Brigham and Women's Hospital
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Challenging Patients in Infectious Diseases
A Diagnostic Toolkit for Internal Medicine

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

MGH 1811

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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- Northwestern University Medical School
- Infectious Disease Fellowship at UCSF
- Master Clinician Chair in Infectious Diseases
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- Clinical, Educational and Research Focus:
  - Diagnostic Reasoning in Infectious Diseases
  - Diagnosis and Management of Opportunistic Infections

Disclosures

None

Learning Objectives

- To utilize a simple *conceptual framework* to apply to patients who may have infectious diseases in your practice
    - Systematic—can help avoid common biases
    - Generalizable--applicable to many areas of medicine
- To use my patient presentations, and your own patients, to build your *contextual experience* in infectious diseases, which you can continually integrate into the framework
- To help you organize some facts related to the *categories of potential pathogens* and their *routes of transmission,* to have at your future disposal

Cases for Today
Fever of Intermediate Duration ("FID")

- A common outpatient problem
- A clinical presentation that bridges the gap between acute, self-limited fevers (<7 days) and classic FUO (fever of unknown origin)
- May be relatively non-localizing or undifferentiated

Patient 1: History of Present Illness

- 79 year old man who contacts your office
  - 2 weeks ago: acute mid abdominal pain (resolved in 2 days), nausea, constipation, loss of appetite, malaise, fatigue
  - 1 week prior ago, onset fevers with shaking chills
  - ROS otherwise negative
- PMH: pre-diabetes, HTN, GERD, BPH, DJD R hip (awaiting R THA) with recent worsening of pain. Oxycodone added to NSAIDs and acetominophen.
- Epi: no bites from his dogs. No known tick bites or exposures. No travel out of the US. No sick contacts. No inhalational or IV drug use.

Your Differential Diagnosis

1. Lyme disease (*Borrelia burgdorferi*)
2. UTI/pyelonephritis
3. Bacteremia of GI origin
4. Septic right hip
5. Other

What Does AI Say?

1. **Tick-Borne Illnesses (High Regional Suspicion)**
    - Anaplasmosis (*Anaplasma phagocytophilum*)
    - Babesiosis (*Babesia microti*)
    - Lyme Disease (*Borrelia burgdorferi*)

2. Gastrointestinal Pathologies & Medication-Induced Complications. The patient's current medication regimen (NSAIDs and recently initiated oxycodone) provides strong anchoring points for gastrointestinal disruptions.

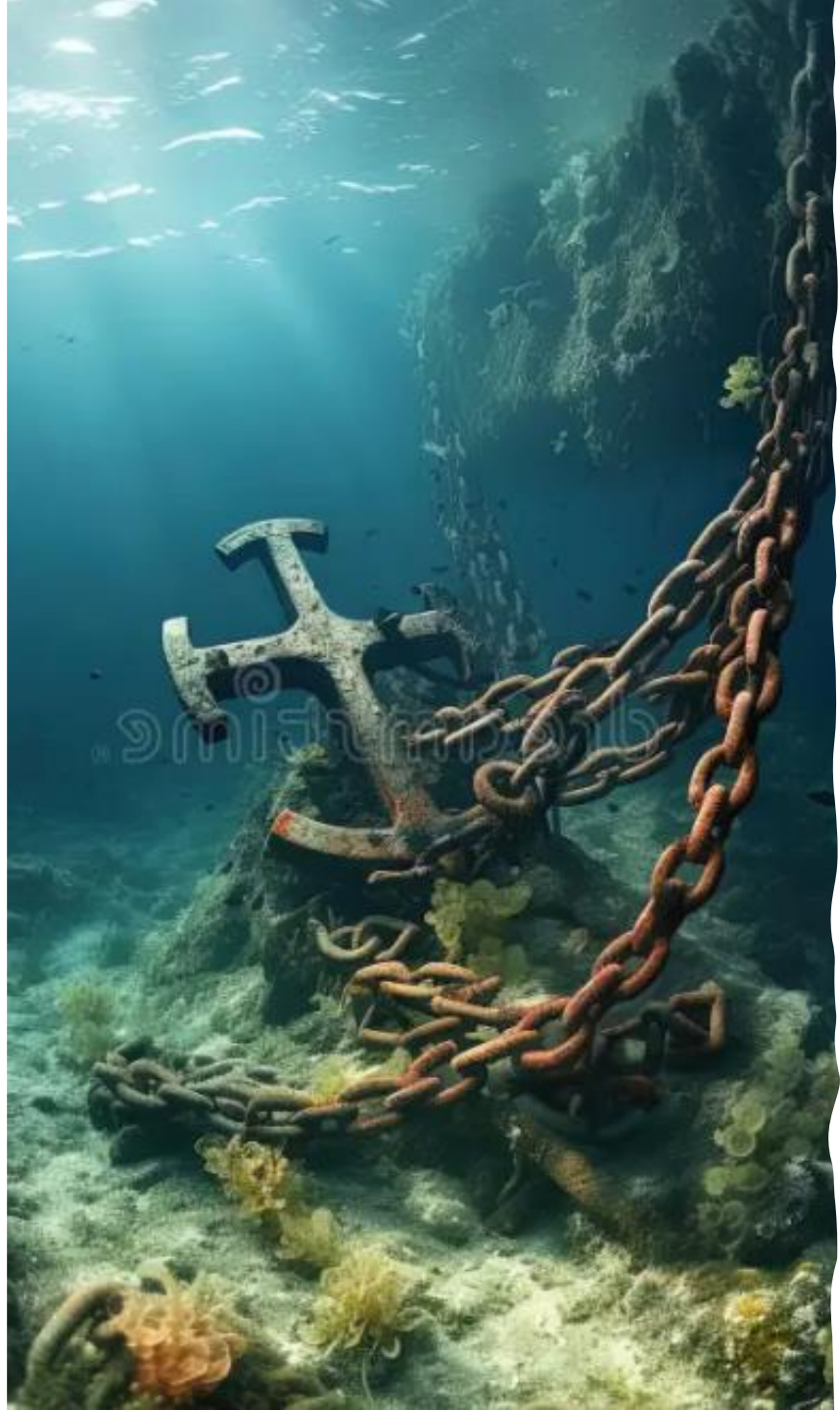
- NSAID-Induced Peptic Ulcer Disease (PUD) with microperforation
- Opioid-Induced Constipation (OIC) vs. Stercoral Colitis with inflammation/translocation or microperforation.
- Atypical diverticulitis or appendicitis
- GERD and aspiration pneumonia

3. **Other Systemic Infections**

- Pyelonephritis
- Infective Endocarditis (IE)

AI demonstrated a common cognitive bias!
“Geographic Anchoring”

Fever in New England = Most likely tick-borne disease

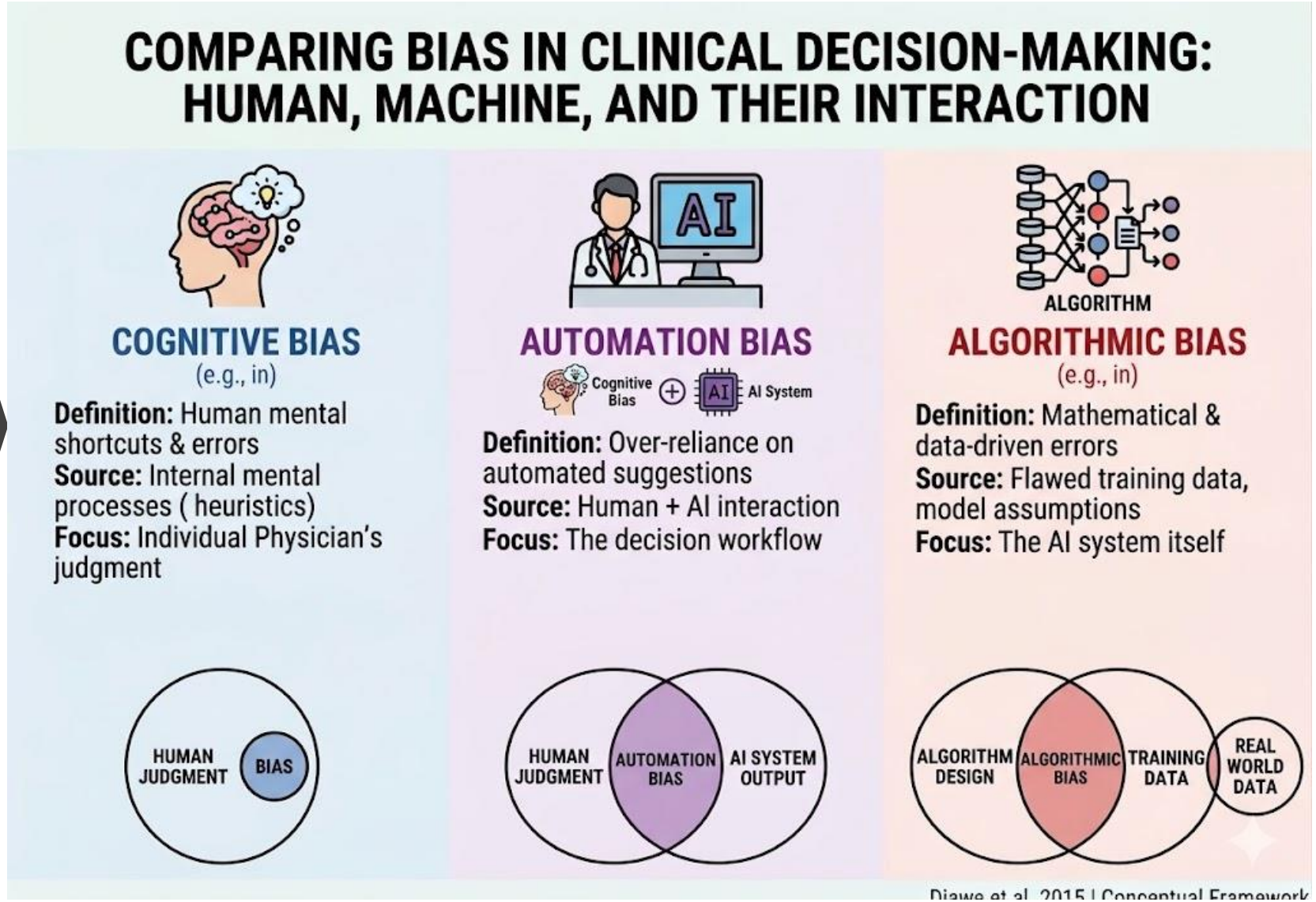


Bias in Clinical Reasoning

- Our diagnostic toolkit in medicine includes cognitive shortcuts or “heuristics”
  - Simple decision-making strategies basing decisions on a few relevant predictors
- Influenced by:
  - Context and conditions
  - Experience
  - Personality

- Possible biases in medical heuristics
  - Alliterative: tendency for your diagnostic impression to be unduly influenced by the impression of ***another clinician or AI***
  - Availability
  - Anchoring
  - Confirmatory
  - Representativeness
  - Overconfidence
  - Bandwagon effect
  - Zebra retreat bias

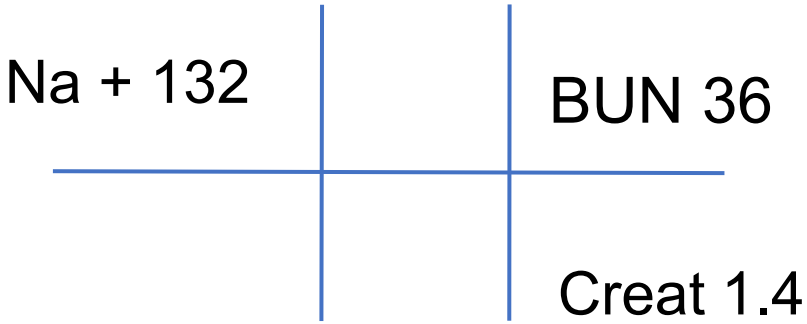
AI Also Has Bias

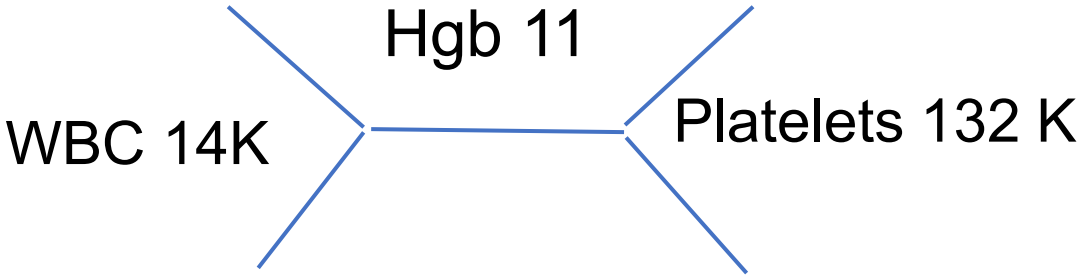


Physical Exam

- *Temperature 37.9 °C (100.2 °F)*
- *Respiratory Rate 18*
- *BP 137/68*
- Appears more *fatigued and thinner* than usual
- HEENT: Mouth dry but OP neg, sclerae/conj neg
- Lungs: *clear* ant and post
- Cor: S1S2 without G/R/M. EJ visible while flat.
- Abd: NABS, ND, *NT, no palpable HSmegaly or mass.* No CVAT. Testes nontender
- Ext: WWP, no edema.
- Skin: we did a full skin exam excepting the perineal skin. No rashes or skin lesions.
- MSK: *no visible swelling or erythema right hip, ROM limited by pain (unchanged)*

Labs and Imaging





Differential:
7% bands

- CXR: streaky bibasilar atelectasis
- Abd and chest CT with oral and IV contrast: large hiatal hernia, bibasilar atelectasis (cannot rule out early pneumonia)

- AST 69
- ALT 80
- Alk phos and bili normal

The Do Re Mi Principle

“Let’s start at …….

ID Clinical Reasoning Toolkit

- Determining a “prior probability” based on a few key features can aid in
  - Managing the vast range of potential pathogens
  - Reducing cognitive bias

Start With Your Own Illness Script

- This is a man whose *PMH is notable for*:
  - Living in New England in the summer, where he walks his dogs
  - Being 79
  - Well controlled DM2
  - GERD, for which he takes a PPI
  - Advanced DJD R hip, for which he takes NSAIDs
- *Recent course* has included: worsening R hip pain now requiring oxycodone
- *Presents with* a *1-2 week illness* with initial *symptoms* of transient acute mid abdominal pain, followed by poor appetite, fatigue and malaise, fevers, and chills
- *Labs notable for* mild leukocytosis with 7% bands, a decline in his Hgb and plts, mild transaminase elevation and AKI
- *CT chest and abdomen notable for* a large hiatal hernia and bibasilar streaky opacities, likely atelectasis

Bayesian Inference or Analysis

- A method of statistical inference in which Baye's theorem is used to update the probability for a hypothesis as more evidence or information becomes available

- Important technique in mathematical statistics, but has applications in a wide range of fields including medicine, and specifically, infectious diseases

Bayes Rule – What Is It? Why Is It Important?

- Reverend Thomas Bayes, 1702 – 1761
  British clergyman & mathematician
- Bayes Rule is fundamentally important to:
  - Bayesian statistics
  - Bayesian decision theory
  - Bayesian models in psychology

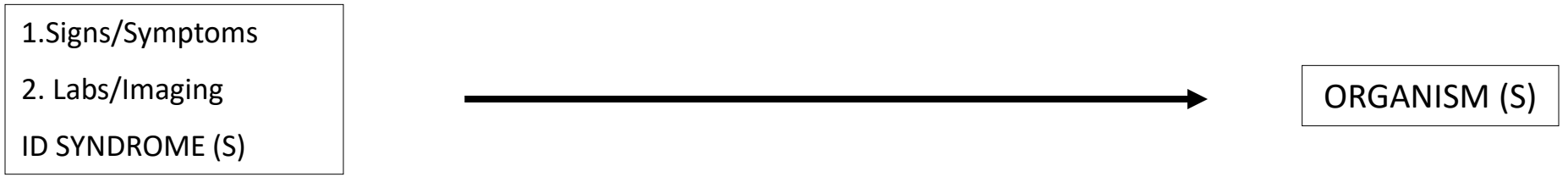
$$P(\text{Hypothesis}|\text{Data}) = \frac{P(\text{Data}|\text{Hypothesis}) \cdot P(\text{Hypothesis})}{P(\text{Data})}$$

$$P(\text{Data}) = \sum_{i=1}^{n} P(\text{Data} \mid \text{Hypothesis}_i) \cdot P(\text{Hypothesis}_i)$$

A Systematic Approach to Diagnosis in Infectious Disease, Using Modified Bayesian Analysis

- Baye's inference helps us to derive the posterior probability (diagnosis or differential diagnosis) as a consequence of two antecedents:
  - A *prior probability* of that infection or illness in that patient
  - A "*likelihood function*" derived from further observed data
- "Fast reasoning" in medicine incorporates aspects of modified Bayesian analysis, but a systematic approach can help integrate all important data and avoid common cognitive biases

Modified Bayesian Approach to Infectious Diseases



What specific questions would you ask about his symptoms?

If I gave you a full glass of water to hold when you had the chills, would the water spill?
When did you last eat a meal?

Clinical Checklist for Bacteremia: Rigors + Inability to Eat

Caveat: Studies with Different Patient Populations and Methods

Fevers	Rigors	Inability to Eat	Rigors + Inability to Eat
What is a fever? Many different definitions for different patient populations and purposes	What is a rigor? How do you elicit a history of rigors?	Anorexia is a feature of many acute and chronic infections	**Positive likelihood ratio 5**
Relatively poor marker of bacteremia/bacterial infection	Much better marker than fever for bacteremia/bacterial infection	In acute infection with or without fever, anorexia alone is a nonspecific, acute-phase response. **Positive likelihood ratio only 1.0-1.3**	In one study, the incidence of true bacteremia was **47.7%**.
Fever > 38.5, positive likelihood ratio only 1.2-1.4	**Positive likelihood ratio 3**		

Coburn B et al *JAMA 2012.* https://doi.org/10.1001/jama.2012.8262. Komatsu T et al. *J Hospital Medicine 2017*, https://doi.org/10.12788/jhm.2764

A Systematic Approach to Infection (modified Bayesian analysis)

1.Signs/Symptoms

2. Labs/Imaging *(with comparators)*

ID SYNDROME (S)

ORGANISM (S)

What is the Time Course of This Illness?

Is this Patient Different Than the Prototypical "Normal Host?"

1. Epidemiology
2. Systemic Alterations
3. Anatomic/Functional Alterations

Time Course of Illness

- *Duration*
- *Pace*
- *? Identifiable incubation period*

A Systematic Approach to Infection (modified Bayesian analysis)

1.Signs/Symptoms

2. Labs/Imaging *(with comparators)*

ID SYNDROME (S)

→ ORGANISM (S)

Time Course of Illness
- *Duration*
- *Pace*
- *? Identifiable incubation period*

Epidemiology

- Place of birth and residence
- Travel
- Season

Exposures

- Antibiotic exposure
- Recent micro
- Hospitalization
- Sick contacts
- Children
- Pets or animal exposure
- Habits, hobbies

Host

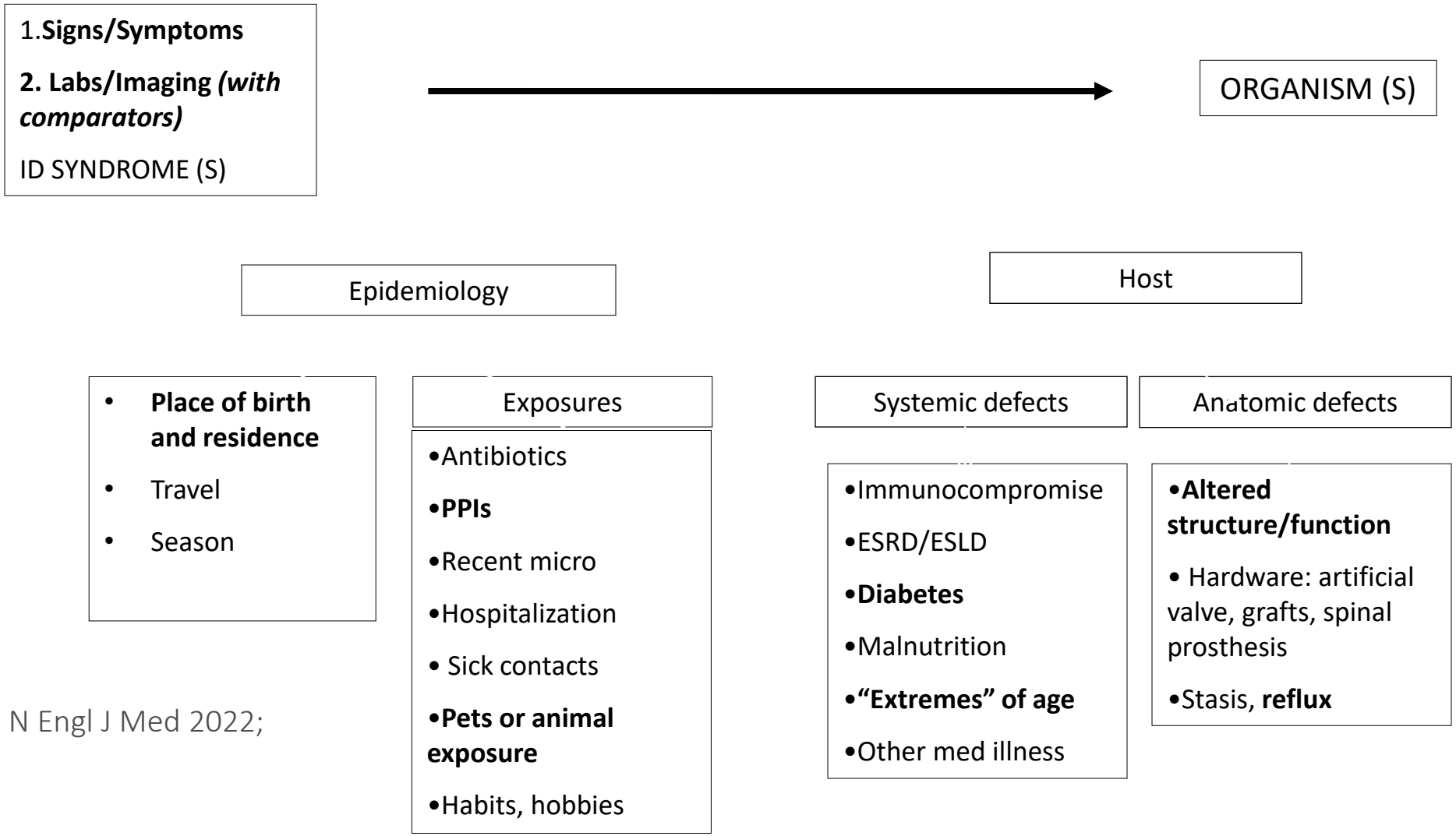
Systemic defects

- Immunocompromise
- ESRD/ESLD
- Diabetes
- Malnutrition
- "Extremes" of age
- Other med illness

Anatomic defects

- Altered structure/function
- Hardware: artificial valve, grafts, spinal prosthesis

A Systematic Approach to Infection (modified Bayesian analysis)

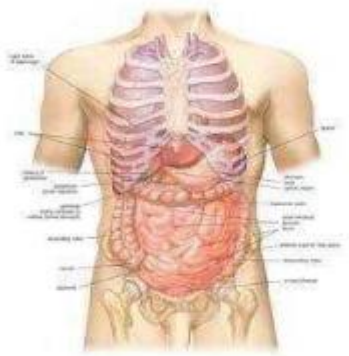


Basgoz N et al. N Engl J Med 2022; 387:547-556

My Major Categories of Potential Human Pathogens to Remember

From within:

- "Normal" translocation or low-grade bacteremia
- Breakdown of tissue barriers (micro or macro)
- Obstruction, tissue ischemia or necrosis



- From without:
  - Inhaled
  - Inoculated
  - Ingested
- Person to person vs environmental

Bacterial

Viral:
Respiratory
GI
Mono-like
CNS
Other

Fungal:
Candida (from within)
Non-candidal (inhaled or inoculated)

Mycobacterial:
TB (human to human)
Nontuberculous (inhaled or inoculated)

Parasitic

"Other" →

- "Other" includes small intracellular bacteria we don't routinely culture eg
  - Tick-borne: ehrlichia, anaplasma
  - Resp/GI/GU: mycoplasma, chlamydia

Non-Infectious (Mimics of Infection)

- Drug reaction
- Immune or autoimmune
- Inflammatory or autoinflammatory, eg Crohn's
- Endocrine
- Vascular eg thromboembolic
- Malignant

My “3 Ls”
From Our Analysis, We Should be Able to Generate the 3 Sets of Differential Diagnoses in Infectious Diseases

1. What’s most LIKELY: diagnoses in order of descending probability
2. What’s most LETHAL: Lower probability, high impact diagnoses. Likely to harm or kill that host if not recognized and treated within a few hours to few days
3. What’s LEFT: Diagnoses to consider when patient not improving and initial evaluation is unrevealing, including “zebras”

Diagnosis

- Blood cultures positive for *Listeria monocytogenes*
  - No evidence of meningitis
  - No evidence of septic arthritis
  - No identifiable risk factor except age
- Listeria accounts for < 1% of reported enteric infections in the US
- 80-90% of Listeria presents as invasive disease.
  - Febrile gastroenteritis is uncommon and self limited
  - Abdominal pain may be present
  - 15-20% mortality

Prevention of Listeria in High-Risk Patients (Pregnant, Immunocompromised, Elderly)

- US outbreaks linked to ready-to-eat refrigerated foods
  - Listeria can multiply at refrigerator temperatures
- Foods to avoid
  - Deli meats and hot dogs
  - Unpasteurized cheeses or dairy, soft cheeses
  - Seafood and meat spreads
  - Raw sprouts or mushrooms, pre-made salads
- Attention to rapid refrigeration and low temp (40 F, 4 C)
- Kitchen hygiene
- Examine need for PPI
  - Associated with a 3-5X risk of enteric infections

Patient 2: HPI

- 32 year old woman with psoriasis, treated with risankizumab (an IL-23 inhibitor, Skyrizi)
- Born and lives in Boston, with her 2 y/o daughter and husband
  - Daughter recently had a mild upper respiratory illness
- Presents to you with a progressive 12-day illness
  - Progressive pharyngitis with exudates + tender cervical lymphadenopathy
  - Fatigue and malaise; mild myalgias and headache
  - Fevers as high as 102.7 F (39.4 C) without rigors
    - All labs normal including WBC 7 with a normal differential
    - Rapid strep and rapid COVID negative
    - No improvement with azithromycin
  - Now developing worsening nasal congestion with anterior facial pain R>L
  - No cough or wheeze, lungs clear

Your Diagnosis Is

1. Influenza
2. Adenovirus
3. Parainfluenza
4. COVID-19
5. Respiratory syncytial virus
6. Human metapneumovirus

You would

1. Send a respiratory pathogen multiplex PCR
2. Start prednisone
3. Start amoxicillin clavulanate
4. #1 and 3
5. #2 and 3

Syndrome	Primary / Most Common Viral Etiologies
Prolonged Fever	**Adenovirus** > COVID-19 > Influenza
Pharyngitis	**Adenovirus** > COVID-19
Sinusitis	**Adenovirus, Influenza, COVID-19** (All viruses can cause this)
Bronchiolitis	**RSV** >> **hMPV** > Parainfluenza (PIV-3)
Pneumonia	**COVID-19, Influenza, RSV, hMPV** (Viral or secondary bacterial)

Indications for Respiratory Multiplex PCR

- Inpatient
- Would impact
  - Antiviral or antibacterial utilization (eg mycoplasma)
  - Infection control
- Outpatient at high risk for complications
  - Immunocompromised
  - Elderly
  - Severe comorbidities
  - Severe or worsening symptoms

Biologics and Infection

- Dermatologic disease is the fastest growing indication for biologics in the US
  - Psoriasis, atopic dermatitis, hidradenitis suppurativa, atopic dermatitis and prurigo nodularis
- The most commonly used biologics are IL-17 and IL-23 inhibitors
  - Greater specificity with lower risk of infection than TNF inhibitors
  - Some increased risk of mild to moderate upper respiratory tract infections
  - IL 17 inhibitors eg secukinumab (Cosentyx) higher risk than IL-23 inhibitors eg risankizumab (Skyrizi), guselkumab (Tremfya)

Indications for Antibacterials After Viral Rhinosinusitis

- Immunocompetent:
  - Persistent symptoms without improvement for ≥7-10 days
  - High fever (≥39°C / 102°F) with purulent nasal discharge or facial pain lasting ≥3–4 consecutive days [3-4]
  - Bimodal illness: initial improvement of a typical viral URI followed by new worsening of symptoms (new-onset fever, increased nasal discharge, or worsening facial pain) after 3–5 days
- Immunocompromised
  - Lower threshold for early antibiotics
  - 72 hour reassessment with consideration of ENT evaluation for exam and endoscopic cultures if no improvement
  - Remember to include fungal sinusitis in your differential

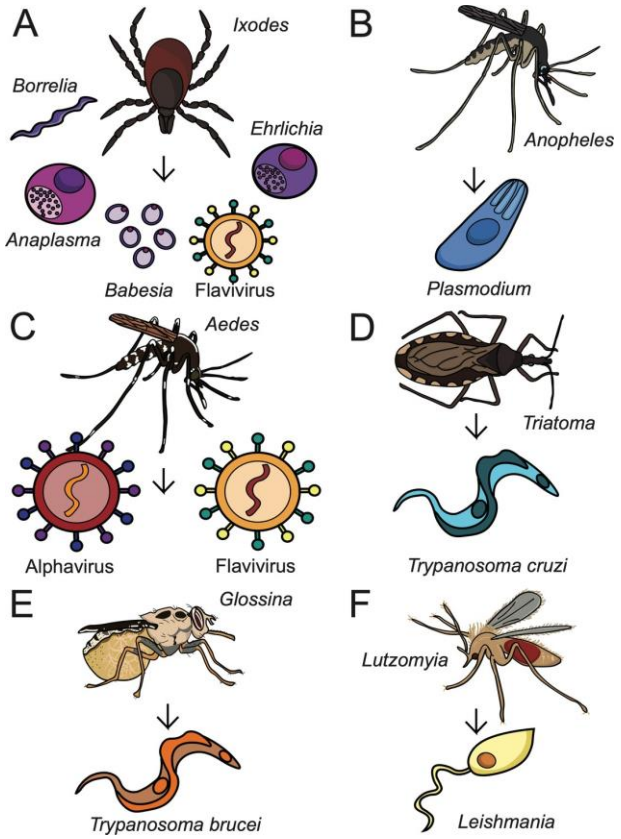
Children, Adults and Respiratory Viruses

- In one surveillance study of children < 2 years, they experienced 9.4 respiratory viral infections/child/year
  - 50% were rhinovirus/enterovirus
    - Remainder RSV, flu, adenovirus, human bocavirus, endemic human coronaviruses, human metapneumovirus, parainfluenza viruses
  - 5-10% coinfected
  - 37% were symptomatic
- In another study of symptomatic children, transmission occurred to about 12% of adult family members within one week

Teoh Z et al. Clin Infect Dis. 77(6): 901–909. McIntyre CR et al. Vaccine 30 (19) 3009-14.

Vectors of Clinical Importance

Not so Adorable Vectors



Adorable Vectors

Finally, Remember Your First Diagnosis May Not Be Your Last!

Francis Picabia 1979-1953

Our heads are round so our thoughts can change directions

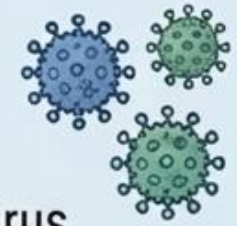
The New Yorker

This IS a second opinion. At first I thought you had something else

DIFFERENTIAL DIAGNOSIS OF
FEVER OF INTERMEDIATE DURATION (1-2 WEEKS) IN ADULTS

RESPIRATORY VIRUSES

- RSV
- Influenza
- Parainfluenza
- Adenovirus
- Metapneumovirus
- COVID-19



MONO-LIKE VIRUSES

- Epstein-Barr Virus (EBV)
- Cytomegalovirus (CMV)
- Acute HIV Infection

OTHER VIRUSES

- Enterovirus/Coxsackievirus
- Parvovirus

BACTERIAL INFECTIONS

- SBE
- Cryptic Bacteremia
- Enteric fever
- Occult abscesses

ZOONOTIC OR VECTOR-BORNE INFECTIONS

- Lyme
- Anaplasma/Ehrlichia
- Babesia
- Q Fever, Brucella

NONINFECTIOUS CAUSES

- Drugs (e.g., beta-lactams, anticonvulsants)
- Early autoimmune
- Subacute Thyroiditis

Take Home Points

- Fevers of intermediate duration are common in clinical practice
- A diagnosis of infectious etiologies of these fevers is aided by
  - A systematic approach utilizing features of Bayesian analysis
  - A framework for the major categories of human pathogens
- Include true rigors + inability to eat in your clinical checklist for bacteremia
- Adenovirus is a common cause of severe exudative pharyngitis

Thank you for your Attention and for your Attendance!