell stimulatory factor-2 Hybridoma or plasmacytoma growth factor Hepatocyte-stimulating factor Cytotoxic T-cell differentiation factor Macrophage granulocyte-inducing factor 2A	Monocytes Macrophages Lymphocytes Fibroblasts Endothelial cells Epithelial cells Keratinocytes Bone marrow stroma Certain tumors	LPS IL-1 TNF IFN-β Calcium Ionophore Mitogenic lectin and PMA Viruses	Corticosteroids Estrogens	↓ TNF ↓ IL-1	B-cell growth, differentiation, and IgG synthesis Myeloma proliferation CTL induction Acute phase response Thymocyte costimulation Weak antiviral activity Megakaryocyte maturation Neuronal differentiation Enhance IL-3–dependent stem cell proliferation
IFN-γ	Type II Interferon Immune Interferon	T cells NK cells	Mitogenic lectins IL-1 IL-2	Corticosteriods Cyclosporine Vitamin D_3	↑ TNF ↑ IL-1	Macrophage priming Antiviral activity Enhance TNF activity MHC induction Enhance NK activity Enhance endothelial ICAM-1 expression Inhibit IL-4–induced B-cell responses B-cell differentiation and IgG2a secretion

Pyrogenic Cytokines

- IL-1, TNF-α, IL-6, and IFN-γ are principle cytokines mediating fever
- IL-1 induces itself, along with TNF-α and IL-1
- TNF-α induces itself along with IL-1 and IL-6
- IL-6 inhibits TNF-α and IL-1, whereas IFN-γ induces these
- IL-1, TNF-α and IL-6 are all found in monocytes, and macrophages, whereas IFN-γ is predominantly found in T cells

Arch Intern Med 1998;**158**:1870-1881

Q: What is fever?

- therefore, either
  - a) you know what is normal for the patient, and you can recognize the temperature is above what is usual for the patient

    or
  - b) you do not know what is normal, and therefore you must assume "normal"/"abnormal" using epidemiology

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Q: What is fever? (cont'd)

- "fever" varies according to
  - a) time of day
  - b) body part of temperature reading
  - c) host factors (e.g. gender, age, immune status)

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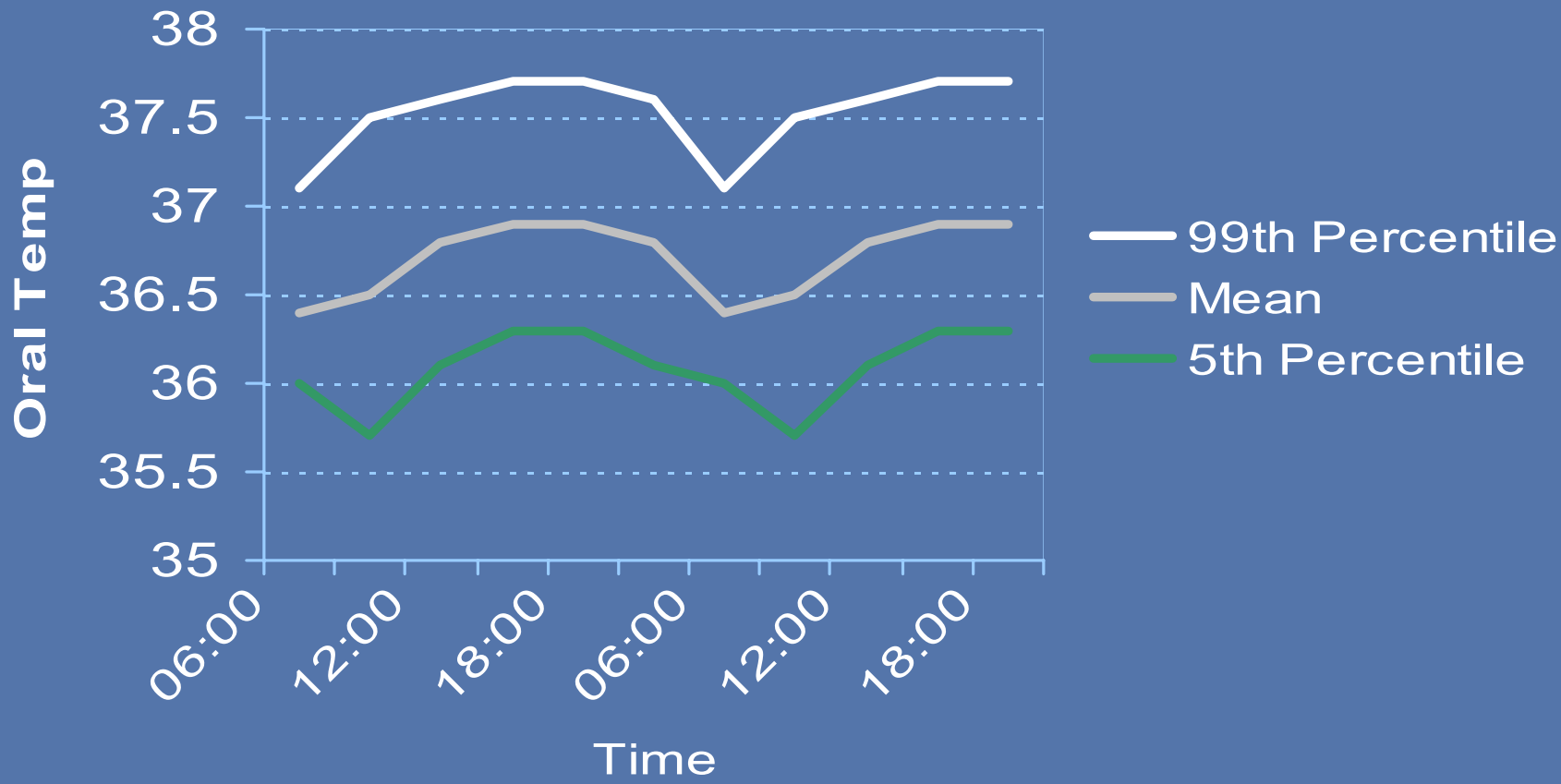
Fever and Time of Day

37.2 in morning, 37.7 in evening



JAMA 1992;**268**:1578-1580

Fever and Body Location

- core temperature refers to an ideal-but-clinically-difficult-to-access temperature
- rectal temperatures are the easiest way of measuring core temperature
- oral temperature is the most practical surrogate for core temperature (and is usually 0.4-0.5 ºC lower)
- axillary temperatures are specific but insensitive surrogates or core temperature
- oral temperature may be falsely low in tachypneic patients

Fever and Body Location
Don't Use Tympanic Thermometers

- tympanic thermometers do not measure temperature, but measure infrared emissions from the external auditory canal
- numerous studies have shown that tympanic thermometers are insensitive for fever
  - in one study, only 19/28 pts with fever were detected
  - in another study, 17/27 pts with fever were detected
  - tympanic thermometers both over- and under-estimate temperatures measured by oral thermometers
- whereas the mean difference in temperature of oral vs. rectal is 0.4ºC, it is 0.8ºC for tympanic thermometers

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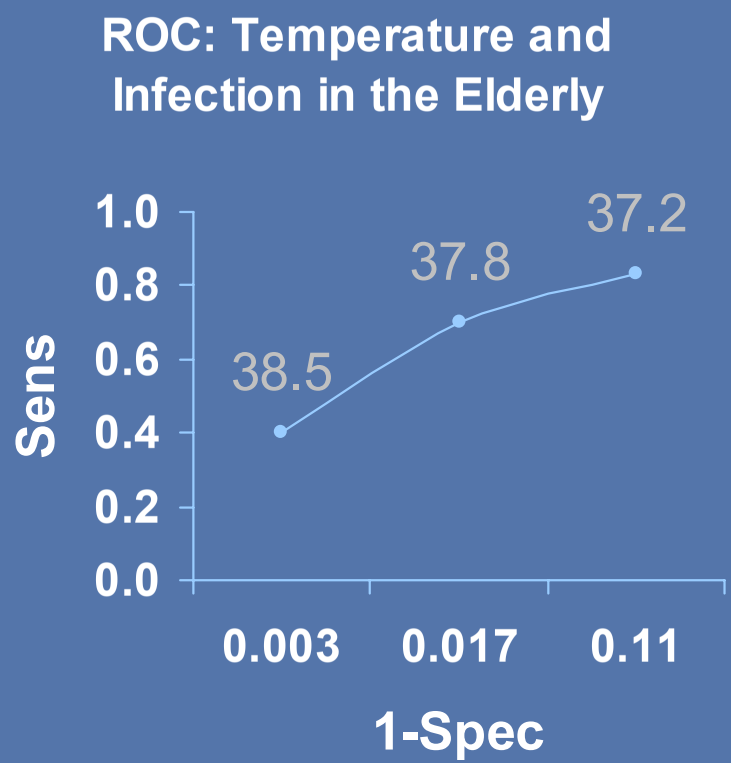
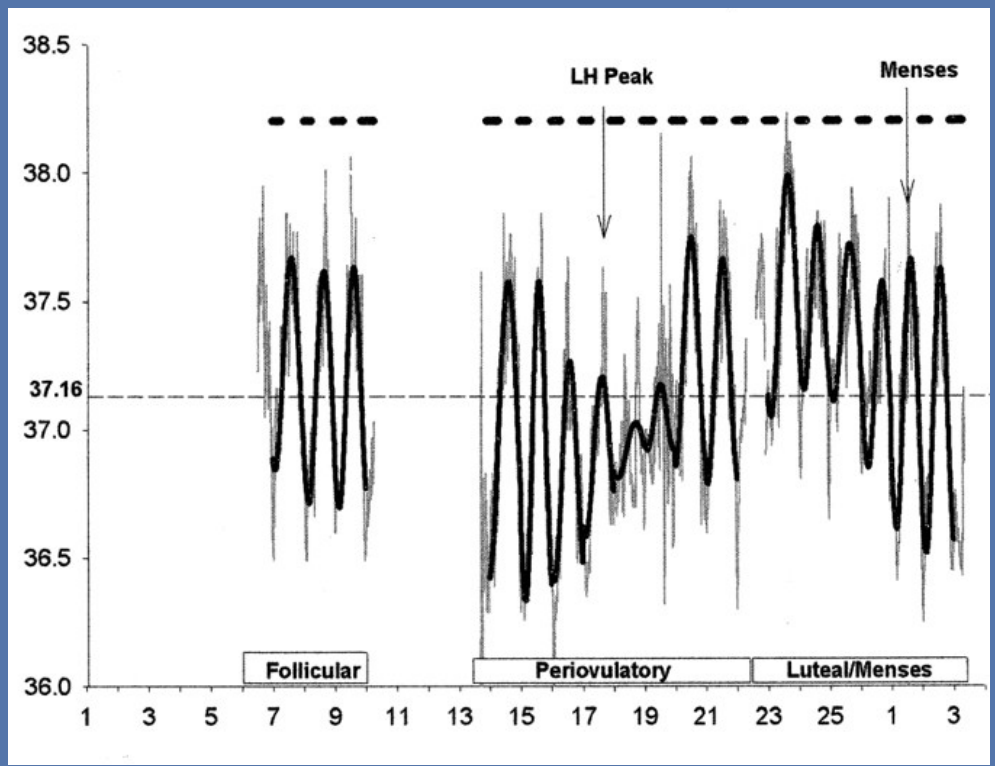
Fever and the Elderly

- baseline temperatures are lower in the frail elderly
- fever onset may be delayed
- 55% of elderly with acute cholecystitis had oral T<37.5ºC
- defining fever as 38.5ºC in the elderly will miss 60% of infections, whereas defining it as 37.2ºC will miss only 17% infections



Adapted from *Aging Immunol Infect Dis* 1993;**4**:67–76

Fever and the Host
Gender



Menstrual Cycle Phase	Mean Temp
Follicular	37.09
Preovulatory	36.92
Luteal	37.40
Menses	37.21

Am J Physiol Regulatory Integrative Comp Physiol 2000;**279**:R1316–R1320

Fever and the Host
Gender

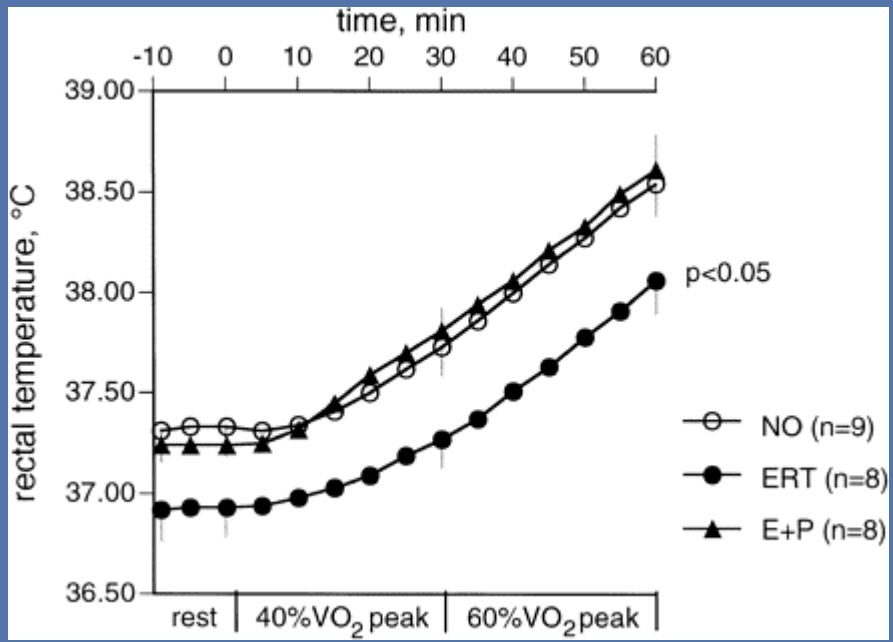


Figure 1. Mean rectal temperature at rest and during exercise at 40% and 60% peak O_2 consumption ($VO_{2\ peak}$) in an ambient temperature of 36°C. Baseline period consists of 10 to 0 min. Exercise began at 0 min and was completed at 60 min. ERT, estrogen replacement therapy; E+P, estrogen plus progesterone therapy; NO, no hormone replacement therapy; *n*, no. of subjects. Bars represent 1 SE.

Journal of Applied Physiology 1997;**83**;477-484

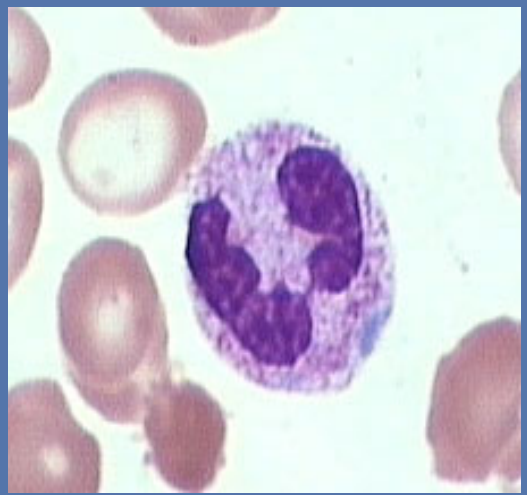
White Blood Cells and Infection

- an ↑ WBC count does not help you diagnostically
- an ↑ neutrophil count does not help you diagnostically
- an ↑ band count does not help you diagnostically

- a left shift (i.e. relative increase of bands compared to mature neutrophils) can occur with acute inflammation, stress responses, burns, and tumour lysis
- **Döhle bodies, toxic granulation,** and **toxic vacuolization** are fairly specific for infection (with respective likelihood ratios for infection of 4.0, 5.6, and 3.0)
  - G-CSF and chemotherapy recovery can produce these “toxic” changes

J Am Geriatr Soc 1989;**37**:537-543

Döhle bodies



Döhle bodies appear as single or multiple light blue or gray staining areas in the cytoplasm of a neutrophil. They are rough endoplasmic reticulum containing ribonucleic acid (RNA) and may represent localized failure of the cytoplasm to mature. **Döhle bodies** are found in infections, poisoning, burns, and following chemotherapy.

Toxic granulation

Toxic granulation is found in severe inflammatory states. The toxic granules are azurophilic, usually found in the promyelocyte, metamyelocyte, band, and segmented stages. The toxic granulation is thought to be due to impaired cytoplasmic maturation, in the effort to rapidly generate large numbers of granulocytes.

Toxic vacuolization

Toxic vacuolization is also found in severe inflammatory states during profound myelopoeisis. They represent the sites of digestion of phagocytosed material. The toxic vacuoles are often found in monocytes, but they may also be found in granulocytes where Döhle bodies and toxic granulation are present.

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WBCs and Infection

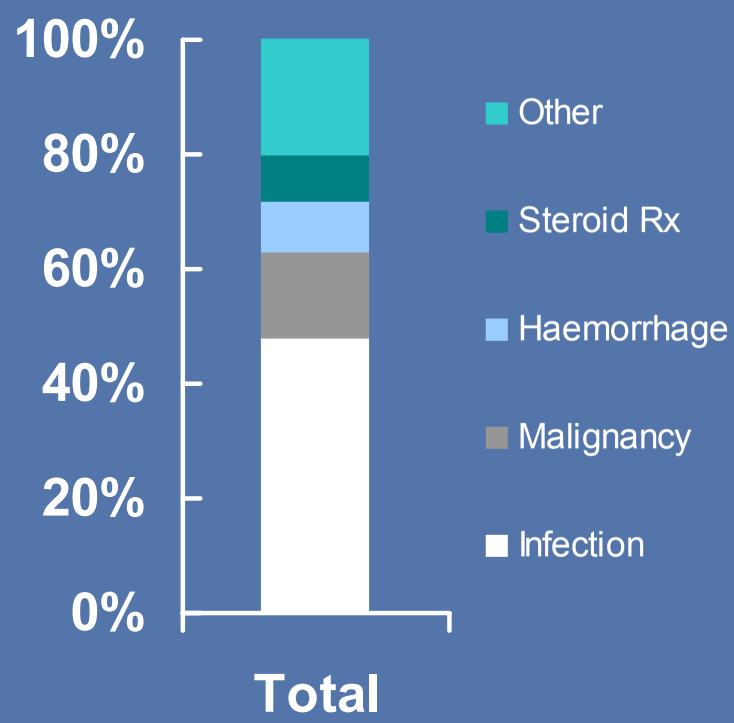
- 3 583 patients seen in ER
  - 860 (24%) had a WBC
    - 172 (20%) had a high WBC
      - 15 (10%) had an impact
        - 8 inappropriate impacts
        - 7 appropriate impacts
- $PPV_{WBC>12.5}$ = 26%
- $PPV_{PMNs>10 \text{ or } Bands>0.5}$ = 33%

Ann Emerg Med 1986;**15**:774-781

WBCs and Infection

- study looked at 100 consecutive cases of WBC > 25 x 10^9/L with >50% being PMNs over a 9-month period
- infection =
  - positive culture from a sterile site

    or
  - clinical improvement with resolution of leukocytosis while on antibiotics



Am J Med 1998;**104**:12-16

Fever and WBCs in Infection

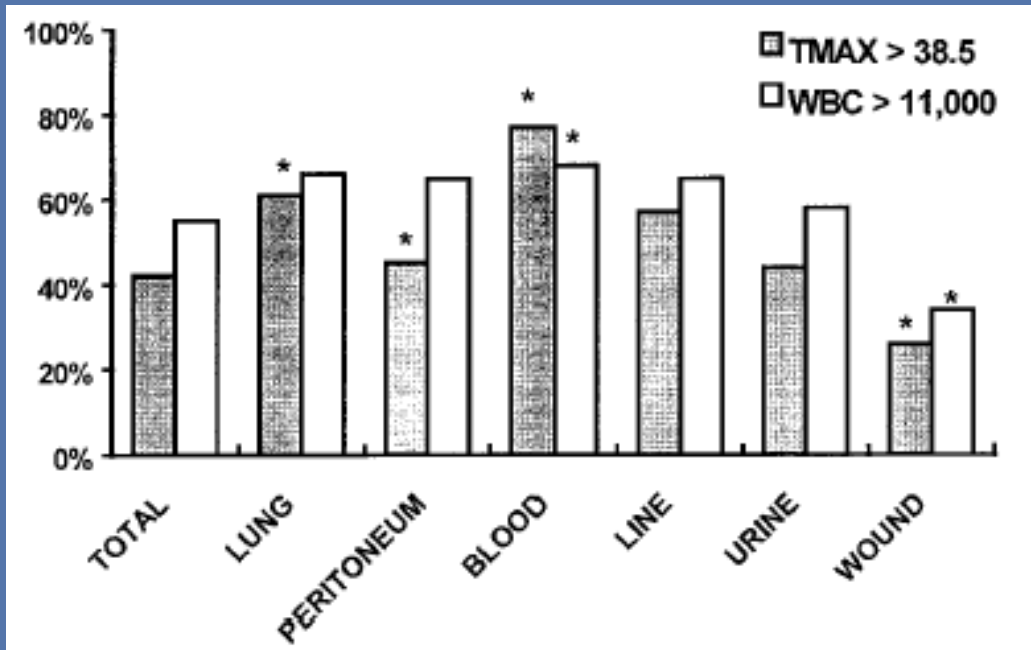


Fig. 1. Incidence of fever and leukocytosis by site of infection. Tmax: maximum temperature; WBC: white blood cell count; LINE: line infections. *$p \leq 0.05$ vs. infections at other sites.

World J. Surg. 2001;**25**:739–744

Fever of Unknown Origin

- definitions are problematic, but the most currently accepted definition is:
  - persistent temperature > 38.3ºC
  - lasting more than 3 weeks
  - at least 1 week of intensive investigation
- I prefer ***persistent fever without focus*** and suggest appending with
  - *critical care*
  - *HIV infection*
  - *solid organ transplantation*
  - *stem-cell transplantation*
  - *steroid- (or other immunosuppressant drugs-) associated*
  - *neutropenia*
  - *returning traveller*
  - *IV drug user*
  - *other predisposing condition*

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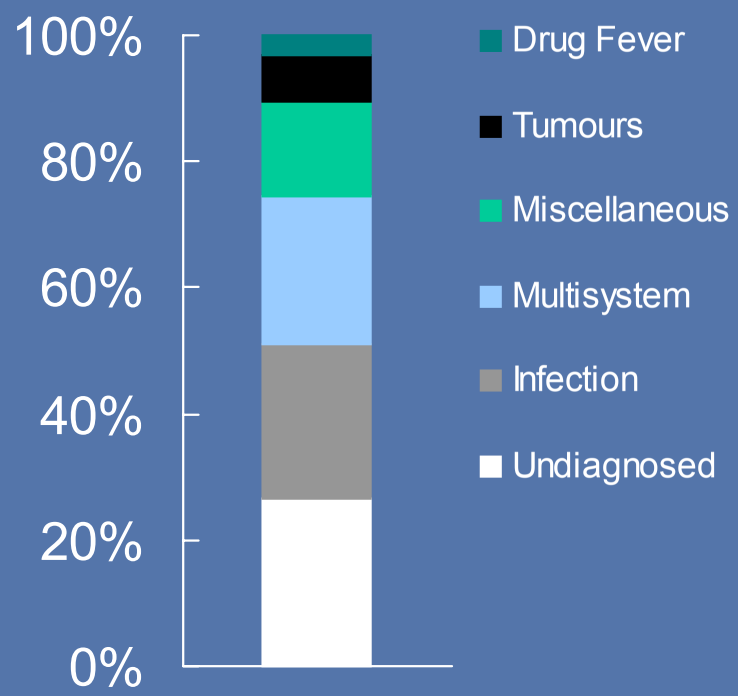
Fever of Unknown Origin



- Tumours usually lymphomas, renal cell ca., or GI malignancy.
- RA, SLE, PAN, giant cell arteritis, Still's disease are most common multisystem diseases.
- Any drug can cause a fever at any time, but most are within a few months of starting.
- Sarcoid, thromboembolic disease, IBD, and intracranial pathology can all cause significant fever.

Arch Intern Med 1992;**152**:51-5

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Not All Fever is Caused by Infection

Fever of Unknown Origin

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

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

- fever is often not infectious
- in the elderly, temporal arteritis is the most frequent cause of fever of unknown origin

Adapted from *J Am Geriatr Soc* 1993;**41**:1187–92, cited in *Clin Infect Dis* 2000;**31**:148–51.

Fever of Unknown Origin

- *Hx*: include foreign travel, contacts with animals and infected people, bites, cuts, surgery, rashes, diarrhea, drugs, immunization.
- *Physical*: include teeth, rectal, vaginal, skin, LNs, liver, and spleen as part of general exam.
- *Labs*: Start off with cheap/simple investigations: CBC with differential, U/A, liver enzymes, blood cultures, CXR, abdo US, reserve baseline serum, consider focal tests
- *Repeat history and physical*.
- Target investigations. Consider RF, ANA, LP, bone marrow, leg dopplers/VQ scan, gallium scan, temporal artery biopsy, TEE, stopping drugs (one at a time)

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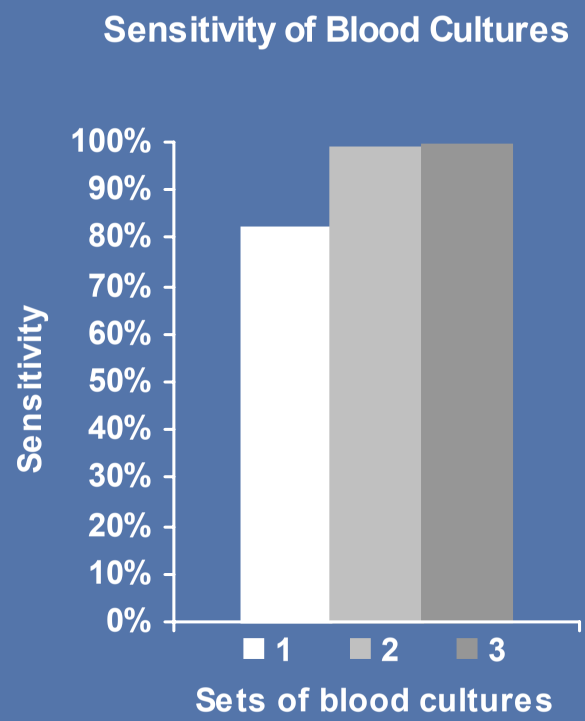
Blood Cultures and Infection

Order at least 2 sets

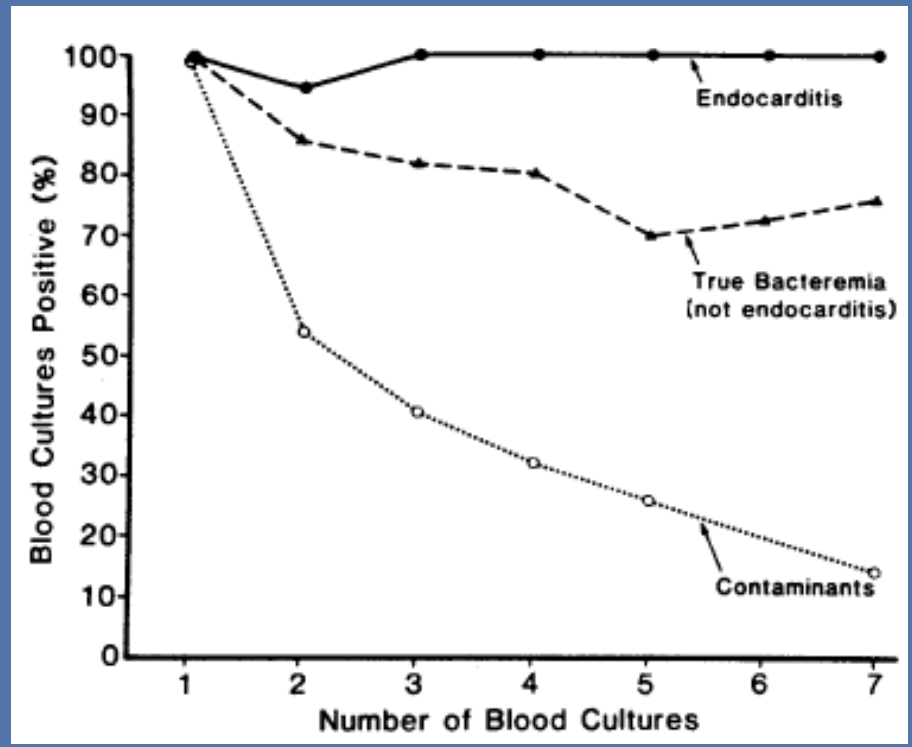
- blood culture sensitivity increases by about 17% when adding a 2nd set
- blood culture sensitivity increases <1% when adding a 3rd set



Mayo Clin Proc 1975;**50**:91–97

Blood Cultures and Infection

- patterns of positivity can help diagnostically
  - endovascular infections (e.g. endocarditis) have continuous bacteremia
  - in contamination approximately, the positivity rate is 1/2 for 2 sets and 1/3 for 3 sets of blood cultures



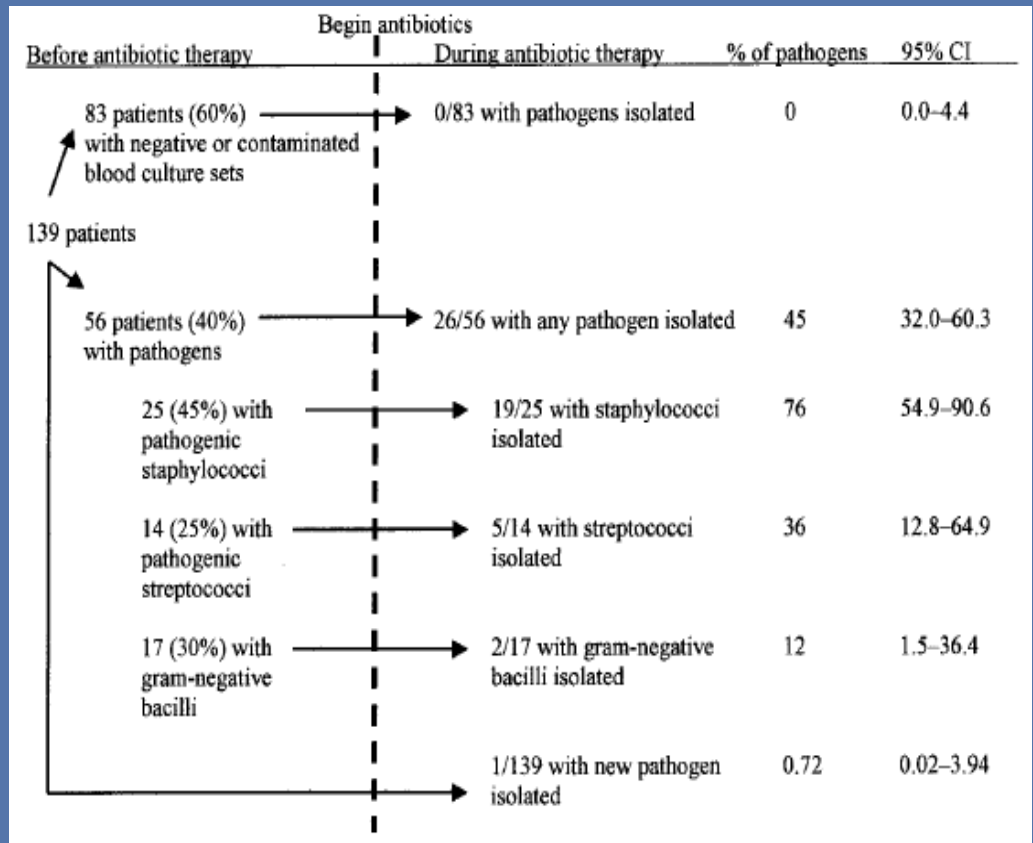
Patterns of positivity in successive blood cultures, showing evidence of the diagnostic importance of separate cultures.

Rev Infect Dis 1983;**5**:35–53

Blood Cultures and Infection

Culturing more than 3 sets is rarely useful

- because 3-5% of all cultures are falsely positive (and because 3 sets of cultures are 99.6% sensitive), repeated culturing increases the likelihood of a false positive without improving sensitivity
- if 2-3 sets are initially drawn, there is rarely value in doing more cultures initially



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Blood Cultures and Infection
Positive Predictive Value

- usually "the real deal" (>90%)
  - *S. aureus*
  - *E. coli* and other members of the *Enterobacteriacae*
  - *Pseudomonas aeruginosa*
  - *Streptococcus pneumoniae*
  - *Candida albicans*
- problematic
  - enterococci (78%)
  - viridans streptococci (38%)
  - coagulase-negative staphylococci (15%)
- usually contaminants (<5%)
  - *Corynebacterium* spp.
  - *Bacillus* spp.
  - *Propionibacterium acnes*

Clin Infect Dis 1997;**24:**584–602

Sterile vs. Non-sterile Culture Sites

- consider sterile site cultures like blood cultures:
  - almost always true pathogens but, occasionally, contaminated (probably less than BCs)
  - sensitivity increases with volume submitted to laboratory
  - sensitivity increases with use of blood culture media
- non-sterile site cultures must be interpreted with caution
- use other information to decide if the culture result is relevant

Sterile vs. Non-sterile Culture Sites

Sterile sites/specimens

- blood
- urine - midstream, clean catch
- CSF
- pleural fluid
- ascitic fluid
- joint fluid
- bone
- bone marrow
- abscess FNAs

Non-sterile sites/specimens

- throat
- sputum
- tracheal aspirate
- urine - catheterized
- stool
- wound swabs

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