



**Brigham and Women's Hospital**

Founding Member, Mass General Brigham

# **Challenging Patients in Infectious Diseases A Diagnostic Toolkit for Internal Medicine**

Nesli Basgoz MD  
Massachusetts General Hospital  
Harvard Medical School



**CONTINUING MEDICAL EDUCATION  
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL**

# Nesli Basgoz MD

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- Northwestern University Medical School
- Infectious Disease Fellowship at UCSF
- For many years, Associate Chief and Clinical Director, Infectious Disease Division @ MGH
- Chief, James Jackson Firm, Department of Medicine @MGH
- Associate Professor of Medicine @ Harvard Medical School
- Clinical, Educational and Research Focus:
  - Diagnostic Reasoning in Infectious Diseases
  - Diagnosis and Management of Opportunistic Infections



# Disclosures

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None

# Learning Objectives

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- To utilize a simple *conceptual framework* to apply to patients who may have infectious diseases in your practice
  - Systematic—can help avoid common biases and heuristics
  - 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

# Patient 1: History of Present Illness

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- 72 y/o man, born in India, presents to urgent care with a 2 week illness
- PMH notable for HTN and a positive PPD, attributed to childhood bCG
- Social history: lives in a densely wooded suburb of Boston. No known tick bites. Yearly travel to India, most recently a month ago
- Symptoms
  - Dry cough
  - Fatigue and malaise, myalgias, arthralgias; no fevers or chills
- Exam:
  - No acute distress. T 37.5 C, RR 16, HR 88 and regular, lungs clear
  - Cardiac exam with I-II/VI SEM LSB (heard previously)
- Treated for bronchitis with azithromycin x 5 days with marked improvement

# Patient 1: HPI continued

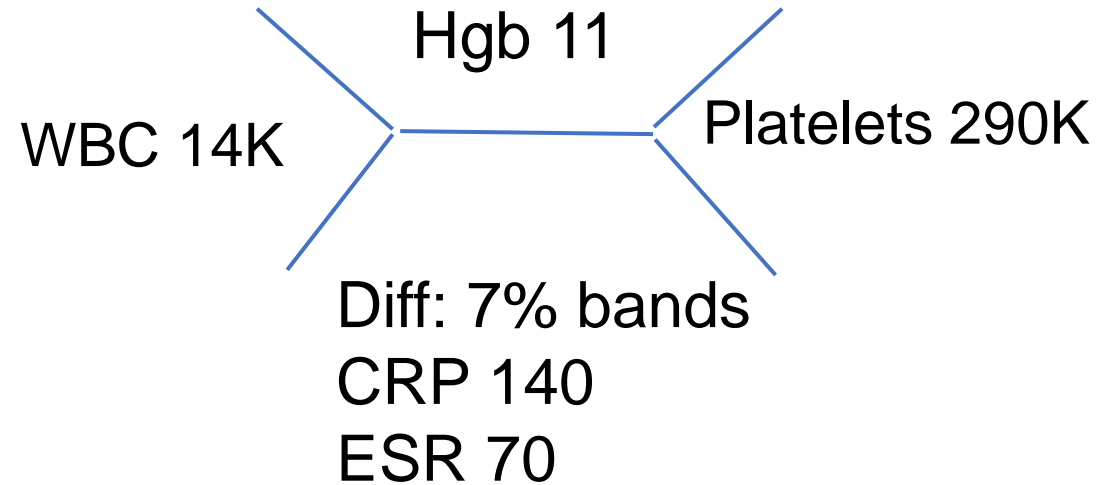
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- 3 days after finishing azithromycin he returns with worsening symptoms, now including night sweats and dyspnea on exertion
- Exam
  - Weak, ill appearing
  - Temp 38, HR 100, 6 lb weight loss documented in record but not commented upon
  - Lungs clear. Cardiac exam I-II/VI SEM LSB (longstanding per record)
  - No rashes

# Labs

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Na + 127



WBC 14K      Hgb 11      Platelets 290K

Diff: 7% bands  
CRP 140  
ESR 70

- Lyme serology positive
- CXR: LLL calcified granuloma, left upper lobe volume loss with apical pleural thickening (unchanged from prior)

- AST 69
- ALT 80
- Alk phos and bili normal
- Albumin 3, globulin 5.4

# The most likely diagnosis is:

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1. Lyme disease (*Borrelia burgdorferi* infection)
2. Pulmonary tuberculosis
3. Endocarditis
4. Malaria
5. Malignancy



# What ChatGPT Thinks

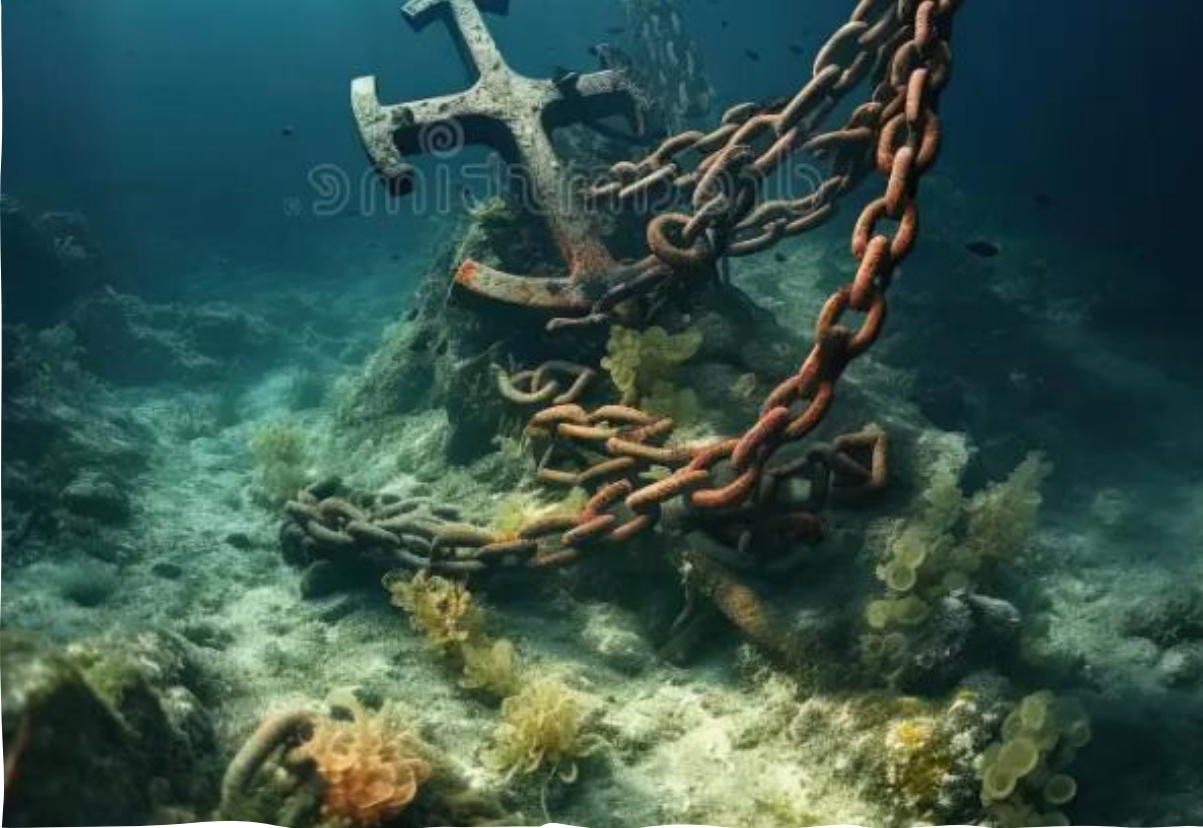
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- The positive Lyme serology combined with systemic symptoms, lung involvement, and elevated liver enzymes points toward **disseminated Lyme disease with pulmonary involvement or a co-infection**
- **Disseminated Lyme disease with pulmonary involvement** is a reasonable primary diagnosis given:
  - Positive Lyme serology
  - Residence in endemic area
  - Constitutional symptoms
  - Liver enzyme elevation
  - Lung findings (pneumonia vs atelectasis)
- However, **reactivation tuberculosis remains a critical differential**, especially with the PPD and calcified granuloma history and constitutional symptoms like night sweats and weight loss

# Chat GPT Recommends

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- Sputum AFB smears/cultures
- Lyme PCR if available:
- Chest CT to clarify lung pathology
- Consider other co-infections or alternative diagnoses (fungal, malignancy)
- Start appropriate antibiotics for Lyme (e.g., doxycycline)
- Monitor clinical response closely



Chat GPT demonstrated a common  
cognitive bias!

Anchoring: overreliance on the first  
piece of information or diagnosis

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Let's use our ID Clinical Reasoning  
"Toolkit" Instead!

# The Do Re Mi Principle



“Let’s start at the \_\_\_\_\_ it’s a very good place to start”

# Your ID Illness Script

This is a \_\_\_\_\_ whose PMH is notable for:

Recent course has included:

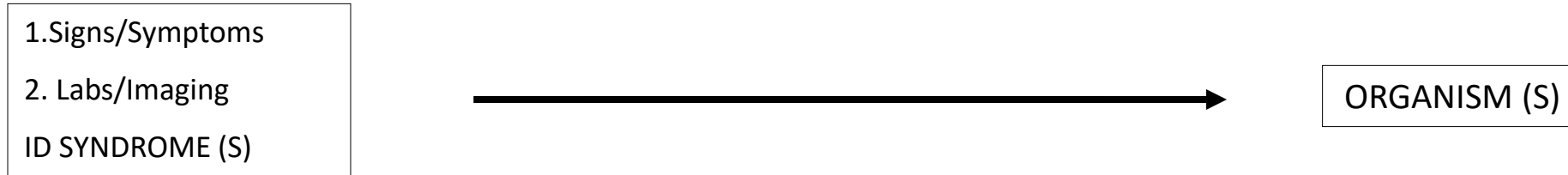
Presented with symptoms of:

Exam demonstrated (presence and absence of):

Data are remarkable for:

Differential diagnosis:

# Use a Modified Bayesian Approach to Infectious Diseases



If we are fortunate, we get an immediate working diagnosis from the above.

If it remains a diagnostic dilemma, here's a stepwise approach

# 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



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

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

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

- The pathogens we recognize, and the microorganisms with pathogenic potential, are vast
- 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



# A Systematic Approach to Infection (modified Bayesian analysis)

1. Signs/Symptoms  
2. Labs/Imaging (*with comparators*)  
ID SYNDROME (S)



ORGANISM (S)

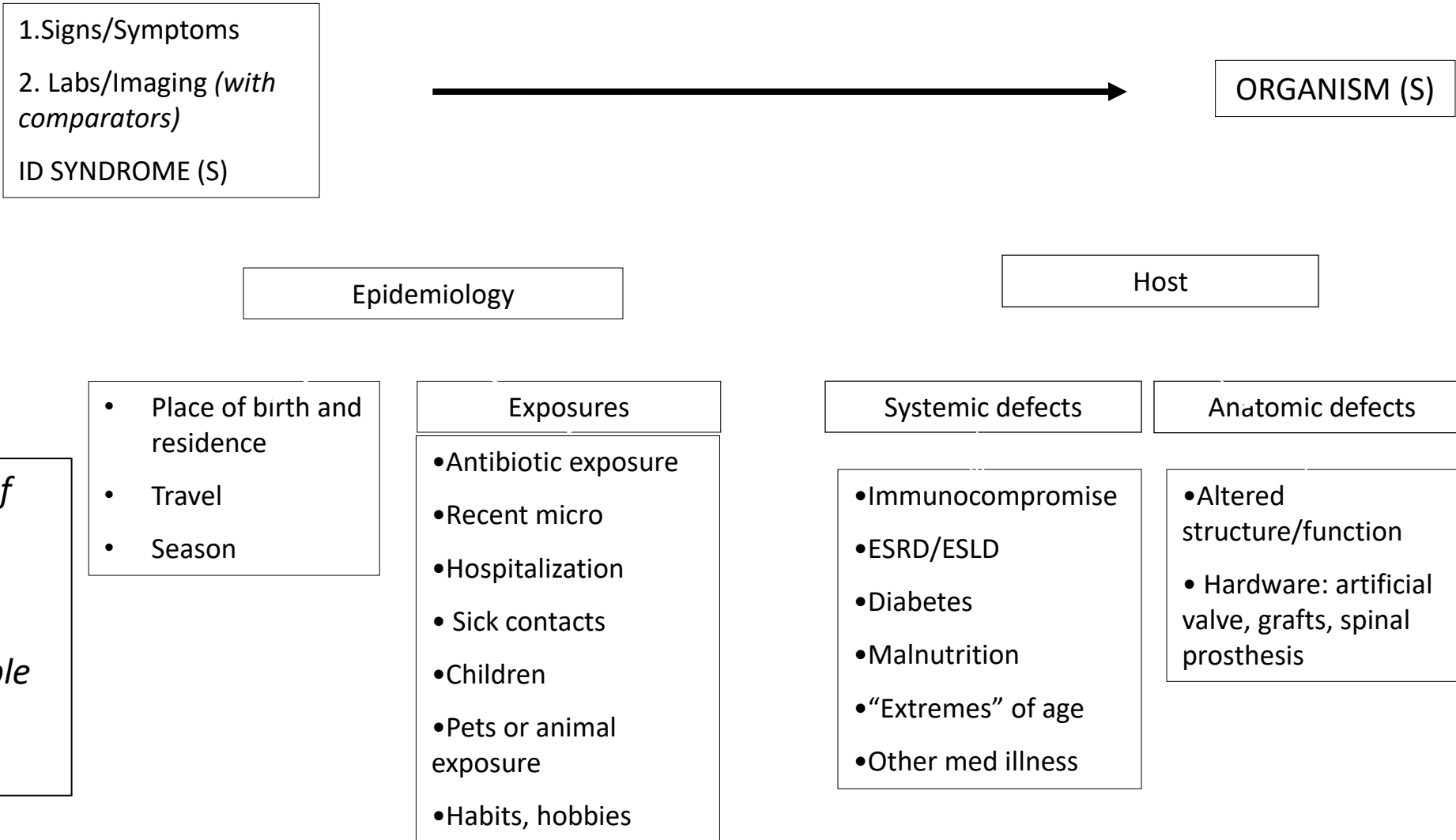
What is the Time Course of This Illness?  
Is this Patient Different Than the Prototypical “Normal Host?”

*Time Course of Illness*

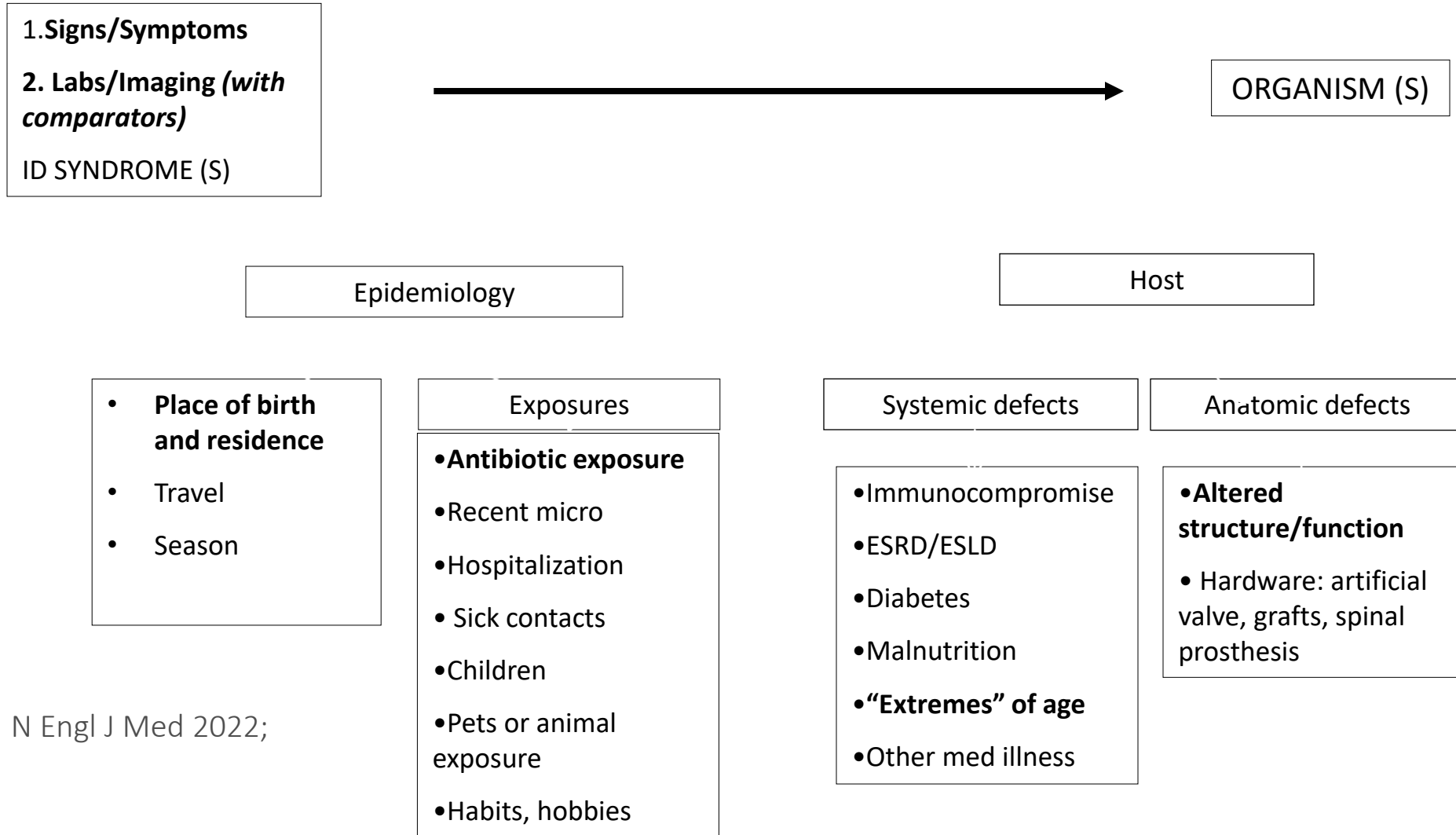
- *Duration*
- *Pace*
- *? Identifiable incubation period*

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

# A Systematic Approach to Infection (modified Bayesian analysis)



# A Systematic Approach to Infection (modified Bayesian analysis)



# Illness Script Derived from our Analysis

- **72 year old healthy man**
- **His epidemiology is notable for** being Indian-born and residing in suburban Boston
- **His PMH is notable for** a positive PPD, a heart murmur, and a CXR with a calcified granuloma and LUL volume loss
- **He presents with** a subacute illness with fatigue, malaise, myalgias, dry cough, DOE, night sweats, without fever. Initially responsive to azithromycin.
- **His exam** now demonstrates an ill appearing man with tachycardia and weight loss, without rash or pulmonary findings.
- **Data are remarkable for:** anemia, leukocytosis, elevated inflammatory markers and absence of new findings on CXR. A screening Lyme serology (EIA) is positive.

# Lyme Diagnostics are Imperfect

- First step: Enzyme immunoassay (EIA) for screening.
  - Previously, antigens were whole cell sonicate of cultured *B. burgdorferi* sensu stricto
    - Sensitive but nonspecific
  - New assay at MGH and many labs: Specific antigens replace whole cell sonicate (VlsE from *B. burgdorferi* and *B. garinii*, OspC from *B. afzelii*)
    - Better specificity
    - Better sensitivity for Euro-Lyme strains
- Second step for confirmation: if EIA positive or equivocal
  - Western Blot:
  - Much better specificity (if CDC criteria used)
    - Patient's WB test result later negative

# 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”

# Based on Your Illness Script, What's Your Working Diagnosis Now?

1. Lyme disease (*Borrelia burgdorferi* infection)
2. Pulmonary tuberculosis
3. Subacute bacterial endocarditis
4. Malaria
5. Malignancy

# Patient 1 Follow Up

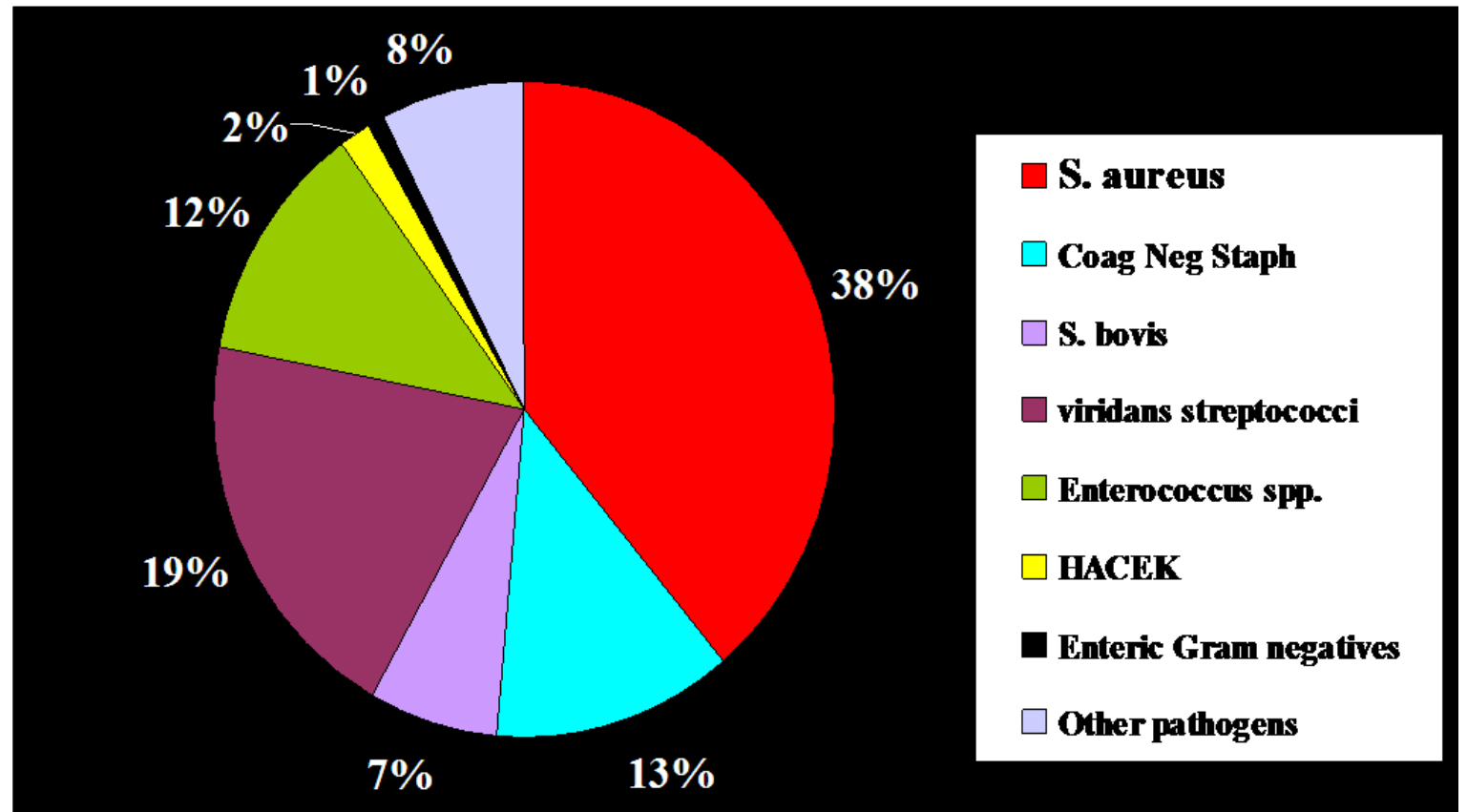
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- He was prescribed 3 weeks of doxycycline for Lyme disease
- 1 week into therapy, he presented with CHF, a diastolic murmur and 4/4 blood cultures with strep sanguis (viridans strep)
- Echo with a bicuspid aortic valve with a vegetation and severe aortic insufficiency
- Requires aortic valve replacement



Staph Aureus is  
Now the Most  
Common Single  
Agent of Infective  
Endocarditis in  
the US

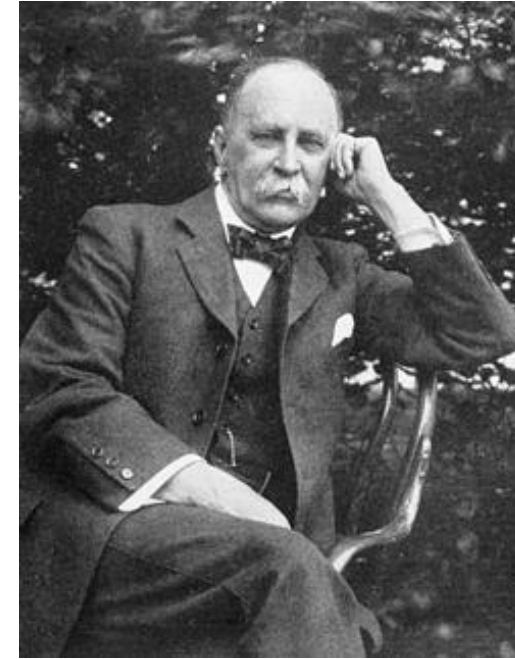
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# Many Clinicians Have Not Seen the Insidious Manifestations of SBE with Strep species

- In series of SBE, fever present in 50-80%, less likely in:
  - Elderly
  - Kidney, liver or other medical illness
  - Protein calorie malnutrition
- CRP and ESR are elevated
- False positive serologies common
- Think of SBE with
  - Progressive fatigue and malaise
  - Anorexia and weight loss
  - Rheumatologic manifestations (“polymyalgia rheumatica”)
  - Dry cough, dyspnea (even without CHF)
  - Stroke, vision loss or other neurologic disease
  - Unexplained, peripheral mucocutaneous lesions

- Before you prescribe the *first* but particularly the *second* course of oral antibiotics for ANY indication, ask yourself:
  1. Does this patient have any risk factors for SBE?
  2. Is any part of this illness compatible with SBE?
- Draw blood cultures from different sites, ideally:
  - 3 sets more than 12 hours apart
  - OR
  - 3 sets drawn over at least an hour



- “One of the first duties of the physician is to educate the masses not to take medicines”

# Patient 1: Takeaways

- The range of potential pathogens in infectious diseases is vast
  - Symptoms and signs may overlap
- Determining a “prior probability” based on a few key features can aid you in diagnosis
  1. Duration and time course
  2. Epidemiology and exposures
  3. Host factors (systemic and anatomic)
- Rule out SBE in cryptic illnesses with a subacute presentation

# Patient 2: History of Present Illness

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- 24 year old graduate student with PMH Crohn's disease, stable on adalimumab (Humira)
- 3 weeks prior to admission: "cold," described as 4 days of rhinorrhea, sore throat, dry cough without fever, chest pain or SOB
- 1 week prior to admission diffuse arthralgias and painful sores of lips and mouth
- Social history: 6 weeks ago, spent Labor Day with her extended family in CT. No other travel. Sexually active with one male partner
- Vaccines up to date. No other meds

# Physical Exam

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- Afebrile, no tachypnea or tachycardia
- Tender oral ulcers
- Few erythematous, pustular facial > upper extremity lesions
- Mild conjunctivitis and periorbital edema
- Mild, diffuse expiratory wheezes, no rales



# Labs and Imaging

## Labs

- Hgb 7.8 (baseline 11), WBC 13,000 with normal differential, platelets normal
- ALT, AST, alk phos normal
- LDH 580
- Tbili 2.3, Dbili 0.4

## Chest X-ray



# What is your Diagnosis?

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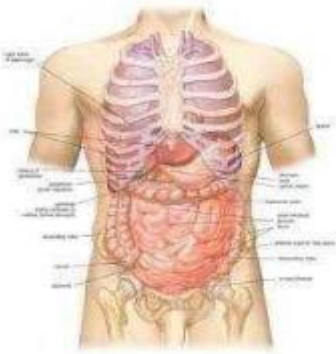
1. Coxsackievirus
2. *Mycoplasma pneumoniae*
3. Adenovirus
4. Mononucleosis syndrome (CMV, EBV or HIV)
5. Crohn's with extraintestinal manifestations



# My Major Categories of Potential Human Pathogens to Remember

From within:

- “Normal” translocation or low-grade bacteremia
- Breakdown of tissue barriers
- 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)

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

# Illness Script Derived from our Analysis

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- **34 year old woman with a PMH notable for** stable Crohn's disease, on adalimumab
- **Epidemiologic and social history:** graduate student, sexually active. 6 weeks ago, Thanksgiving get together family (children and adults)
- **Recent history** of self-limited rhinorrhea, sore throat and dry cough 3 weeks ago
- **Current symptoms** of subacute but progressive diffuse arthralgias and painful sores of lips and mouth
- **Exam** demonstrates an erythematous, pustular rash mouth and extremities
- **Data show** a new anemia with mild elevation of LDH and indirect bili. CXR with patchy LLL infiltrate

# October 2024 CDC Alert: Rising Mycoplasma Activity

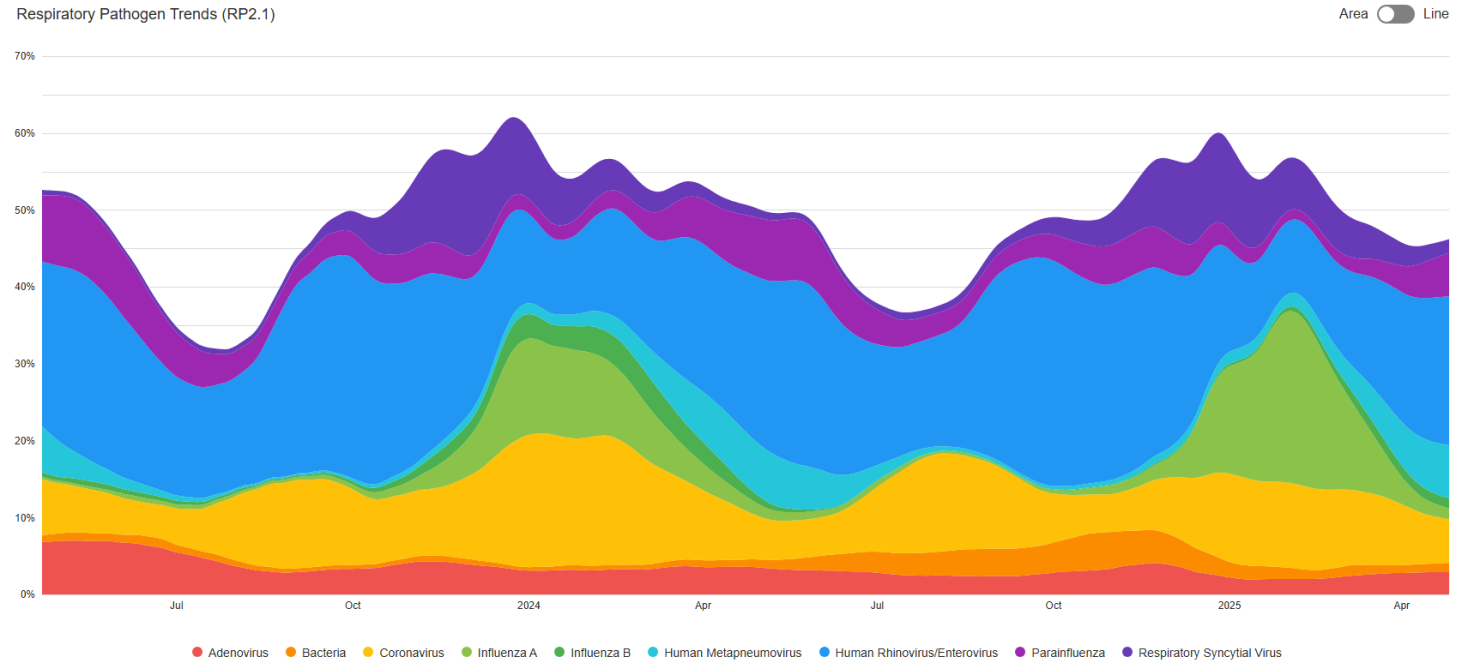
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- National Surveillance Programs
- bioMerieux BIOFIRE based syndromic trend data (available for respiratory and GI agents)

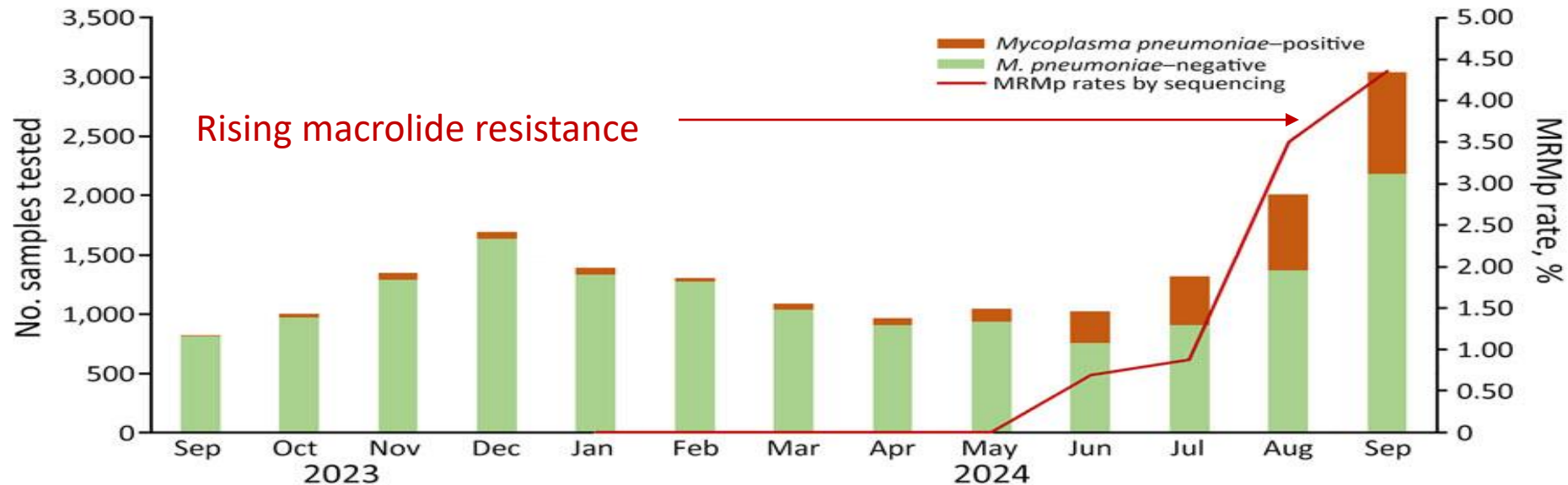
<https://syndromictrends.com>

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- Mycoplasma not demonstrated here, but data available



# Excess *M. pneumoniae* Cases US 2023-2025



- EPIC Cosmos database > 280 million patients
- 9 fold increase in cases (exceeded that seen in cyclic outbreaks every 3-5 years)
- Subset of cases studied for macrolide resistance, as shown
  - Reported US resistance 2-22%, up to 30% worldwide
    - Regimen for suspected mycoplasma pneumonia should include a quinolone or doxycycline

# Protean Manifestations of *Mycoplasma pneumoniae* Infection

## Respiratory

- Asymptomatic
  - Prolonged carriage
- URI, bronchitis, bronchiolitis
- Pneumonia
- Rarely, necrotizing/cavitary pneumonia, lung abscess, empyema, ARDS, bronchiolitis obliterans, death
- High risk: older adults, medically ill, immunocompromised, sickle cell disease

## Nonrespiratory (immune mediated)

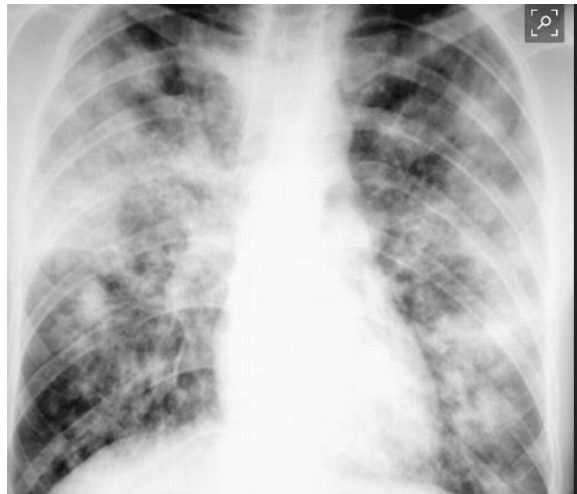
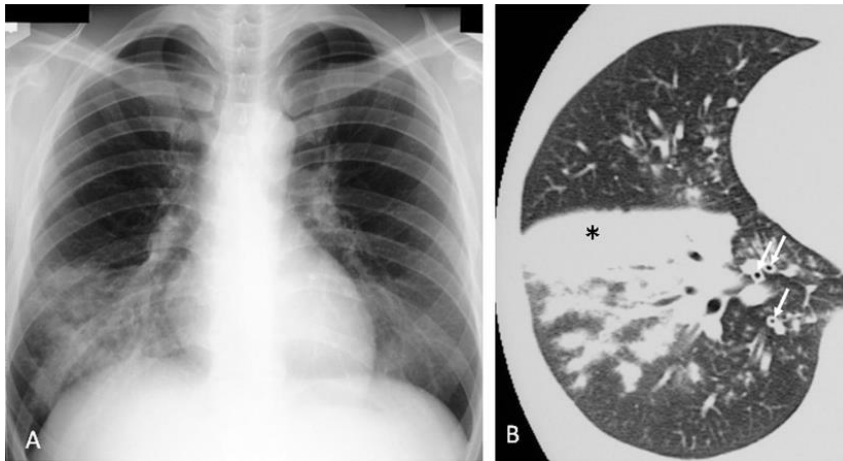
- Hemolysis (IgM antibodies to the I antigen on RBC)
- Polymorphic exanthem and/or enanthem
- CNS involvement
- Polyarthralgias or polyarthritis
- Cardiac or renal disease

# RIME (Reactive Infectious Mucocutaneous Eruption)

- Exam and pathology distinct from that seen with erythema multiforme and SJS
  - Orolabial ulcers, hemorrhagic crusting
  - Conjunctivitis, orbital edema
  - Sparse pustular or vesiculobullous lesions, face, trunk, extremities
    - No target lesions
- Pathogenesis?
  - Indirect: immune complex deposition, complement activation, molecular mimicry between P1 adhesion and keratinocyte antigens
  - Direct via inflammation, cytokine release

# Mycoplasma Radiology is Heterogeneous

Bronchiolitis, Bronchitis, Bronchopneumonia



Lobar Pneumonia





# Patient 2 Follow Up

- NP swab negative for mycoplasma and other respiratory pathogens
  - Later, IgM and IgG positive
    - Beware limitations of serologic testing!
- Probable mycoplasma based on clinical features of probable 3 week incubation period, subacute illness, compatible rash and CXR, concordant serology
- Slow improvement with levofloxacin and supportive care

## Patient 2: Takeaways

- Consider nonviral respiratory infections in your differential
- Year round occurrence and extra-respiratory manifestations may be an important clue to mycoplasma infection
- Immunocompromised hosts may have more severe manifestations of disease



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

Bayes wants you to integrate new data

Francis Picabia 1979-1953



The New Yorker



Picabia "Our heads are round so our thoughts can change directions."

