Brigham and Women's Hospital
Founding Member, Mass General Brigham

Pulmonary Infections in the Immunocompromised Host

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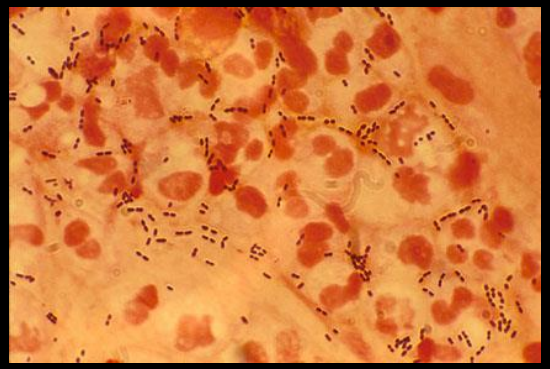
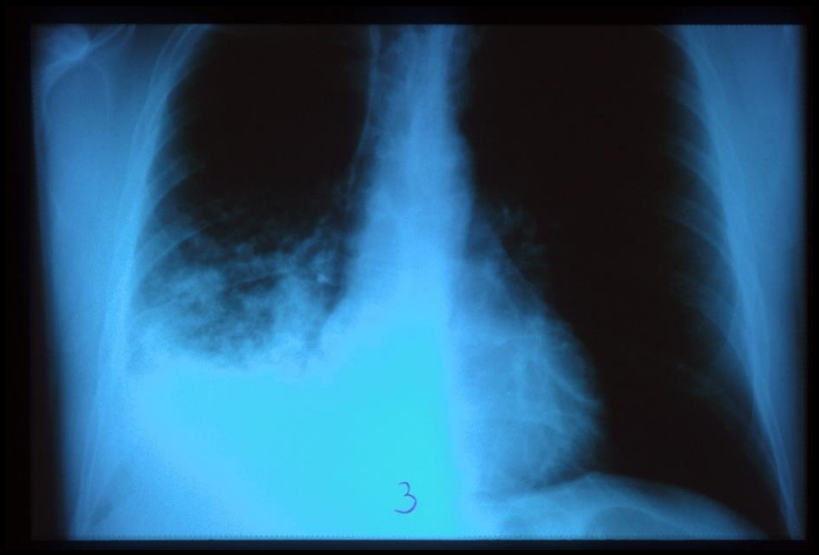
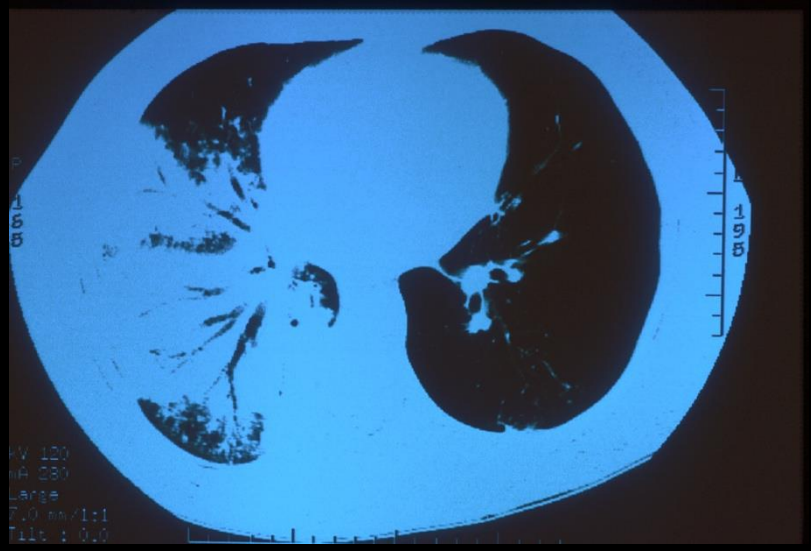
Disclosures

None

Classic Pneumonia







60-year-old man presents with SOB, fever, and cough productive of rusty-brown sputum

Fundamental Principles

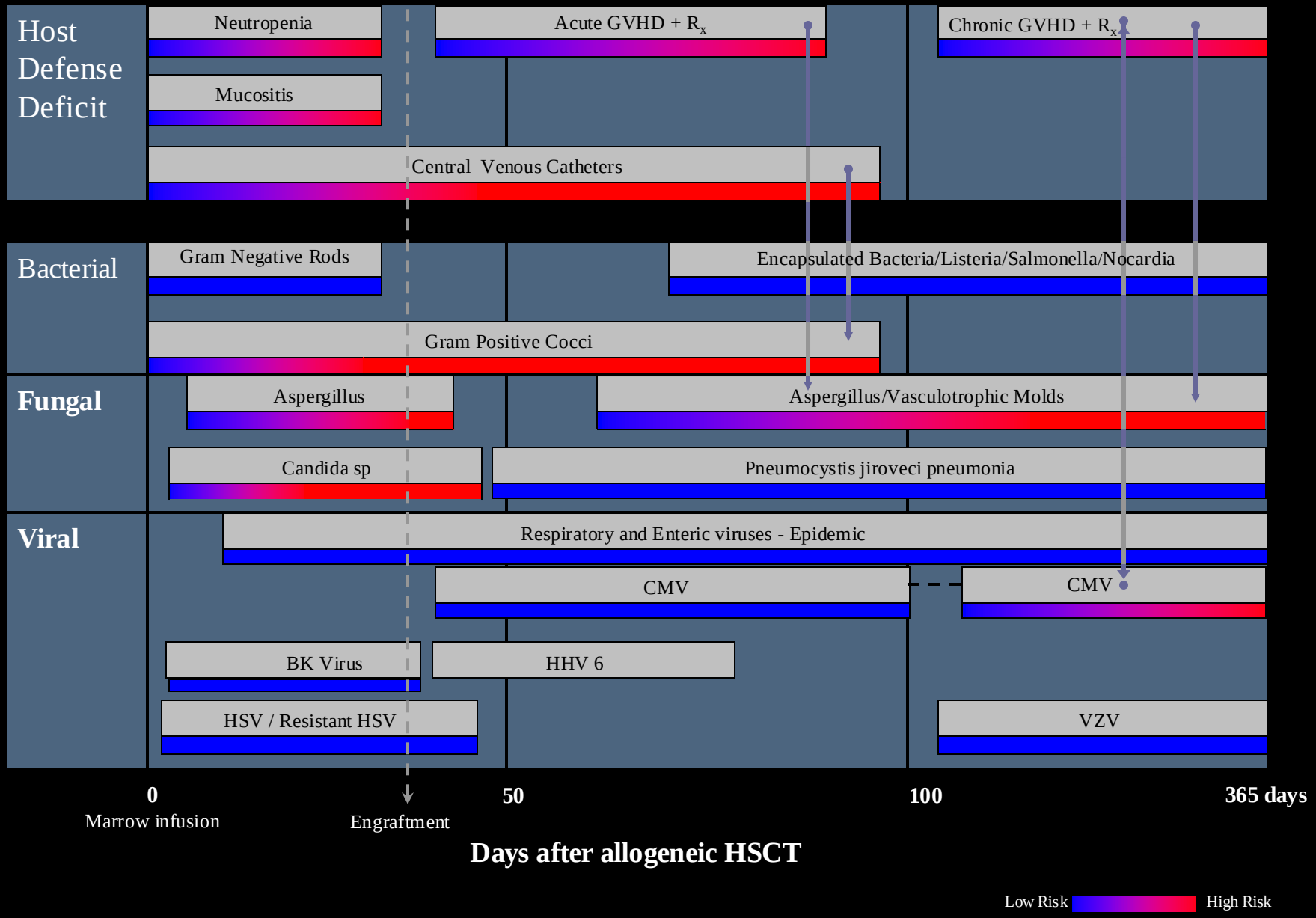
$$\text{Infection} = \frac{\text{Inoculum} \times \text{Virulence}}{\text{Net State of Immunosuppression}}$$

- Infection is a function of
  - Pathogen exposure/ inoculum
    - Reservoir, vector, mode of transmission
      - *Candida*: person to person with acquisition likely via ingestion (GI tract reservoir) or via catheters
      - *Aspergillus*: air, ?water with acquisition via the respiratory tract
  - Pathogen virulence
  - Host susceptibility
    - Net state of immunosuppression

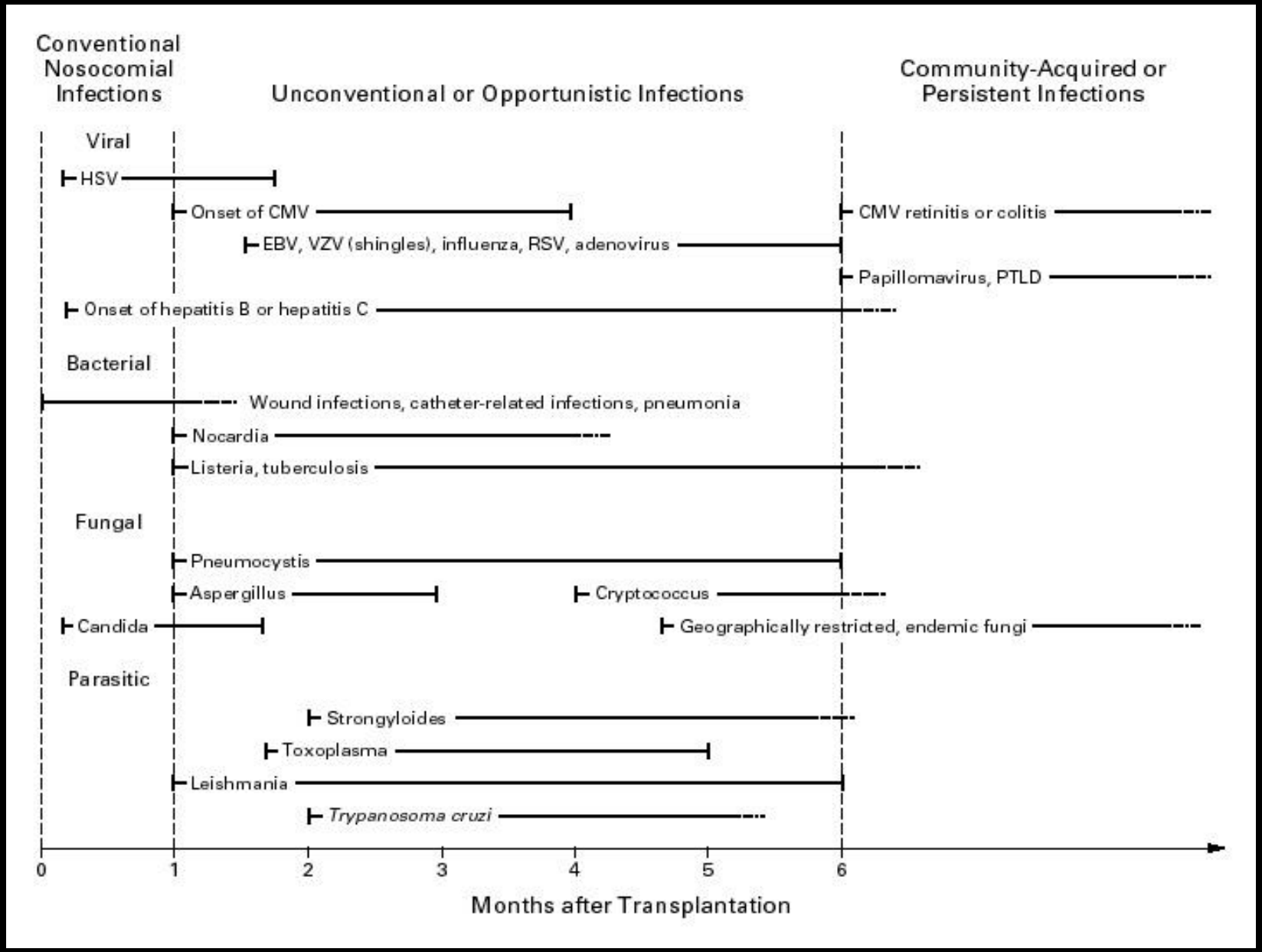
Critical Factors in Assessing the Risk for Infection - Host

- Net State of Immunosuppression
  - Dose, duration, sequence of immunosuppressive medications (e.g., pulse steroids, OKT3)
  - Rejection
  - Leukopenia
  - Breakdown of barriers, devitalized tissue
  - Metabolic factors (malnutrition, uremia)
  - Infection w/ immunomodulating viruses (CMV, HIV)
- Consequence of invasive procedures
  - Supportive (lines, Foley, ET tube)
  - Technical aspect of the surgery

Transplant ID Principles (allo-HCT)



Usual Sequence of Infections after Solid Organ Transplantation



Fishman JA, Rubin RH. N Engl J Med 1998;338:1741-1751

Exposure to Organism

- Ubiquitous
  - Intrinsically virulent: Pneumococcus, MTb
  - Opportunistic: PJP, Cryptococcus
- Specific environmental sources
  - Nosocomial
  - Community: legionella, tularemia, anthrax
- Geographically restricted organisms
  - Endemic mycoses
- Epidemic
  - Influenza, SARS-CoV-2
- Latent
  - MTb, endemic mycoses, viruses (herpes group)

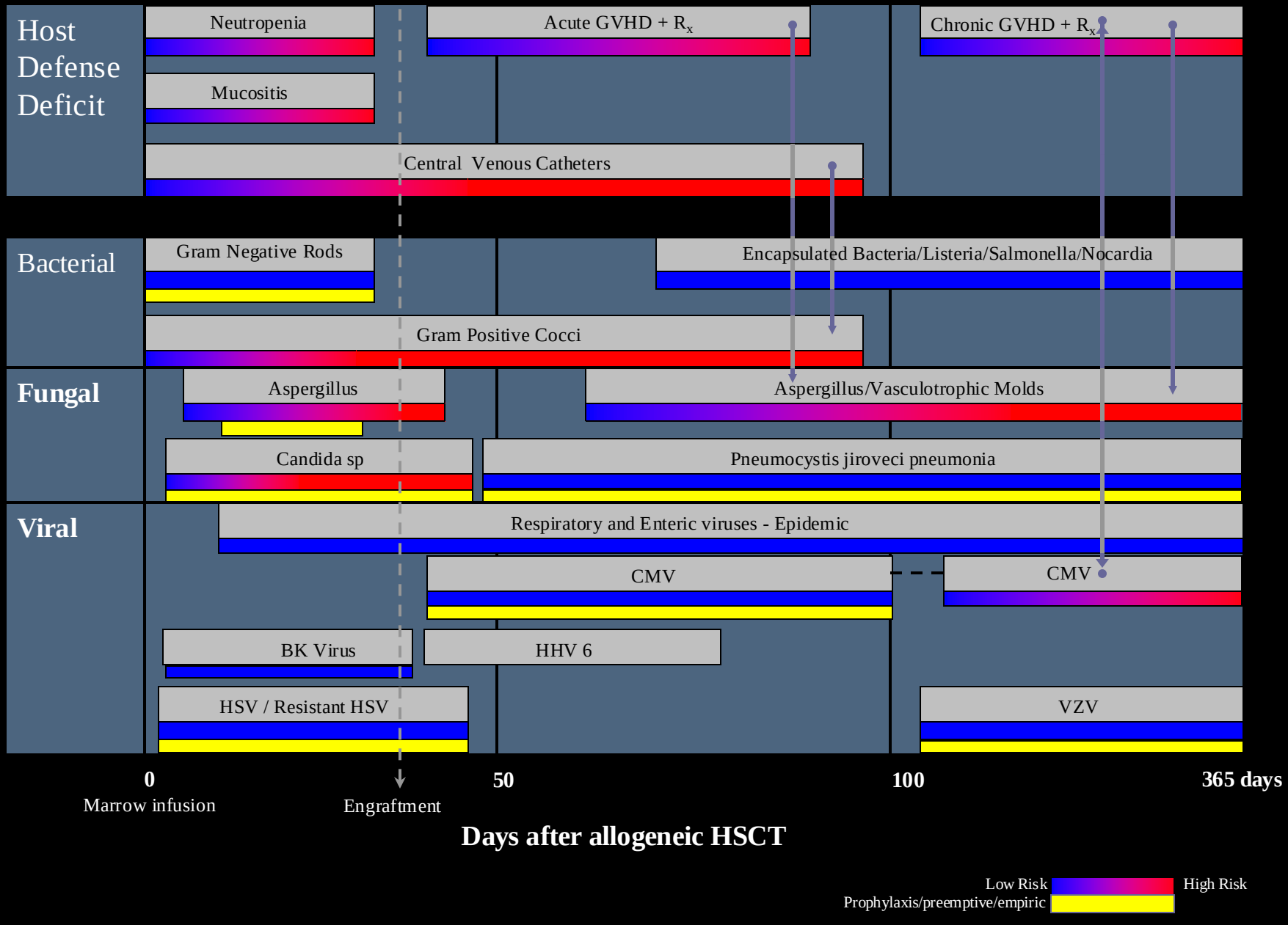
Table 8. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.

Condition	Commonly encountered pathogen(s)
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella carar-rhalis, Chlamydophila pneumoniae*
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis*, atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti* (Q fever)
HIV infection (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late)	The pathogens listed for early infection plus *Pneumocys-tis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to or residence in southwestern United States	*Coccidioides* species, *Hantavirus*
Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei,* avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*
Injection drug use	*S. aureus*, anaerobes, *M. tuberculosis, S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

NOTE. CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

Antibiotic Strategies

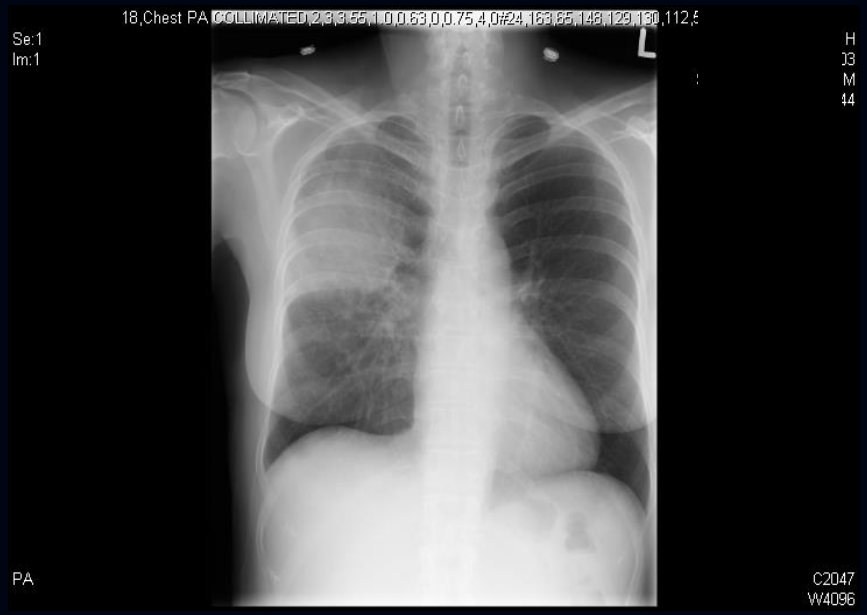
- Therapeutic
  - Treat established clinical infection
  - Diagnostic dilemma vs. therapeutic emergency
- Prophylactic
  - Given to all members of a population to prevent the occurrence of clinical infection
- Preemptive
  - Given to the individuals at the highest risk for clinical infection based on a laboratory or epidemiologic marker
- Empiric
  - Given to individuals with signs of a possible infection

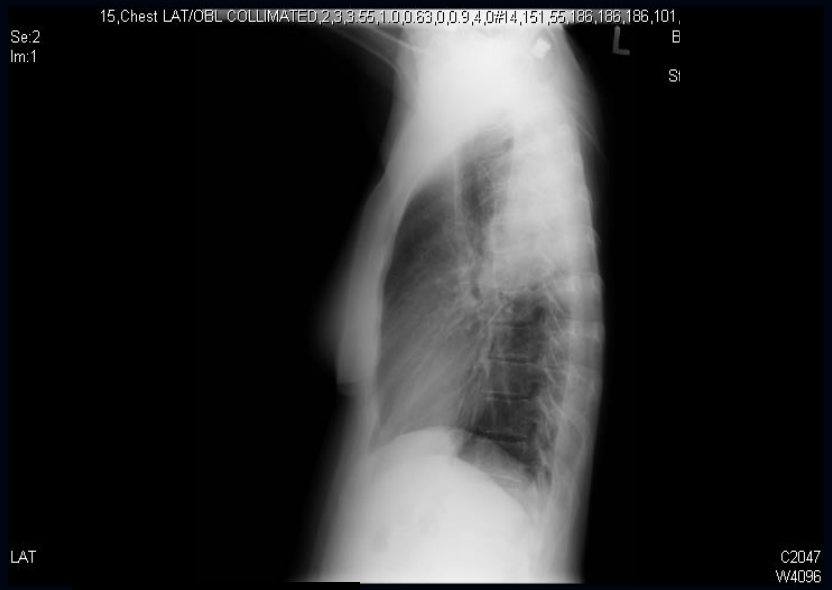

Host Defense Deficit
Neutropenia
Acute GVHD + Rx
Chronic GVHD + Rx
Mucositis
Central Venous Catheters
Bacterial
Gram Negative Rods
Encapsulated Bacteria/Listeria/Salmonella/Nocardia
Gram Positive Cocci
Fungal
Aspergillus
Aspergillus/Vasculotrophic Molds
Candida sp
Pneumocystis jiroveci pneumonia
Viral
Respiratory and Enteric viruses - Epidemic
CMV
CMV
BK Virus
HHV 6
HSV / Resistant HSV
VZV
0
Marrow infusion
Engraftment
50
100
365 days
Days after allogeneic HSCT
Low Risk
High Risk
Prophylaxis/preemptive/empiric

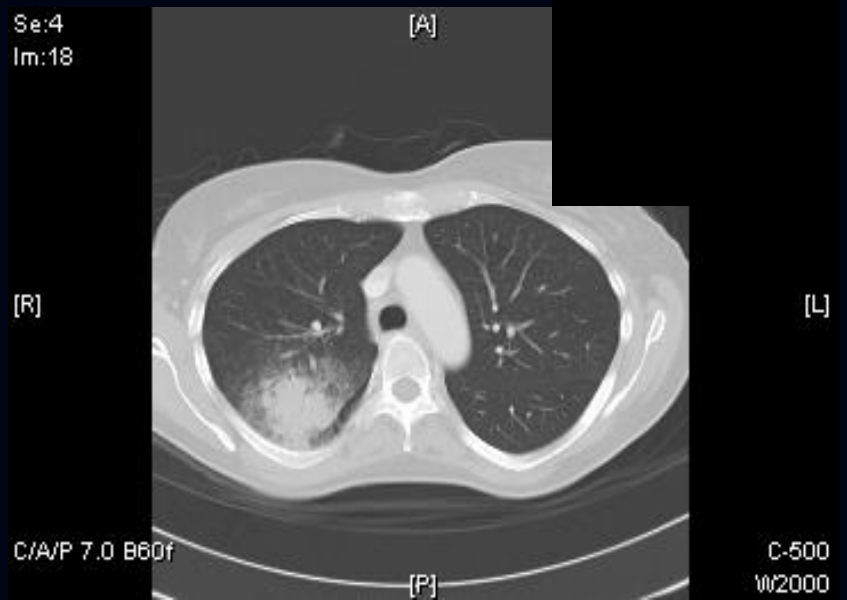
Syndrome

- Symptoms
  - Acute, chronic
- Host risk factors
  - Immunocompromised
- Setting
  - Community, nosocomial
- Imaging pattern

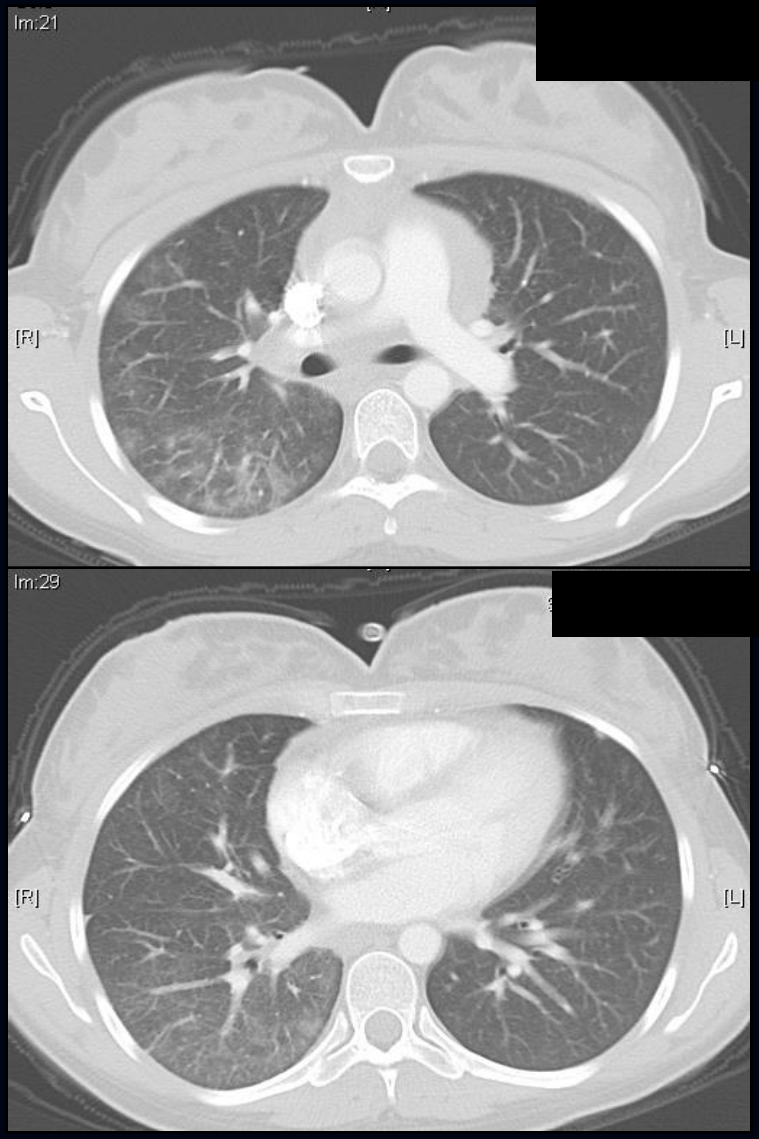
Lobar Infiltrate

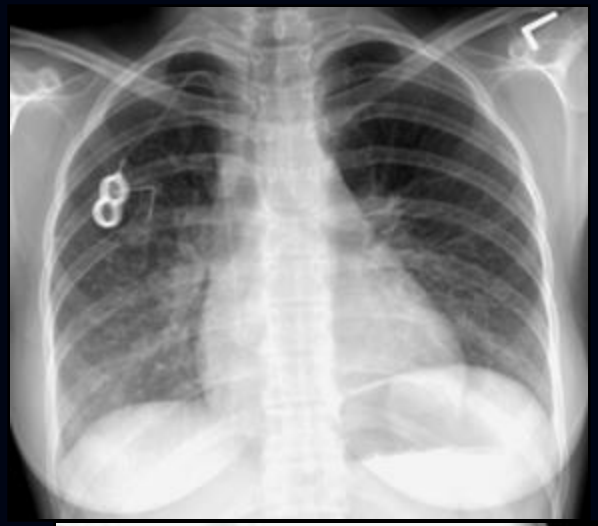


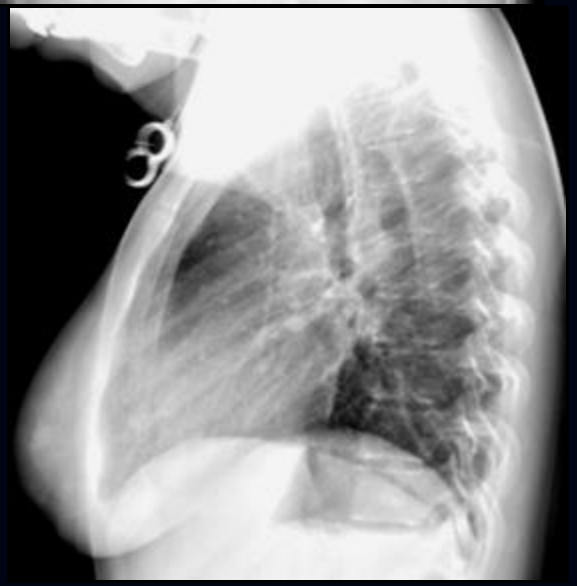




Diffuse Interstitial Infiltrates

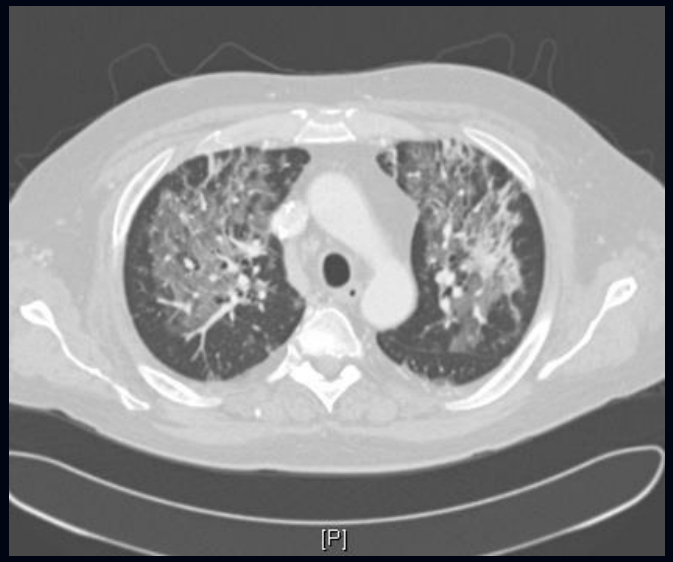


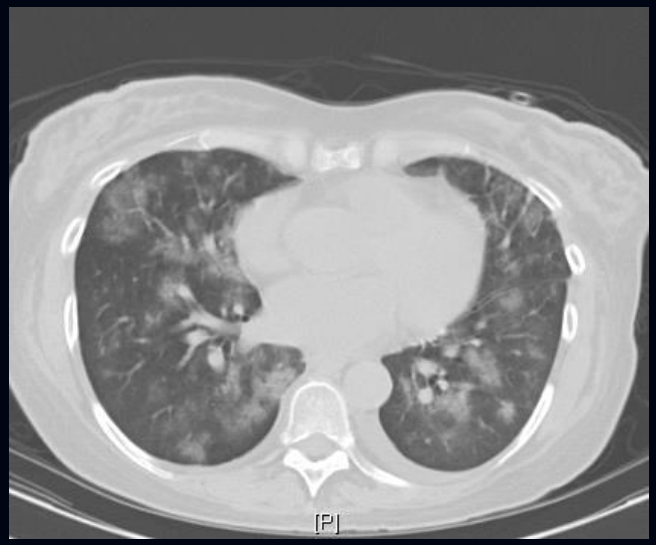


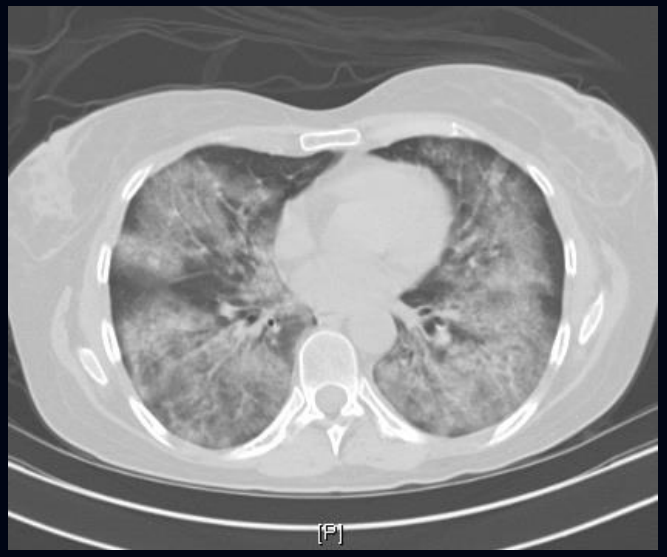


Waks AG et al. Breast Cancer Res Treat 2015; 154:359-67

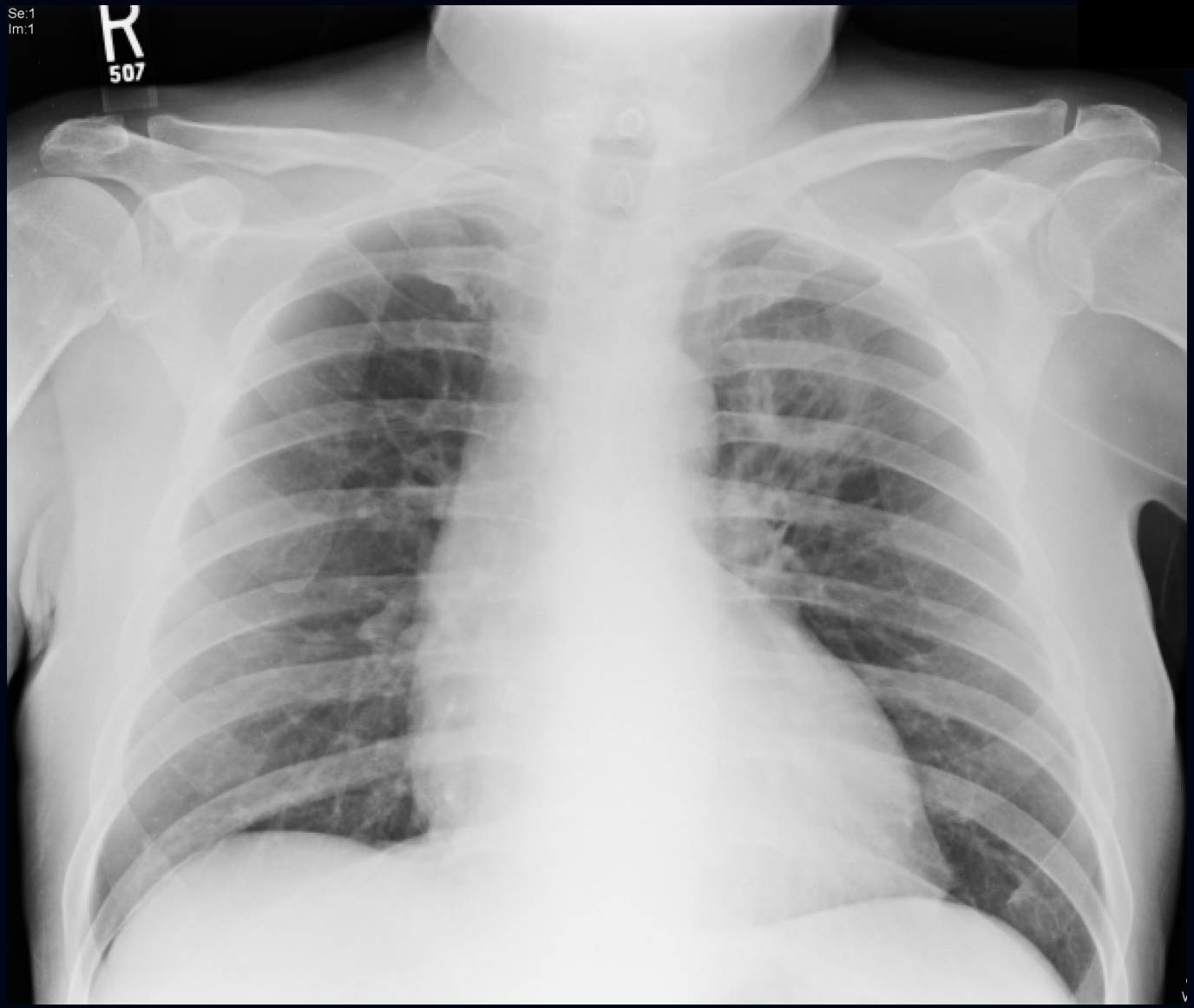
Diffuse Interstitial Infiltrates



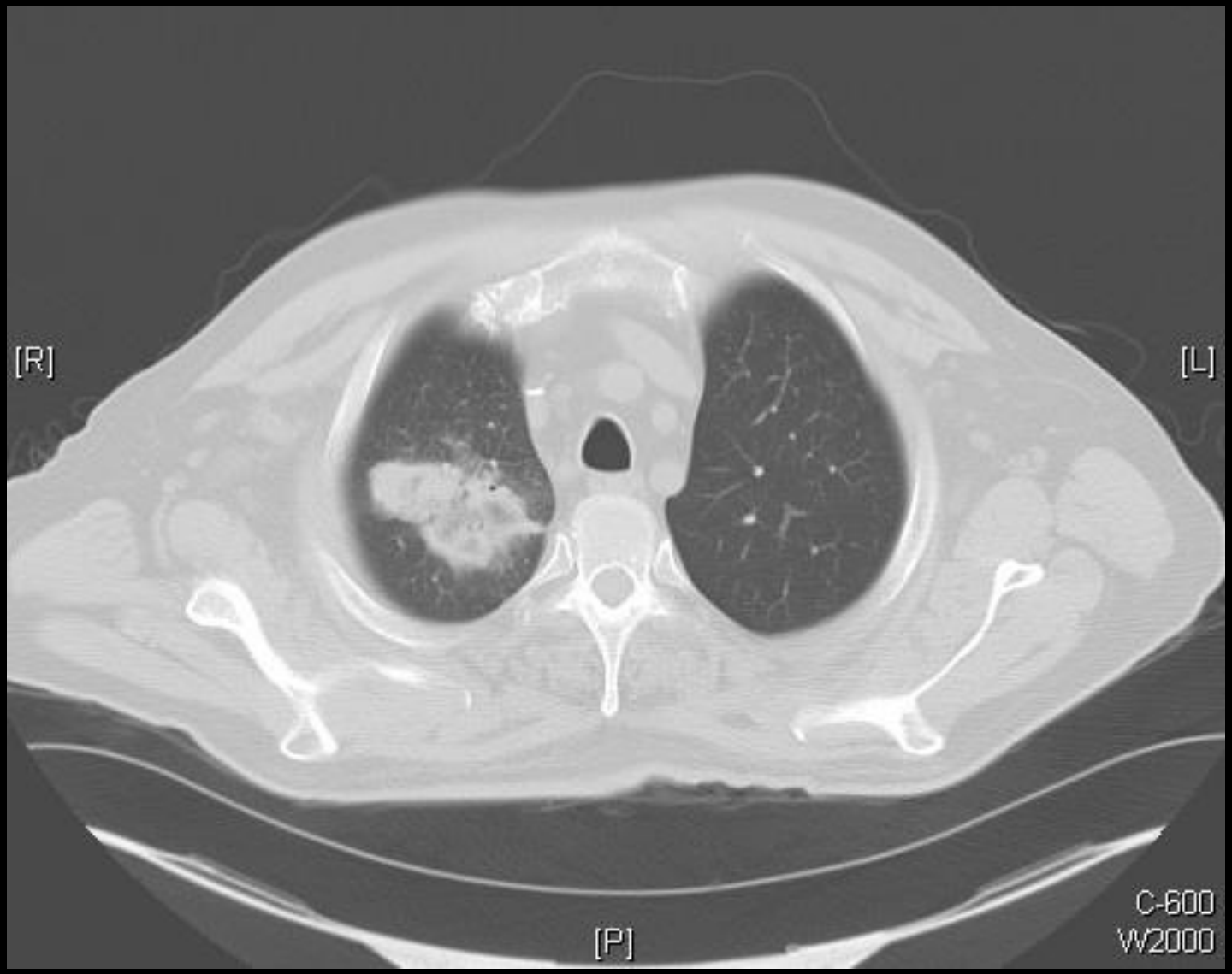




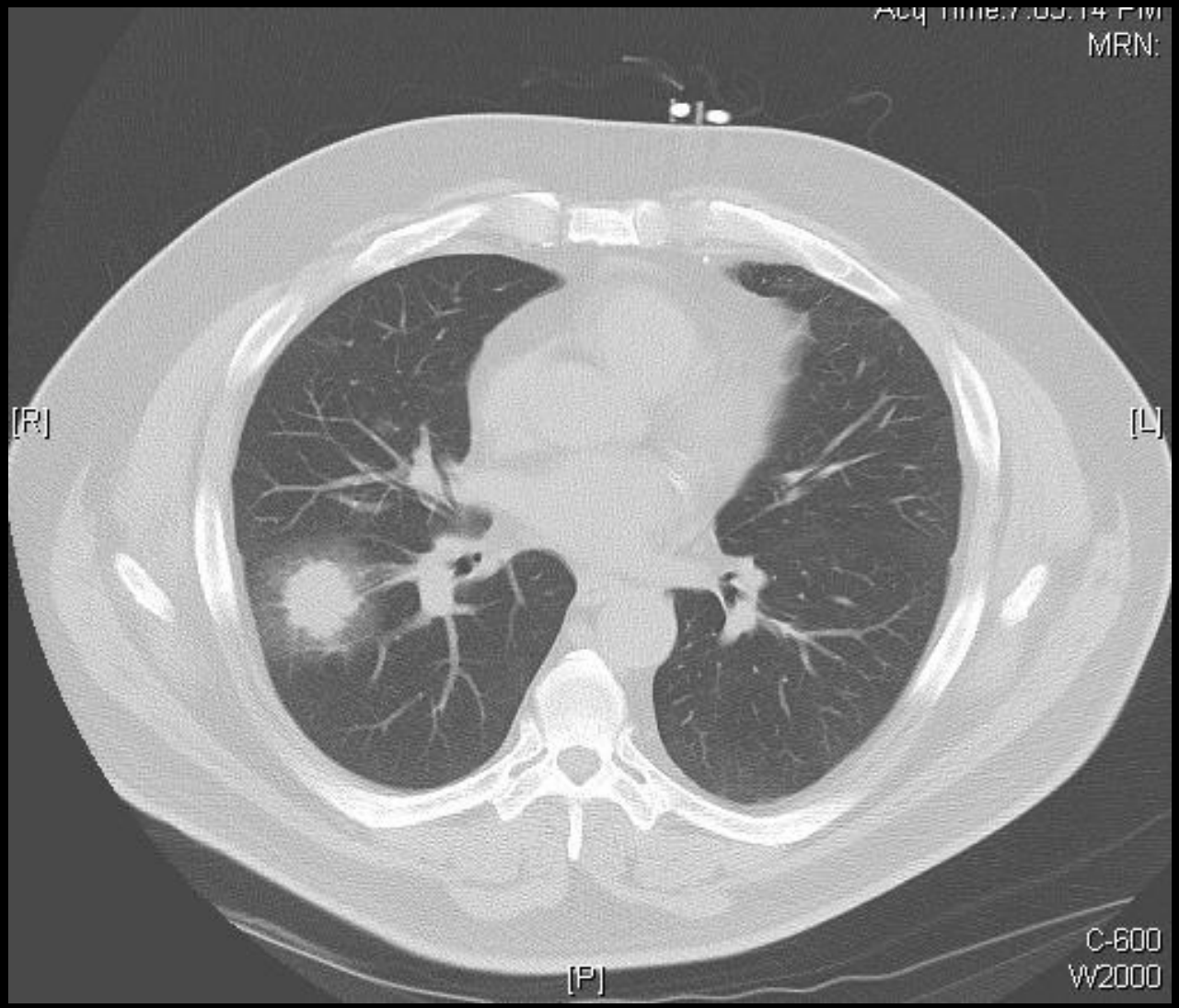
Nodular and Cavitary Infiltrates



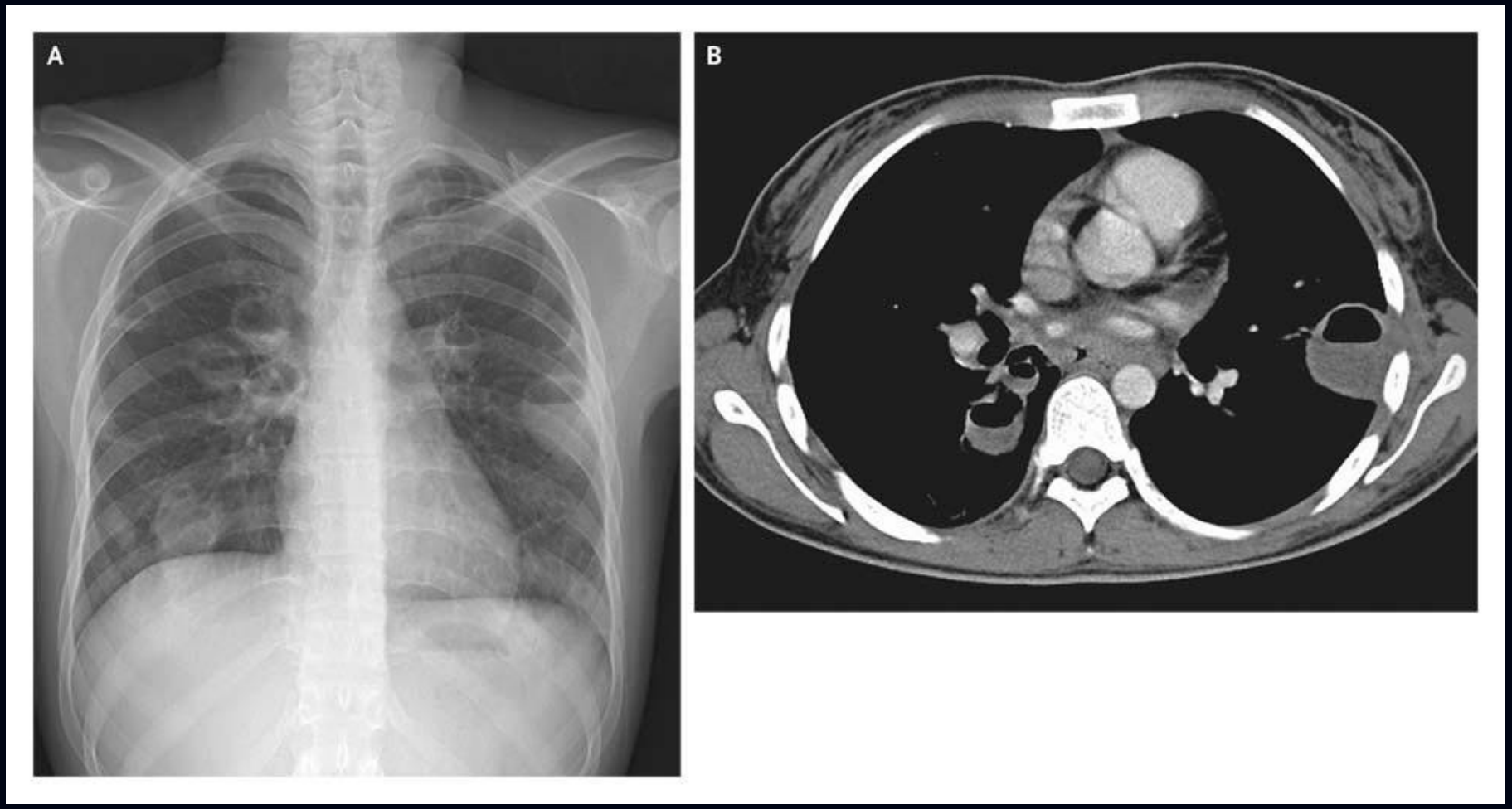
Nodular and Cavitary Infiltrates



Nodular and Cavitary Infiltrates



Hematogenous



Chen J and Li Y. N Engl J Med 2006;355:e27

Diagnostics

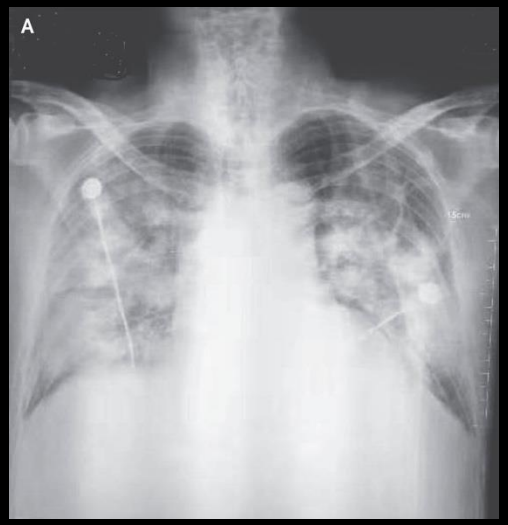
- Microbe non-specific
  - Procalcitonin, CRP
- Microbe specific
  - Culture
    - Bacterial/mycobacterial, fungal
  - Molecular
    - Different sites: respiratory (NP, AN, LRT), blood, urine
    - Antigen
      - Cryptococcus, legionella, pneumococcal, galactomannan, beta-glucan
    - Nucleic acid amplification (NAAT)
      - Targeted, multiplex
      - Complex regulatory environment in US/FDA – Commercial vs laboratory-developed assays (CLSI guidance)
  - Investigational

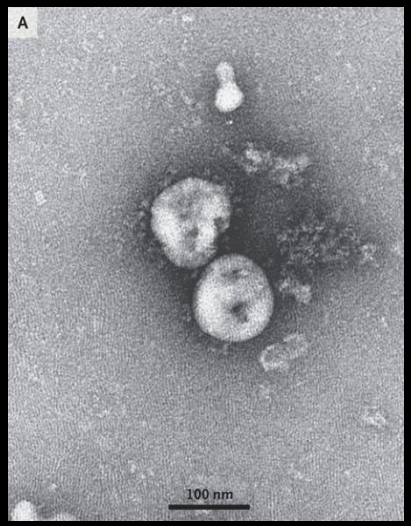
Epidemic Setting

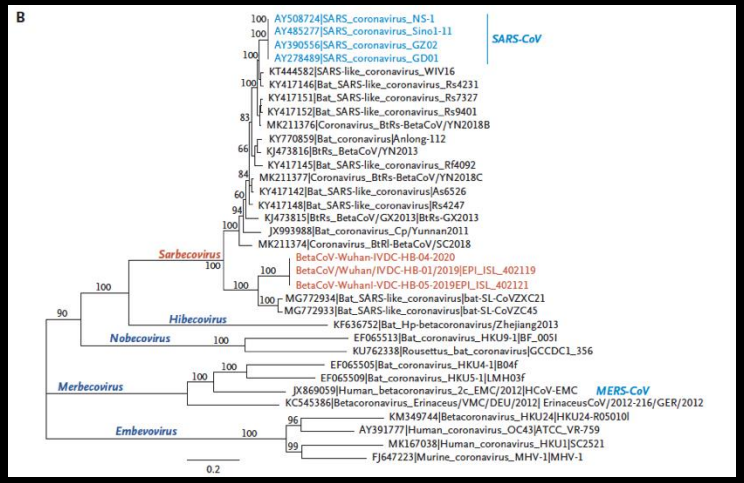
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019







Zhu Net al NEJM 24Jan2020

AMERICAN THORACIC SOCIETY DOCUMENTS

Released May 2021

Nucleic Acid–based Testing for Noninfluenza Viral Pathogens in Adults with Suspected Community-acquired Pneumonia

An Official American Thoracic Society Clinical Practice Guideline

Scott E. Evans, Ann L. Jennerich, Marwan M. Azar, Bin Cao, Kristina Crothers, Robert P. Dickson, Susanne Herold, Seema Jain, Ann Madhavan, Mark L. Metersky, Laura C. Myers, Eyal Oren, Marcos I. Restrepo, Makeda Semret, Ajay Sheshadri, Richard G. Wunderink, and Charles S. Dela Cruz; on behalf of the American Thoracic Society Assembly on Pulmonary Infection and Tuberculosis

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED FEBRUARY 2021

Outpatients: we suggest <u>not</u> performing routine NAAT testing for respiratory viral pathogens other than influenza.

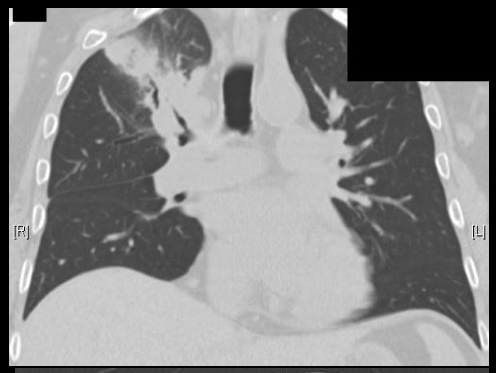
Inpatients: we suggest performing NAAT testing for respiratory viruses other than influenza <u>in patients with severe CAP or immunocompromised state</u>

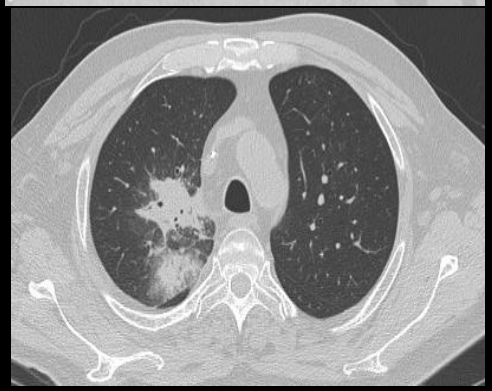
recommendations regarding whether routine diagnostics should include nucleic acid–based testing of respiratory samples for viral pathogens other than influenza in suspected CAP. The evidence addressing this topic was generally adjudicated to be of very low

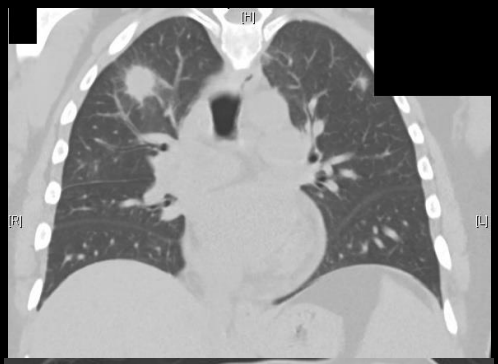
pathogens other than influenza for patients with suspected CAP.

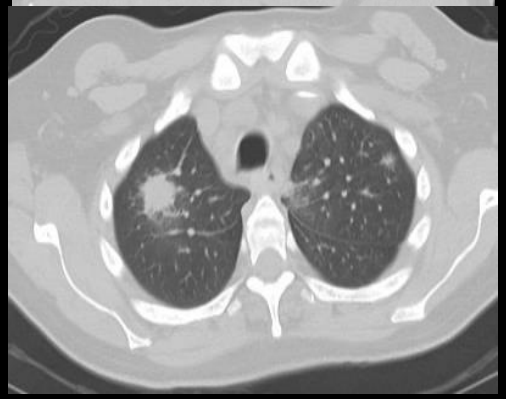
Keywords: community-acquired pneumonia; pneumonia; viral diagnostics

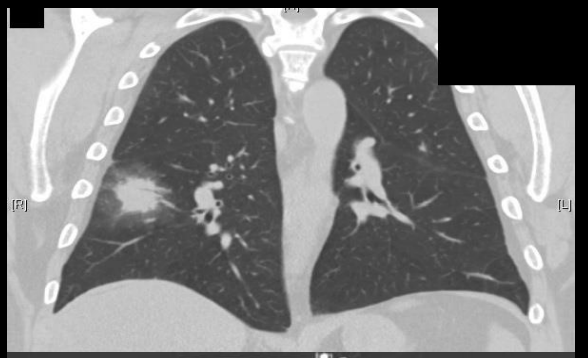
Radiologic Diagnosis for IFI

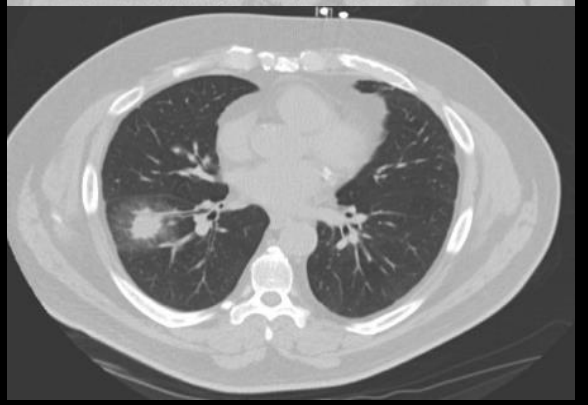


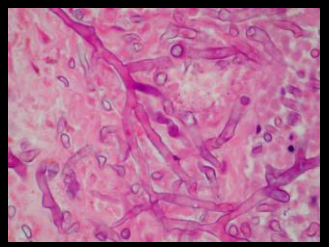






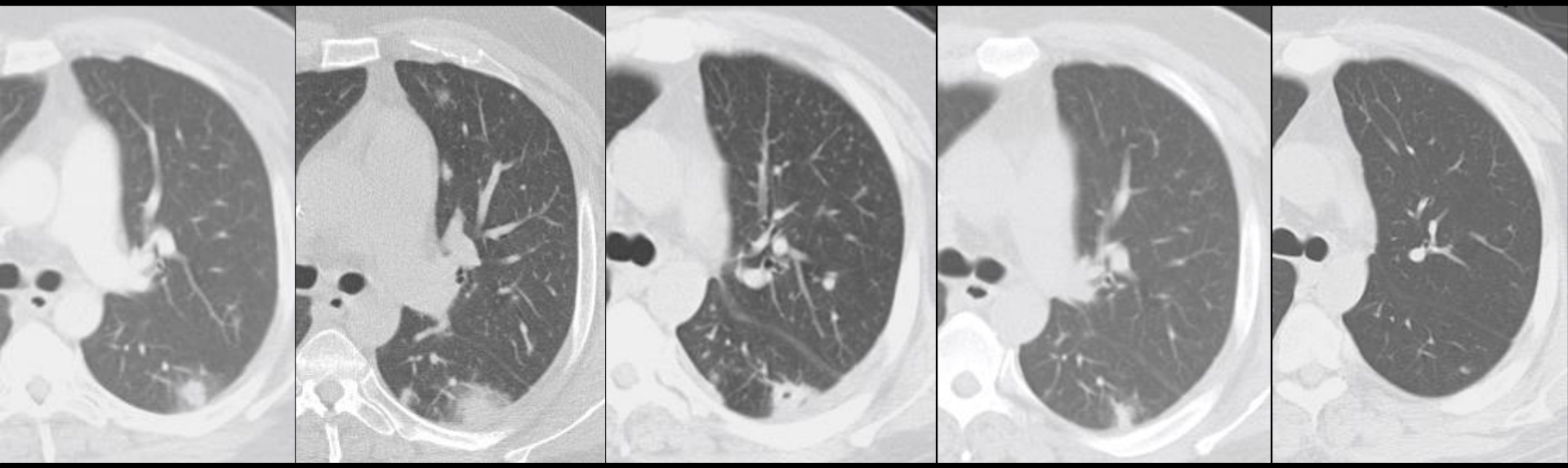






Letourneau A et al., *Curr Opin Pulm Med* 2014;(20(3):272-9

Nodular Infiltrate Over Time and Treatment



1/20/07 1/26/07 2/05/07 2/23/07 4/04/07

What Makes IFI Diagnosis Difficult?

- Histopathology and culture from sterile sites remain the gold standard tests for proven IFI
- Cultures are negative in 50% of histologically proven cases
- Require invasive procedures to obtain tissue for optimal results (Biopsy, FNA, VATS)

Diagnostic Approaches

- Radiology
- Serology
- Pathology
  - Histology, IHC
- Mycology
  - Culture, Antigen, PCR

Currently Available Non-Invasive Assays

- Galactomannan enzyme immunoassay
  - (Platelia, Bio-Rad)
- Beta-D-Glucan
  - (Fungitell or Glucatell)

Galactomannan

- A component of the fungal cell wall and an exoantigen of *Aspergillus*
- ELISA-based method higher sensitivity and specificity compared to previous latex agglutination assay
- Galactomannan antigen positivity is among the microbiological diagnostic criteria proposed by EORTC/MSG

Galactomannan

Prospective serial GM measurement in 362 consecutive high-risk treatment episodes in 191 patients (BMT and leukemic). Time period: 1/97-2/00. EORTC/MSG definitions of IFI with autopsy confirmation. Based on 2 or more positive GM samples.

	Sensitivity	Specificity	PPV	NPV
Proven IA	**100**	**98.1**	**85.7**	**100**
Probable IA	**55.5**	**98.1**	**50**	**98.4**
Proven + probable IA	**89.7**	**98.1**	**87.5**	**98.4**
Possible IFI	**7.4**	**98.1**	**44.4**	**83.8**

Maertens Blood 2001:97;1604

Galactomannan for IA

Cox Model GM_0 & one-week GM decay

Risk of 6-week Mortality

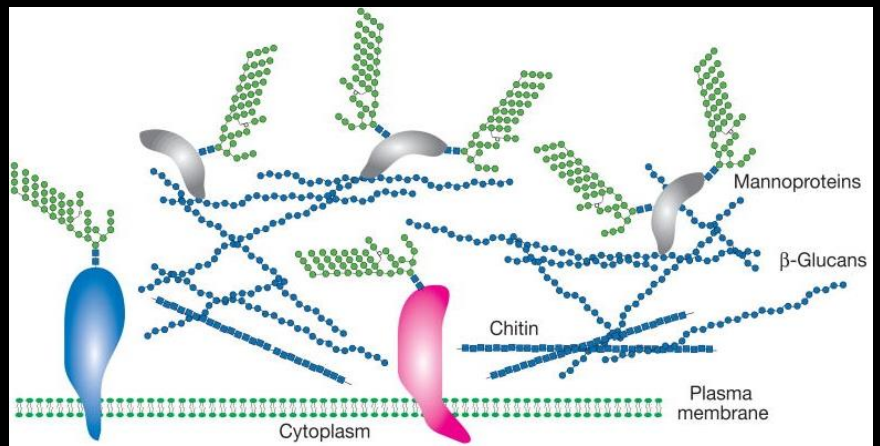
Covariate	Univariate HR (95% CI)	p	Adjusted HR* (95% CI)	p
GM_0, Per EIA unit increase	1.27 (1.08-1.49)	0.005	1.25 (1.01-1.54)	0.04
One-week GM decay, per EIA unit/week decline	0.82 (0.66-1.02)	0.07	0.78 (0.63-0.96)	0.02

* Adjusted for age, HSCT status, neutropenia and corticosteroid use

Koo, et al. JCM 2010

Beta-D –Glucan

- ß-D-glucan is found in cell wall of various fungal genera
- ß-D-glucan is typically absent in patients with cryptococcal infection as well as those patients with infections due to zygomycetes



Diagnostic Indices of Initial (1→3)-β-d-Glucan (BG) for Proven or Probable Invasive Fungal Disease (IFD) within 1 Week after Testing

BG level, pg/mL	No. of patients	No. (%) of possible or non-IFD cases	No. (%) of proven or probable IFD cases	BG diagnostic cutoff value, pg/mL	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
<31	421	400 (95.0)	21 (5.0)	…	…	…	…	…
31–59	200	187 (93.5)	13 (6.5)	31	0.81 (0.73–0.88)	0.53 (0.49–0.56)	1.72 (1.36–2.16)	0.36 (0.23–0.55)
60–79	54	48 (88.9)	6 (11.1)	60	0.70 (0.60–0.78)	0.77 (0.74–0.80)	3.07 (2.35–4.02)	0.39 (0.28–0.55)
80–99	29	24 (82.8)	5 (17.2)	80	0.64 (0.55–0.73)	0.84 (0.81–0.86)	3.93 (2.94–5.26)	0.43 (0.31–0.59)
100–199	74	57 (77.0)	17 (23.0)	100	0.60 (0.50–0.69)	0.87 (0.84–0.89)	4.54 (3.33–6.19)	0.46 (0.34–0.63)
200–499	37	23(62.2)	14 (37.8)	200	0.45 (0.35–0.54)	0.94 (0.92–0.96)	7.88 (5.24–11.9)	0.59 (0.45–0.76)
⩾500	56	20 (35.7)	36 (64.3)	500	0.32 (0.24–0.42)	0.97 (0.96–0.98)	12.2 (7.06–21.1)	0.70 (0.55–0.88)
Total	871	759 (87.1)	112 (12.9)	…	…	…	…	…

Koo S et al. Clin Infect Dis. 2009;49:1650-1659

Diagnostic Indices of an Initial (1→3)-β-D-Glucan (BG) Level >80 pg/mL in Selected Patient Populations, Excluding Patients Who Received IV Immunoglobulin, Albumin, or Hemodialysis

Variable	Hematologic malignancy	HSCT	Pneumonic syndrome	Febrile neutropenia	Other presenting syndrome[a]
No. of patients[b]	497	251	304	212	294
Initial BG assay for IFD at 1 week, % (95% CI)					
Sensitivity	0.51 (0.36–0.66)	0.43 (0.18–0.71)	0.70 (0.54–0.83)	0.38 (0.07–0.65)	0.62 (0.46–0.75)
Specificity	0.89 (0.86–0.92)	0.93 (0.89–0.96)	0.83 (0.78–0.87)	0.93 (0.88–0.96)	0.83 (0.77–0.87)
Positive likelihood ratio	4.69 (2.88–7.64)	5.97 (2.36–15.2)	4.05 (2.55–6.42)	5.10 (1.48–17.6)	3.54 (2.21–5.68)
Negative likelihood ratio	0.55 (0.36–0.84)	0.62 (0.30–1.25)	0.37 (0.21–0.64)	0.67 (0.28–1.64)	0.46 (0.29–0.75)
ROC AUC	0.74 (0.66–0.83)	0.73 (0.58–0.87)	0.79 (0.70–0.88)	0.63 (0.40–0.86)	0.78 (0.70–0.85)
Highest BG level for IFD at end of hospitalization, % (95% CI)					
Sensitivity	0.62 (0.46–0.75)	0.64 (0.35–0.87)	0.77 (0.61–0.88)	0.50 (0.16–0.84)	0.66 (0.51–0.79)
Specificity	0.86 (0.83–0.89)	0.91 (0.87–0.94)	0.81 (0.76–0.85)	0.90 (0.85–0.94)	0.81 (0.75–0.85)
Positive likelihood ratio	4.55 (2.93–7.08)	7.26 (3.32–15.8)	4.01 (2.58–6.22)	4.86 (1.67–14.1)	3.43 (2.20–5.35)
Negative likelihood ratio	0.44 (0.20–0.71)	0.39 (0.16–0.95)	0.29 (0.15–0.54)	0.56 (0.21–1.50)	0.42 (0.26–0.69)
ROC AUC	0.78 (0.69–0.86)	0.77 (0.63–0.92)	0.82 (0.73–0.90)	0.68 (0.45–0.92)	0.79 (0.72–0.86)

NOTE. HSCT, hematopoietic stem cell transplantation; IFD, invasive fungal disease; ROC AUC, area under the receiver operating characteristic curve.

[a] Meningitis, encephalitis, sinusitis, and mental status changes.

[b] Categories are not mutually exclusive.

Koo S et al. Clin Infect Dis. 2009;49:1650-1659

PCR in Fungal Diagnostics

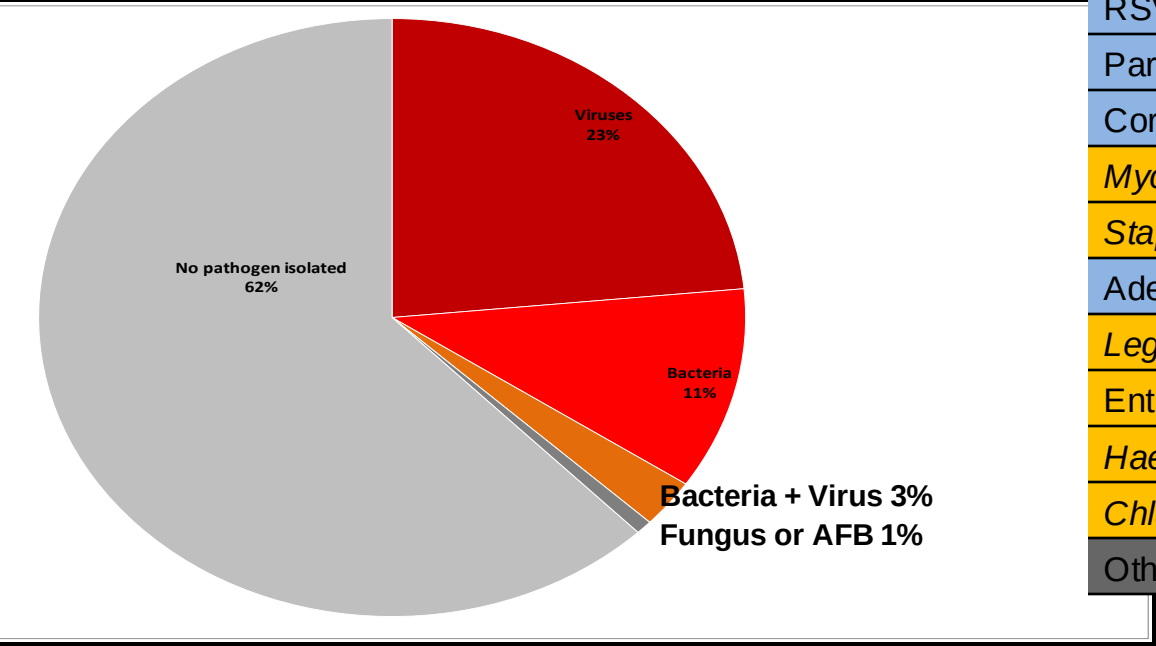
- Fungal rDNA as PCR target
  - rDNA subunits are highly conserved with variable regions
  - Multicopy nature enhances PCR sensitivity 10-100X over single copy genes
  - Universal PCR primer sites in conserved regions
  - ITS1 and 2, and D1/D2 regions (variable regions) are species-specific
  - Used for both sequence-based identification and PCR-based detection

PCR in Fungal Diagnostics

- Challenges in developing molecular techniques for diagnosis of IFI
  - Animal models (reproducible outcome, recapitulates human disease, late mortality that would allow multiple time point sampling without survivor bias)
  - Distinction between colonization vs disease
  - Development of DNA standard for calibration
  - Impact of sample types, collection, storage
    - Pellet vs supernatant for BAL, CSF, pleural fluid, urine
    - Ideal sample type: whole blood, serum, plasma
    - What's circulating in infected host: Conidia vs free nucleic acids

Etiology of Community-Acquired Pneumonia

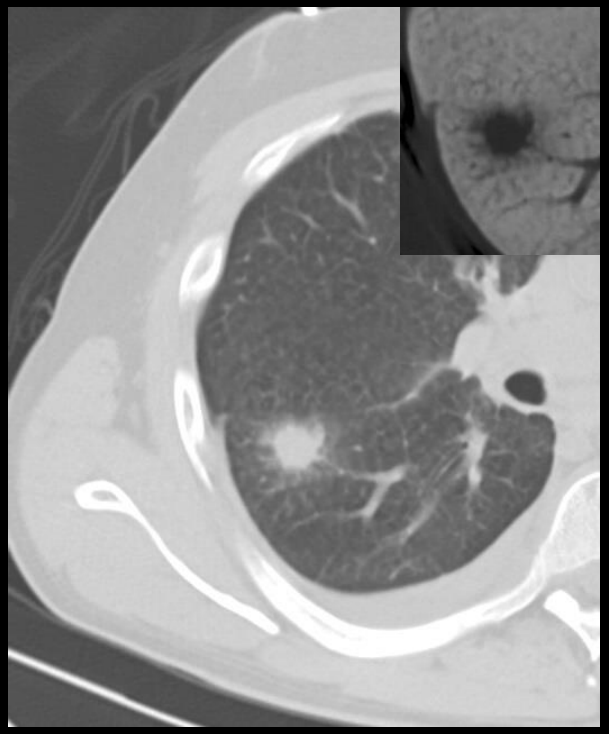
2,259 adults admitted to 5 hospitals in Chicago and Nashville, Jan 2010-Jun 2012



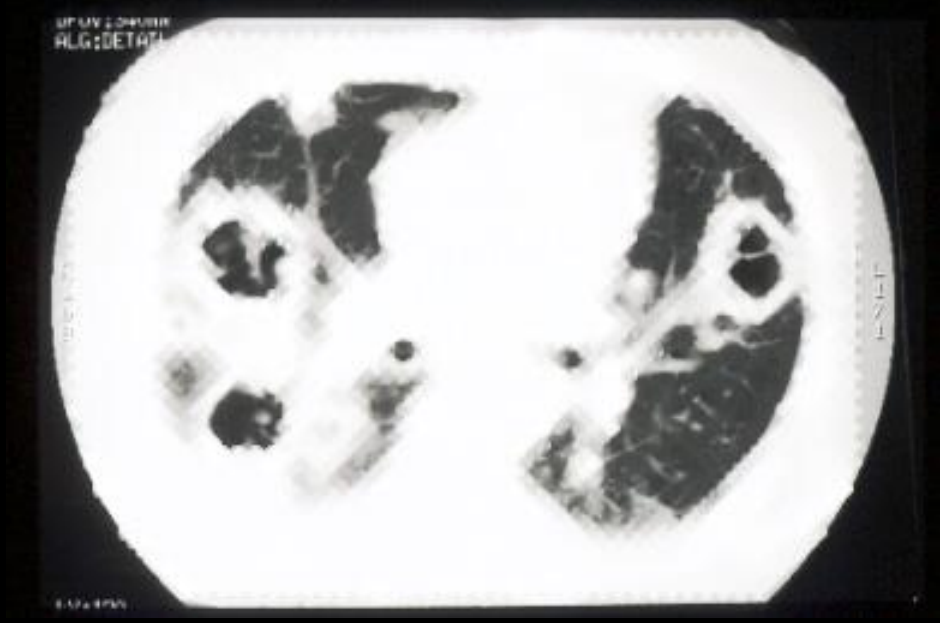
Rhinovirus	8.6%
Influenza	5.8%
Strep. pneumoniae	5.1%
Metapneumovirus	3.9%
RSV	3.0%
Parainfluenza	3.0%
Coronavirus	2.3%
Mycoplasma pneumoniae	1.9%
Staph. aureus	1.6%
Adenovirus	1.4%
Legionella pneumophila	1.4%
Enterobacteriaceae	1.4%
Haemophilus influenzae	0.5%
Chlamydia pneumoniae	0.4%
Other	2.3%

Jain S et al. N Engl J Med 2015;373:415-427

Duration of Therapy?



23yoM w/AML D+9 of an Allo-BMT has persistent F+N and a dry cough develops. A single pulmonary nodule is seen on Chest CT (above).
VATS demonstrated IPA.



25yoM w/ AML undergoing an Allo-BMT develops fevers and cough. Chest CT demonstrates multiple cavitary lesions. A fumigatus was recovered from the sputum.

Courtesy: Francisco Marty, MD

Conclusions

- Diagnosing pneumonia requires clinical judgement
- Emerging/improving therapies in other disciplines are complicating how to characterize the host
- Syndrome, exposure(s), and radiographic pattern important

- Emerging molecular technologies have great potential
  - Presence of an organism does not disease make
  - Access to technologies variable
- Specific etiologic diagnosis valuable
  - Target treatment (de-escalation), determine antimicrobial susceptibility, define epidemiology
- Gold standard problem