FEVER: 101°

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Learning Objectives

- 1. Definition of Fever
- 2. Brief Pathophysiology of temperature regulation
- 3. Infectious Causes of fever vs non-Infectious Causes of fever
- 4. Investigation of Fever
- 5. Neutropenic Fever
- 6. FUO
- 7. Drug Fever

Definition of Fever

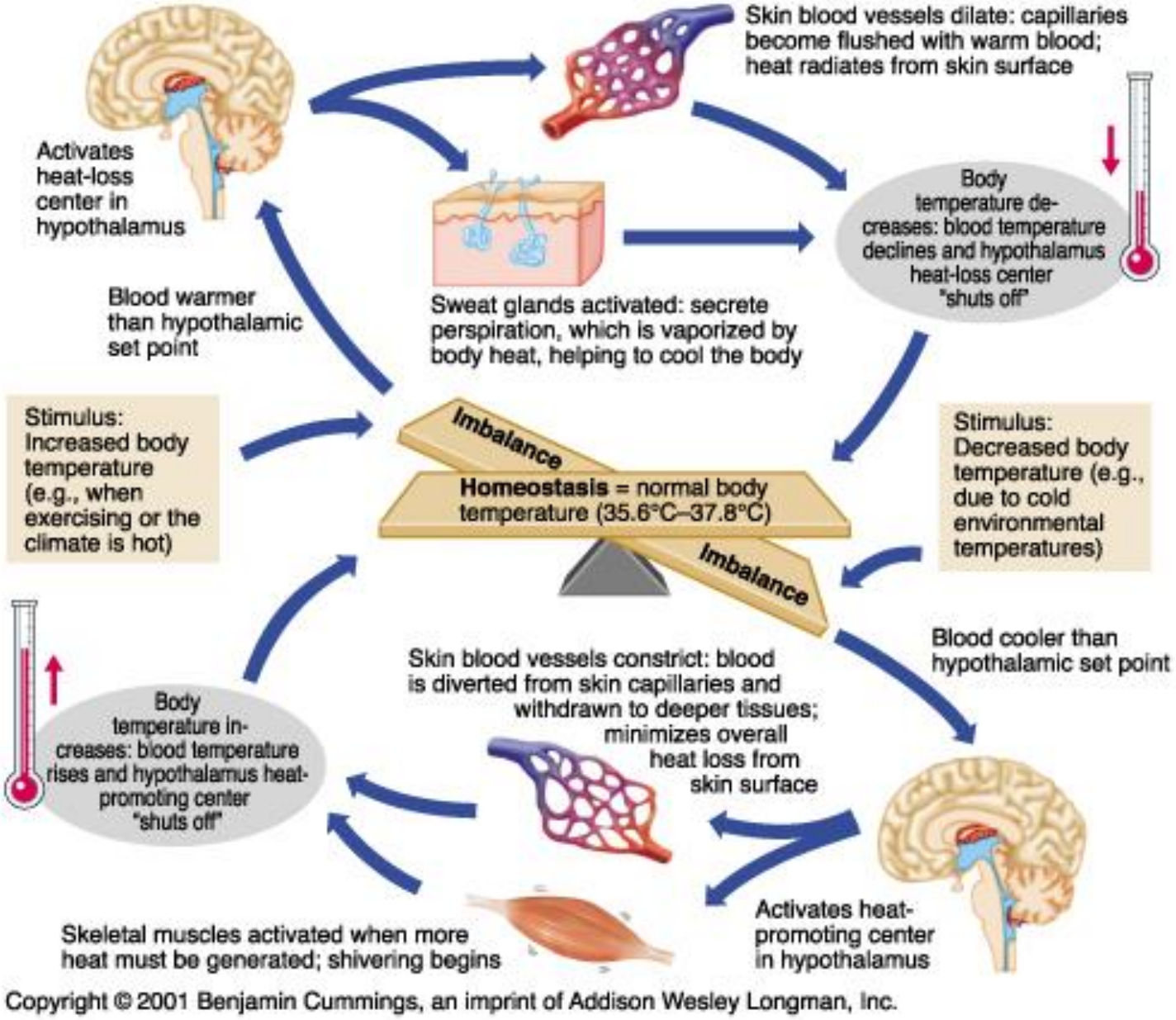
T>38.3°C once

T>38°C persisting over 1 hour

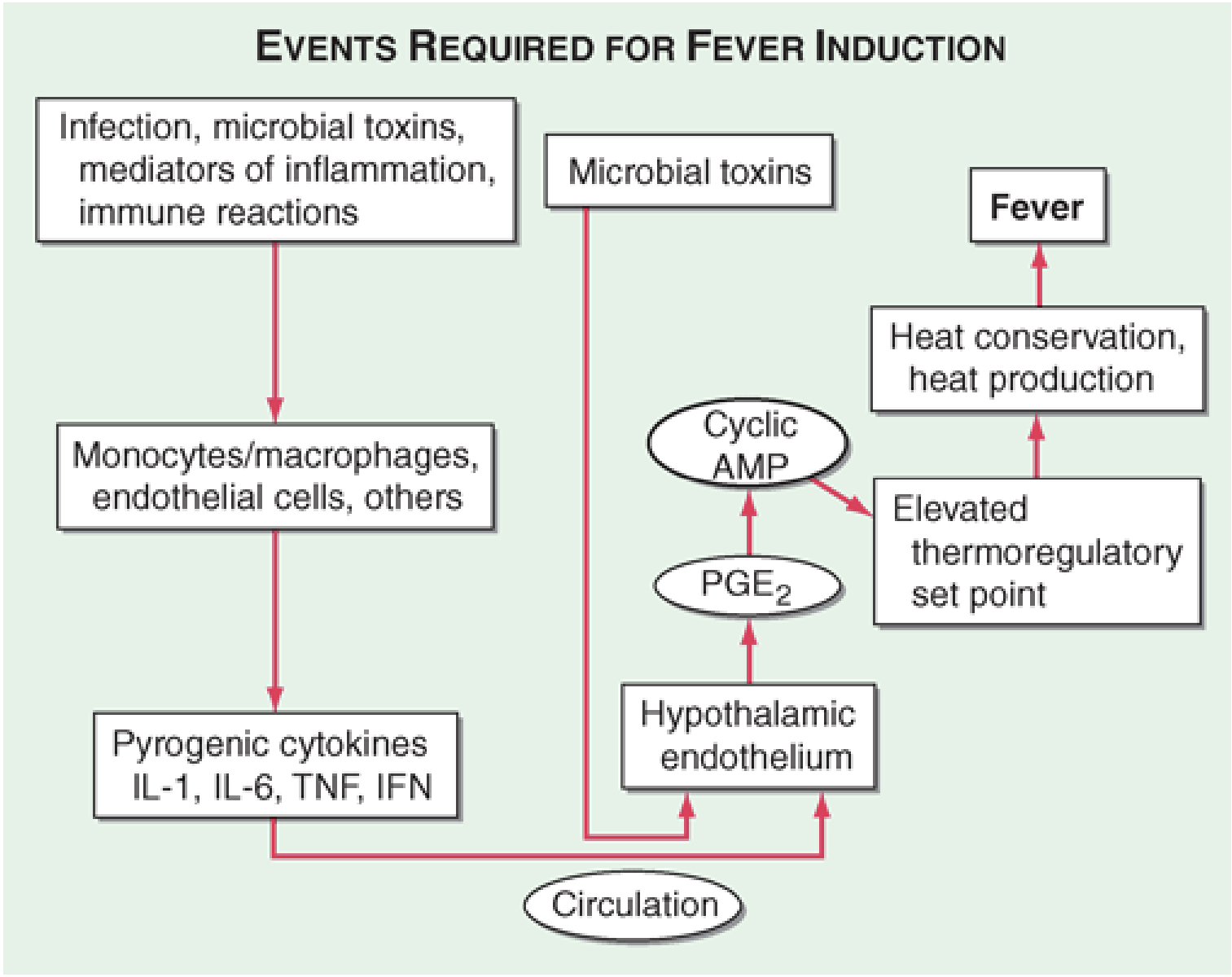
Diurnal temp pattern leads to highest temps in evening

- difficult to make clinical diagnosis based on temp patterns

"a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host."



Balance between heat production and dissipation



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Fever: Friend or Foe

- **Benefits:**
- - present in other species, evolutionary conserved
- - increases resistance to pathogens
- - positive correlation between fever and survival in G- sepsis, SBP, Candidemia
- - production of cytokines and cell mediated death

- **Risks:**
- - discomfort
- - increased metabolic demands
- - elevated HR/tachypnea

When to treat hyperthermia?

- MI, Stroke. Fevers correlates with worse outcome
- Vfib/Vtach arrest +/- other forms of arrest
- CV/Pulm disease
- Temp above 41°C
- fever induced mental dysfunction

in elderly

Case #1: Night Float

- A Nurse calls you after midnight vitals and tells you Mr. B's temp was 38.7. A quick glance at sign out tell you he is 70 years old and was admitted from a nursing home for altered mental status. To do list says not sure if this is an infection so we did not give abx, please "watch for fever". What is your move?

  A. start broad spectrum antibiotics

  B. order blood and urine cultures followed by broad spectrum antibiotics

  C. Observe and repeat temp in one hour

  D. STAT order more cowbell

Evaluation of a Patient with Fever

- Infectious disease Review of Systems
  - Sick contacts
  - Travel history
  - Recent antibiotics
  - Sexual History
  - Occupational/exposure history
  - Drug Hx
- Past Medical History
  - Immune system deficits
    - HIV, splenectomy, sickle cell disease, BMT
  - Chronic Meds
    - Steroids, biologic agents, chemotherapy, immunosuppresants

Evaluation of Patient with Fever

- Old Data
  - Previous cultures results – resistant organisms
  - Allergic rxns
  - Surgeries, especially with left over hardware
- "Pan-culture"??
  - Low diagnostic yield
  - Not wrong but stop and think
    - Sputum production
    - Dysuria
    - Skin breakdown
    - Chest pain
    - Joint exam
    - Look at the IV pole!

Diagnostic Approach

- Blood cultures
  - A must for new onset fevers
  - 2 sets = 4 vials
  - Ideally 60 minutes apart from two peripheral sites
    - Avoid "surgical cultures"
  - Contamination is common (~2.5% in one large study)
    - Coagulase neg staph, strep skin flora
    - Polymicrobial
  - If patient has hardware all bets are off!

Hall, et al

Diagnostic Approach

- Patients with Indwelling catheters
  - At least one set from the catheter and one set peripherally
    - PPV of true bacteremia if 2 sets of blood cultures are +
    - Both peripherally drawn: 98%
    - One catheter + one peripheral: 96%
    - Two catheter: 50%
  - Infection vs contamination vs colonization

Hall, et al

Case #2: Night Float

- Mr. F is a 67 year old male with previous heart attack and HFrEF s/p AICD placement (2014). He presented two days ago with palpitations and LEE. You get a call from the lab saying patient's admission blood cultures are growing gram + cocci in clusters. You check the CDV and patient's temp is 38.1. What is the next most appropriate step?

  A. Clinical observation

  B. Administer vancomycin

  C. Repeat blood cultures

  D. Pretend you didn't get the page

Interpretation of Other Common Cultures

- Urine Cx
  - Colony # is not really relevant
  - Treat Asymptomatic Bacteuria?
    - Pregnancy → pyelo
    - Recent or planned urologic instrumentation
    - Kidney transplant
- Sputum Cx
  - Hard to obtain correctly
  - Colonizer vs pathogen
  - True utility is when organism is isolated in clinically diagnosed PNA

Key to Infectious Work-up

- #1: Identify the host and risk factors
- #2: Identify an infectious syndrome and obtain appropriate culture data
- #3: Choose antibiotics to cover common organisms based on #1 and #2
- #4 Obtain source control
- #5: Narrow to appropriate antibiotics when organism isolated
  - Ex: Treat MSSA with cefazolin not vancomycin
- EXCEPTION!!!!

Persistent Fevers

- Patient who does not defervesce on antibiotics
  - Think about holes in your coverage
    - MRSA, pseudomonas, anaerobes, intracellular
  - If you don't have source control call a surgeon
    - Abscess, bad sinusitis, empyema
  - Non-infectious causes of fever
  - Non-bacterial causes of fever
  - Consider drug fever

Tip to Surviving Intern Year #1

- Stop to remember the good outcomes!

Case #3

- Mr. F is a 50 year old male with extensive alcohol consumption who presents with acute epigastric pain, N/V, and shaking chills at home. Vitals on arrival T: 39, HR 110, BP 110/80, RR 20, sating 98% on RA. WBC: 18,000 with 83% neut. Serum lipase 6,000. CT A/P with inflammation and edema around pancreas with 2 cm central area of necrosis. Next step in management?

  A. Blood cultures → ertapenem, NPO and pain control

  B. Blood cultures, NPO, pain control

  C. Depends on your attending

Antibiotics are not always the Answer

- Cochrane review in 2010 concluded no evidence of benefit for empiric antibiotic use in necrotizing pancreatitis
- 2012 meta-analysis calculated NNT of 1,429
  - Increased risk of candida super-infection and c diff
  - Low likelihood of positive cultures and prolonged natural progression of disease lead to long, broad empiric courses
- Ultimately still controversial but take home point is SIRS does not equal sepsis

Non-infectious Causes of Fever

- Pancreatitis
- PE (probably not DVT)
- Drugs (more on this later)
- Transfusion reactions
- Gout + other rheum conditions
- Vasculitis
- Serotonin Syndrome
- Autoimmune disease

Tip to Surviving Intern Year #2

- The 20-80 Rule

Case #4: Seidman

- Mrs. N is a 35 year old female with PMH of recently diagnosed AML who underwent induction chemotherapy via a newly placed port. She called her oncologist after feeling “shakes” at home and was told to come to the ED for evaluation. Vital signs on arrival significant for a T of 38.5
  - White count of 0.5
  - ANC 300

Neutropenia

Definition

Mild: 1000 < ANC < 1500

Moderate: 500 < ANC < 1000

Severe: 0 < ANC < 500

Causes

Constitutional

Drug induced

Nutritional

Collagen/vascular

Infection

Heme (MDS)

Neutropenic Fever

- Infection
- Tumor burden, Tumor death
- Chemotherapy breakdown of mucosa
- Immune re-constitution

~80 percent of heme malignancy patients will have >1 episode of fever during first round of chemo

Neutropenic Fever ?s

- Do all patients with neutropenic fever receive empiric coverage for MRSA?
  - No but add vanc if PNA, catheter, skin or hypotension
- Do all patient with neutropenic fever receive empiric pseudomonal coverage?
  - Yes
- Do all patients with neutropenic fever receive empiric fungal coverage
  - No, add if not responding in 4-7 days or evidence of infx
- Do we use CSF to treat febrile neutropenia?
  - Nope, only PPX

Neutropenic Fever ?s

- Do we provide ppx abx for patients at risk?
  - Yes if likely to have >1 week neutropenia or severe <100 ANC → cipro or levo

Who will get sicker and who will get better?

- MASCC score
  - “burden of illness”
  - BP > 90
  - Active COPD
  - Solid tumor
  - Previous fungal infection + heme malig
  - Requiring IV fluids
  - Fever onset outpatient vs inpatient
  - Age < 60

Fever of Unknown Origin

	CLASSIC FUO	NOSOCOMIAL (HEALTH CARE –ASSOCIATED) FUO	NEUTROPENIC (IMMUNE-DEFICIENT) FUO	HIV-RELATED FUO
Definition	>38.3° C (100.9° F), >3 wk, >2 visits or 3 days in hospital	>38.3° C (100.9° F), >3 days, not present or incubating on admission	>38.3° C (100.9° F), >3 days, negative cultures after 48 hr	>38.3° C (100.9° F), >3 wk for outpatients, >3 days for inpatients, HIV infection confirmed

Classic FUO

INFECTION, 25-50%	MALIGNANT DISEASE, 20-30%	CONNECTIVE TISSUE DISEASE, 15-30%	MISCELLANEOUS, 10-20%	UNDIAGNOSED, 10-30%
Cytomegalovirus	Carcinomatosis	Polyarteritis nodosa	Drug-induced fever	
Endocarditis	Leukemia	Rheumatoid arthritis	Granulomatous hepatitis	
Intra-abdominal	Local tumor	Still's disease	Inflammatory bowel disease	
Mycoses	Lymphoma	Systemic lupus erythematosus	Pancreatitis	
Occult abscess		Temporal arteritis	Pulmonary embolism	
Tuberculosis				

If All Else Fails Blame the Drugs

- hypersensitivity reaction —> most common!
- altered thermoregulatory mechanisms
- reactions that are directly related to administration of the drug (phlebitis, pyrogenic contaminants)
- reactions that are direct extensions of the pharmacologic action of the drug (cell lysis, necrosis, Jarisch-Herxheimer reaction)
- idiosyncratic reactions (malignant hyperthermia, NMS, serotonin syndrome)

Drug-induced fever

- Diagnosis of exclusion
- Can be accompanied by exanthema, hepatic, renal or pulmonary dysfunction
- Peripheral eosinophilia or monocytosis can be seen
- Most common: beta-lactams, sulfonamides, anticonvulsants
- "Lag time" varies considerably but can start weeks or months after initiation

	Episodes in Dallas (n=51)	Episodes in Lit. (n=97)	Total Episodes (n=148)
	n	*n*	%
Gender (male/female)	27/18	53/44	56/44
Hx of atopic disease	0	3	2
Previous hx of drug allergy	4	12	11
Fever patterns reported	51	41	62
Continuous	0	9	10
Remittent	19	7	28
Intermittent	6	13	21
Hectic	26	12	41
Rigors	26	52	53
Relative bradycardia	5	4	11
Hypotension	6	21	18
Rash	20	6	18
Pruritus	11	0	7
Leukocytosis (>10K)	11	0	7
Eosinophilia (>300/mm^3)	21	12	22
Hematologic	1	12	9
Deaths	2	4	4

Mackowiak and LeMaistre Ann Intern Med 1987;106:728

Tip to Surviving Intern Year #3

- If you aren't sure what to do, go see the patient.

Take Home Points

- #1 – There is always time to get cultures before antibiotics are given. Unless there isn't.
- #2 – Not all fevers require antibiotics
- #3 – Investigation of fevers is complicated and dynamic, key is to be prepared to reassess diagnosis and therapy daily

THANK YOU!