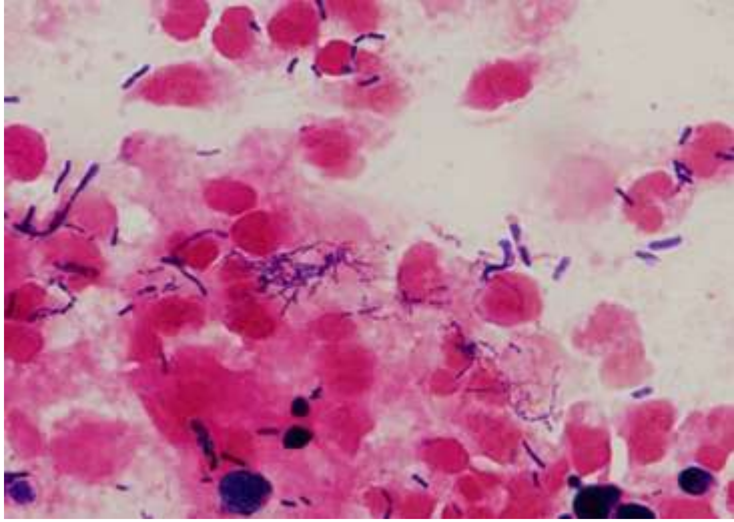

Respiratory Infections Diagnosis

Mir H. Noorbash, PhD, D(ABMM)

Oct 2019 - PAMET

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Objectives

- Introductions
- Common Pathogens, culture, CIDT's
  - Upper respiratory tract infections
  - Lower Respiratory Infections
- Testing strategy impact
  - Clinical case

Introductions to RTI

- Most common infectious disease[1, 4]
  - 1 billion colds/year in US[5]
  - 25 million physician visits[6]
  - Medical Cost >$10 billion/year[4]
- Pneumonia the leading cause of Hospitalization in the US[2,4]
- One of the leading cause of death in the US (51,537 in 2016)[3,4]

1. CDC: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_06.pdf
2. Biscevic, Tokic, and Pfuntner A. 2013
3. Laessig, K - 2015
4. American Thoracic Society – 2015
5. The Common Cold Fact Sheet. Nat'l Institute of Allergy and Inf. Dis., NIH – 2004
6. Gonzales er al. Clin Infect Dis. 2001; 33(6):757-762

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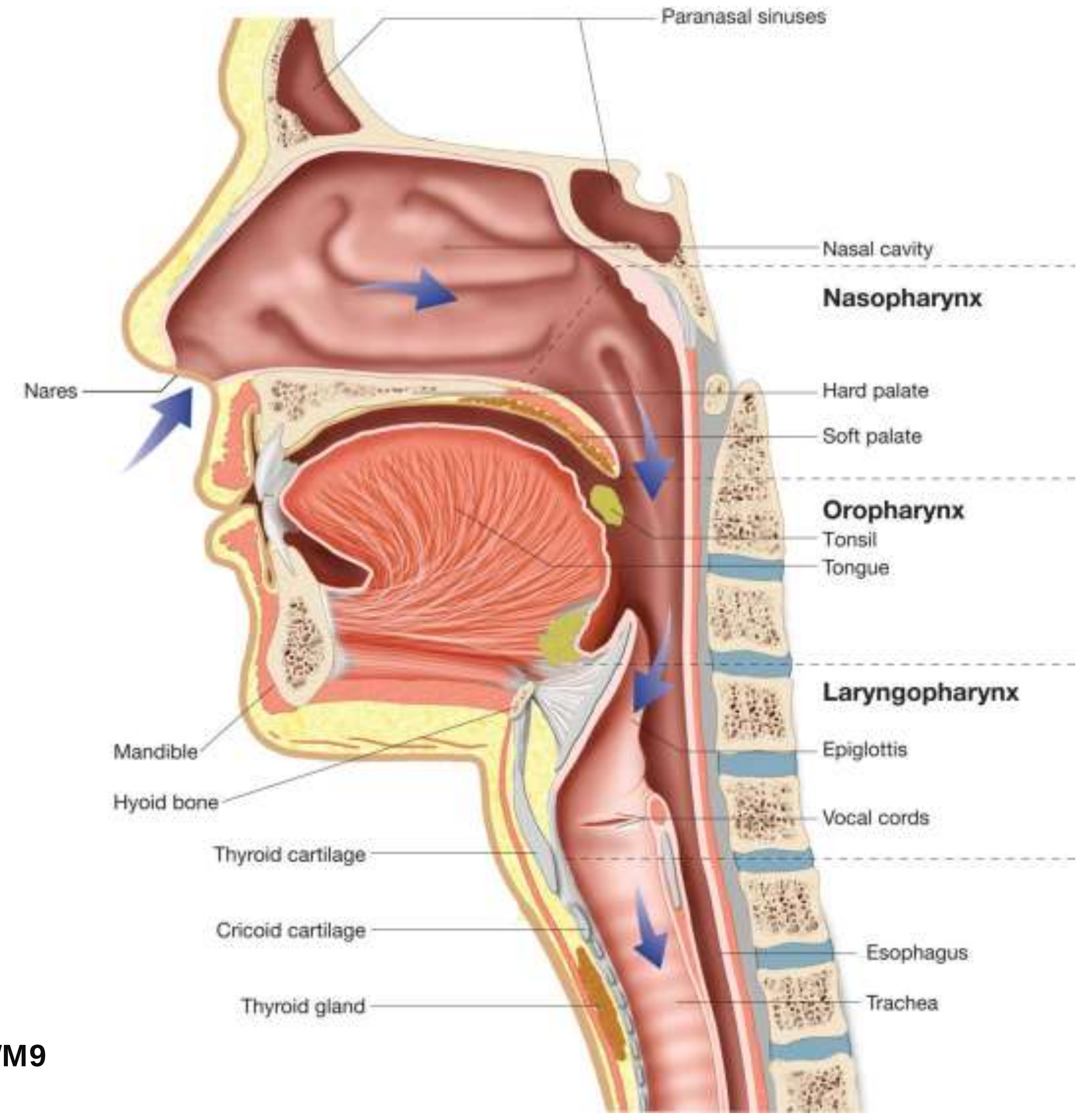
Upper Respiratory Infection (URTI)

- Main cause of workforce loss-productivity in the US[1]
- Mostly viral
- In 2005, 65% receive antibiotics!

1. Gonzales et al. *Clin Infect Dis*. 2001;33(6):757–762.
2. Gilll et al. *Fam Med*. 2006; 38349-354.

Upper Respiratory - Anatomy



https://images.app.goo.gl/BJ6XuP8hzDn6RHWM9

Common URT infections

Mostly self-limited includes

- Laryngitis
- Laryngotracheobronchitis (Croup)
- Epiglottitis
- Pharyngitis
- Tonsillitis
- Peritonsillar Abscess
- [Otitis]
- [Sinusitis]

Viral causes of acute pharyngitis

Pathogen	Syndrome or disease	Estimated % of cases[b]
Viral		
Rhinovirus (100 types and 1 subtype)	Common cold	20
Coronavirus (≥3 types)	Common cold	≥5
Adenovirus (types 3, 4, 7, 14, and 21)	Pharyngoconjunctival fever, acute respiratory disease	5
Herpes simplex virus (types 1 and 2)	Gingivitis, stomatitis, pharyngitis	4
Parainfluenza virus (types 1 to 4)	Common cold, croup	2
Influenzavirus (types A and B)	Influenza	2
Coxsackievirus A (types 2, 4 to 6, 8, and 10)	Herpangina	<1
EBV	Infectious mononucleosis	<1
Cytomegalovirus	Infectious mononucleosis	<1
HIV type 1	Primary human immunodeficiency	<1

***J Clin Microbiol*, Aug. 2003, p. 3467–3472 Vol. 41, No. 8, 0095-1137/03/$08.000 DOI: 10.1128/JCM.41.8.3467–3472.2003**

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Bacterial causes of Acute Pharyngitis

Pathogen	Syndrome or disease	Estimated % of cases[b]
Bacterial		
Streptococcus pyogenes (group A beta-hemolytic streptococci)	Pharyngitis and tonsillitis, scarlet fever	15–30
Group C beta-hemolytic streptococci	Pharyngitis and tonsillitis	5
Neisseria gonorrhoeae	Pharyngitis	<1
Corynebacterium diphtheriae	Diphtheria	<1
Arcanobacterium haemolyticum	Pharyngitis, scarlatiniform rash	<1
Chlamydial (*Chlamydia pneumoniae*)	Pneumonia, bronchitis, and pharyngitis	ND[c]
Mycoplasmal (*Mycoplasma pneumoniae*)	Pneumonia, bronchitis, and pharyngitis	<1

Group A streptococcal infection

- Sudden onset of sore throat
- Age 5 to 15 years
- Fever
- Headache
- Nausea, vomiting, abdominal pain
- Tonsillopharyngeal inflammation
- Patchy tonsillopharyngeal exudates
- Palatal petechiae
- Anterior cervical adenitis (tender nodes)
- Presentation in winter or early spring
- History of exposure to streptococcal pharyngitis
- Scarlatiniform rash

IDSA Updates Guideline for Managing Group A Streptococcal Pharyngitis
http://cid.oxfordjournals.org/content/early/2012/09/06/cid. cis629.full.pdf+html

Viral infection symptoms

- Conjunctivitis
- Coryza
- Cough
- Diarrhea
- Hoarseness
- Discrete ulcerative stomatitis
- Viral exanthem

IDSA Updates Guideline for Managing Group A Streptococcal Pharyngitis
http://cid.oxfordjournals.org/content/early/2012/09/06/cid. cis629.full.pdf+html

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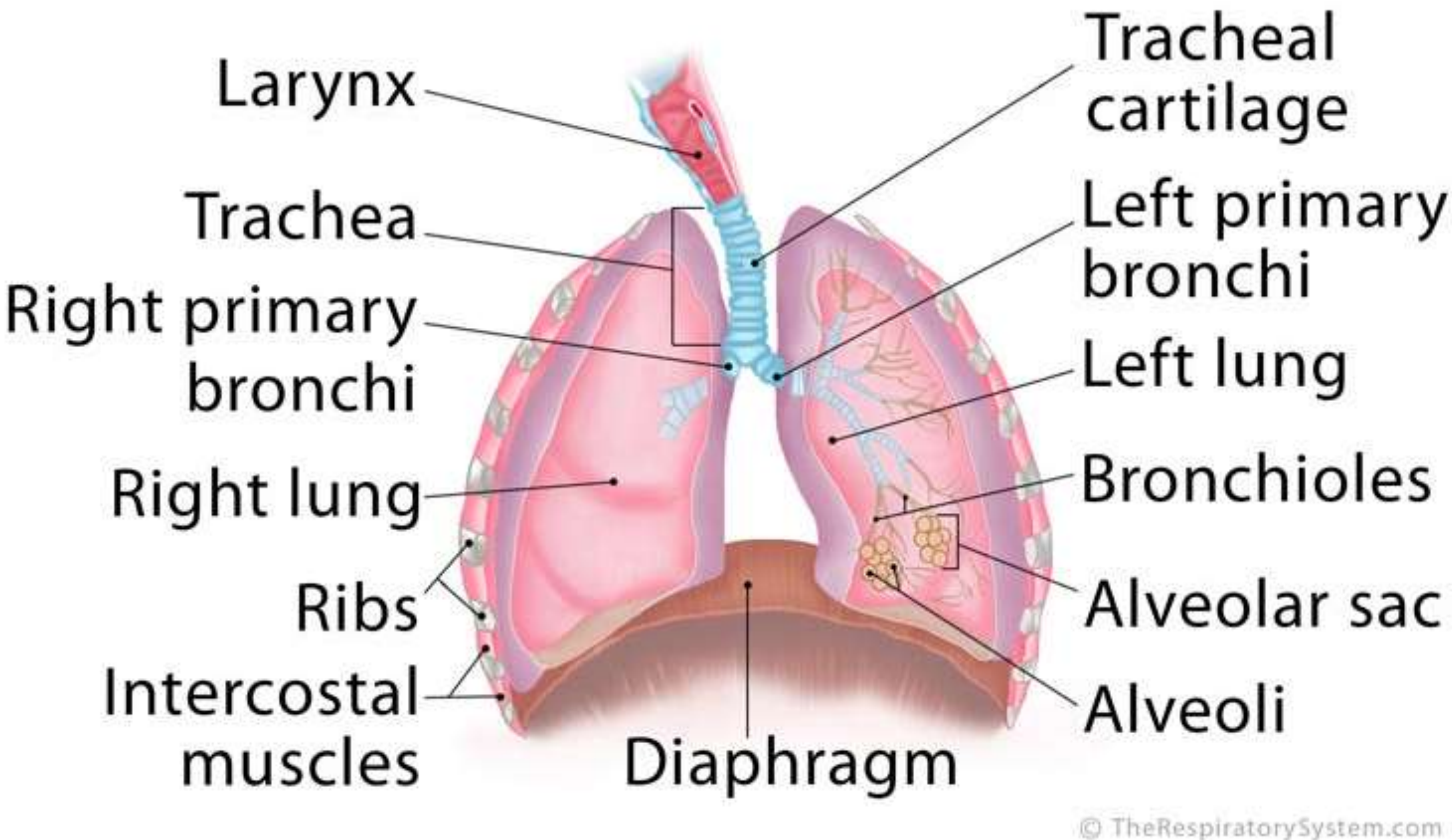
Lower Respiratory Tract (LRT)



https://www.therespiratorysystem.com/wp-content/uploads/2015/12/Lower-Respiratory-Tract.jpg

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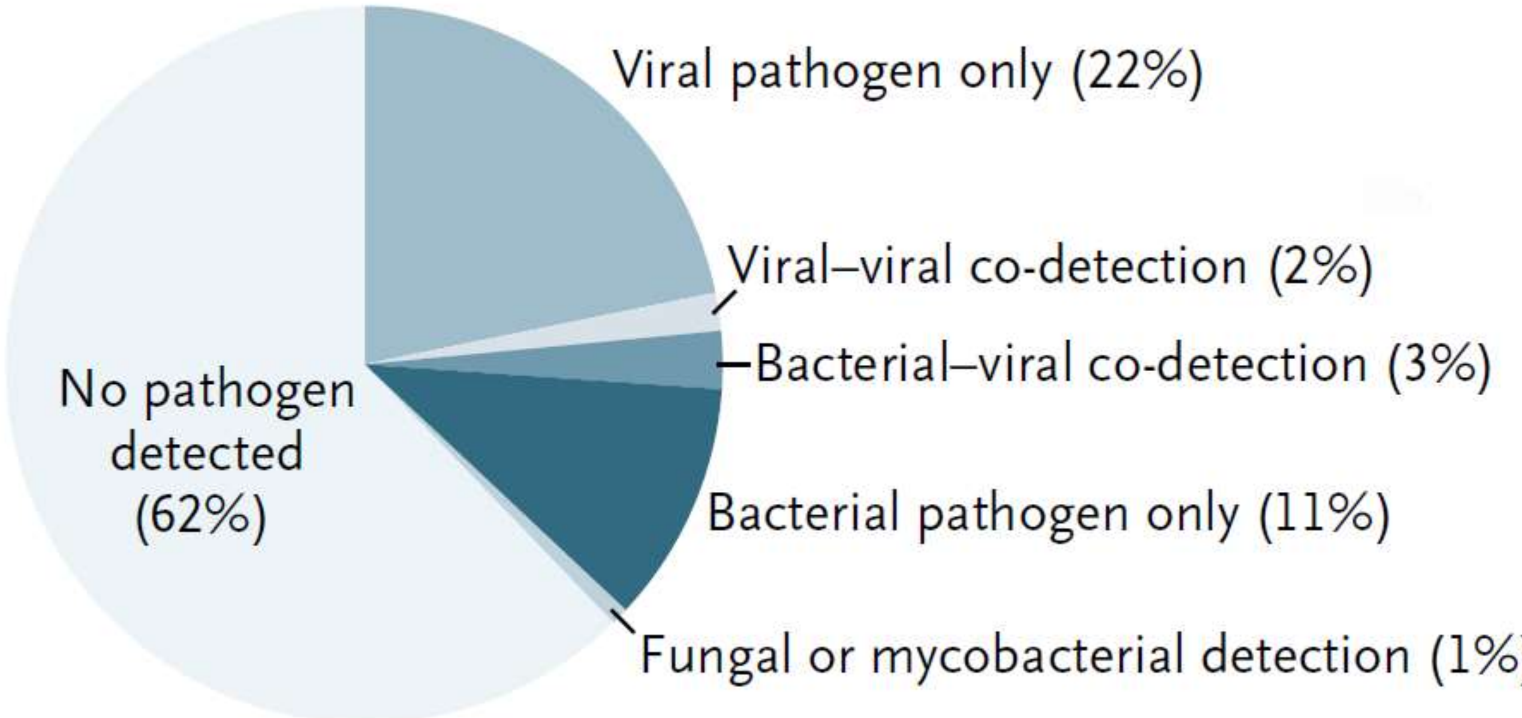
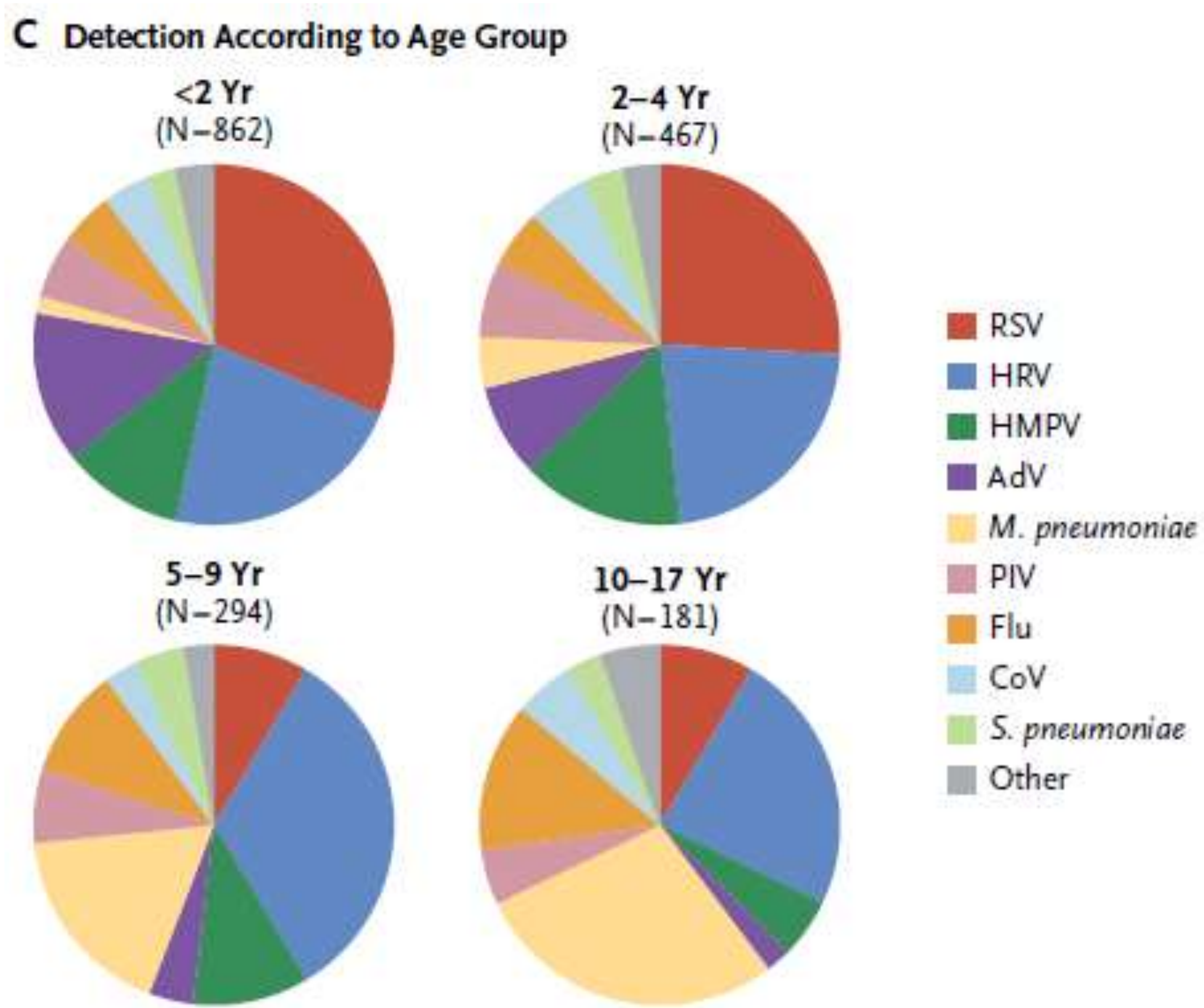
Lower Respiratory Tract Infections (LRTI)



Jain et al. *N Engl J Med* 2015;373:415-27.

Pneumonia Etiology PED's (Jain NEJM 2015)



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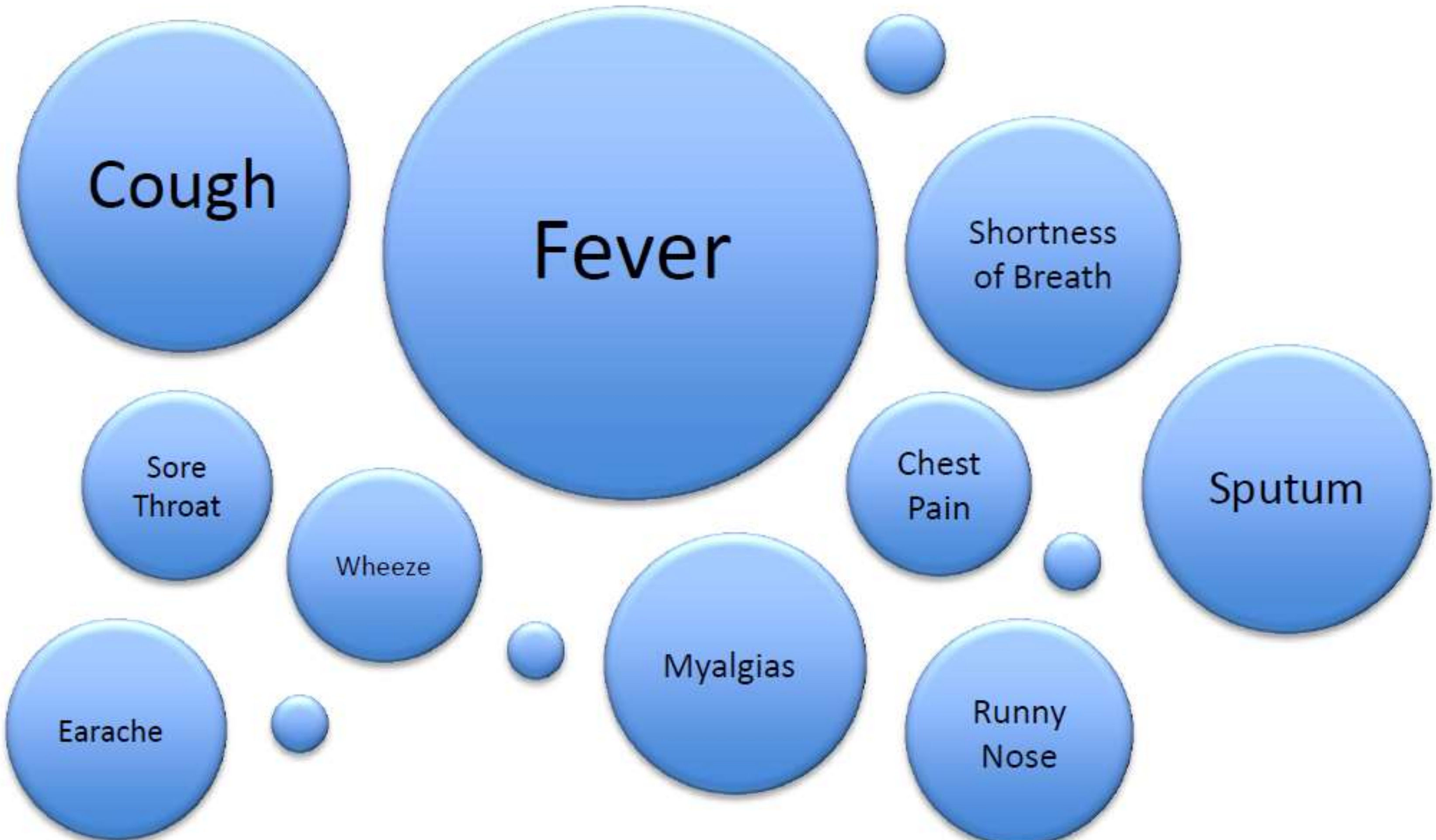
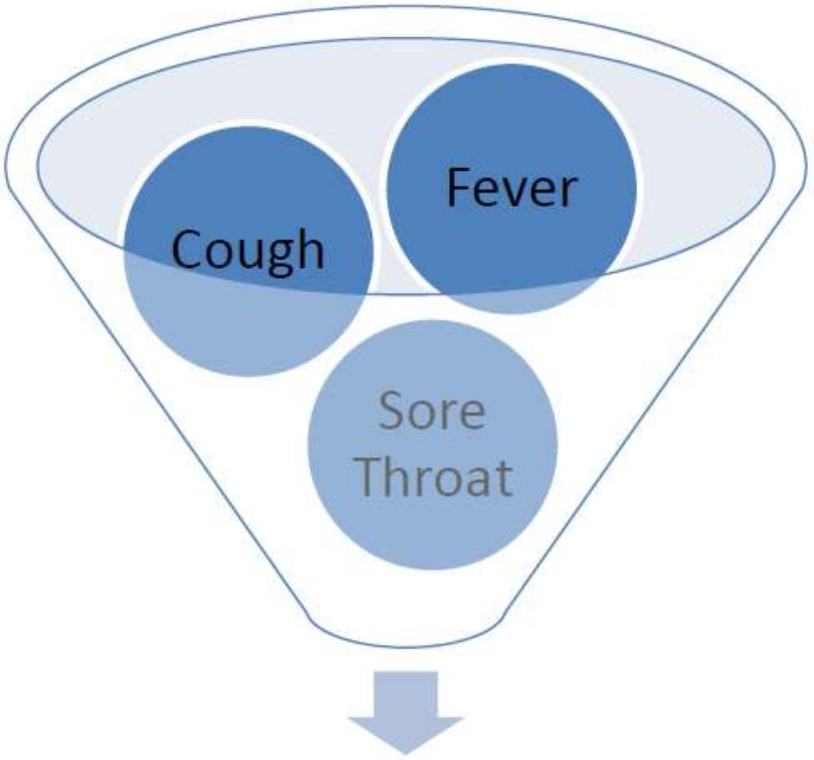
Clinical Approach to ARI



Clinical Case (Part-1)

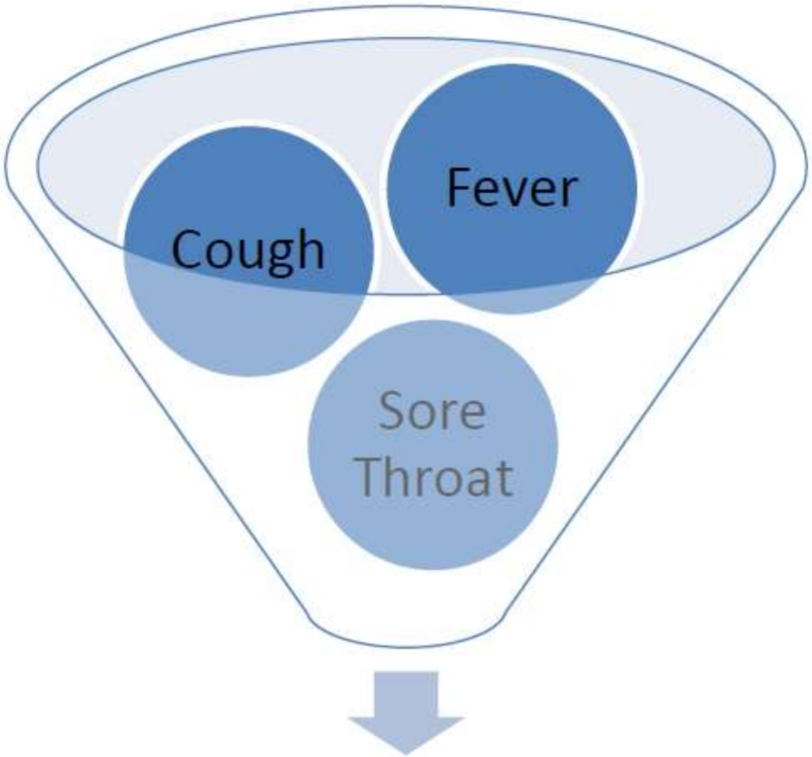
- 28-year old woman with asthma sees her primary care provider
- Four days of fever, sore throat, nasal congestion, and dry cough
- Four year old son with similar symptoms who had a positive rapid strep test
- Exam is consistent with a diffuse upper respiratory infection but not Strep pharyngitis
- Testing not performed at this visit

Clinical Approach to ARI



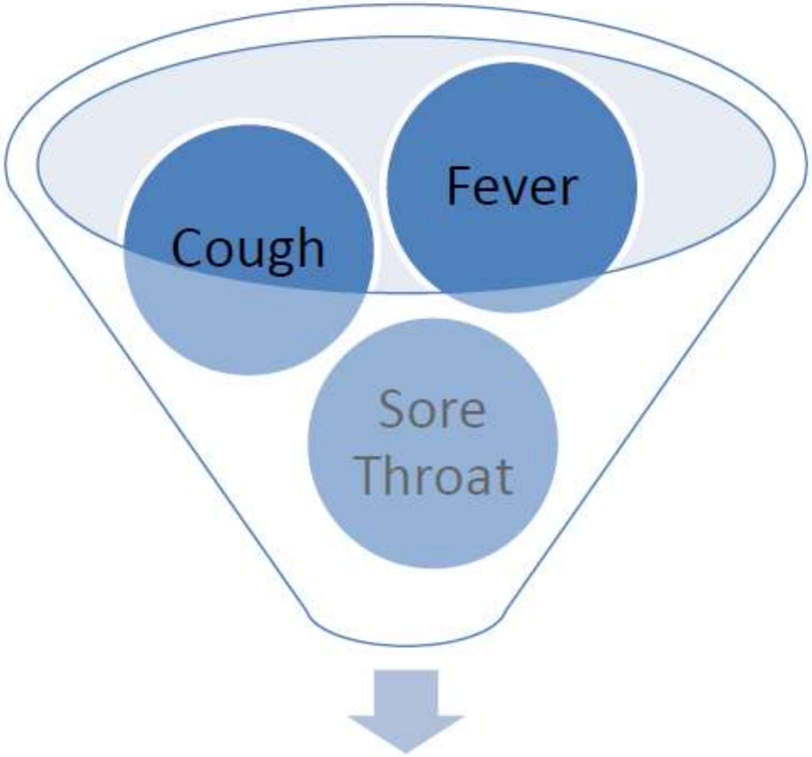
- **Bacterial**
- **Viral**
- **Both**
- **Neither**

Clinical Approach to ARI



- **Antibacterial?**
- **Anti-Viral?**
- **Neither?**

Clinical Approach to ARI



- **Discharge?**
- **Admit?**
- **Isolate?**

Location of testing is important

- Location impacts clinical decision
  - Minute Clinic
  - Primary Care/Out patient
  - Urgent Care
  - ER
  - Hospital
- It directly relates to:
  - Patient acuity
  - Disease prevalence
  - Visit duration
  - Support services (laboratory, radiology)
  - CLIA vs. non-CLIA
  - Follow up feasibility

Clinical Case (Part-2)

- The next day, the patient goes to Urgent Care for shortness of breath and wheezing.
- <u>Fever</u> resolved but still has <u>cough</u> and nasal <u>congestion</u>.
- Exam is similar to yesterday but she now has diffuse <u>wheeze</u>.
- She receives bronchodilator treatment and steroids for asthma exacerbation.

Testing that can support this decisions

- Culture Based testing
  - Bacterial Culture
  - Viral Culture (obsolete)
- Molecular Tests
  - Targeted
  - Syndromic panels
- Others:
  - Antigen detection (Rapid Antigen tests)
  - DFA

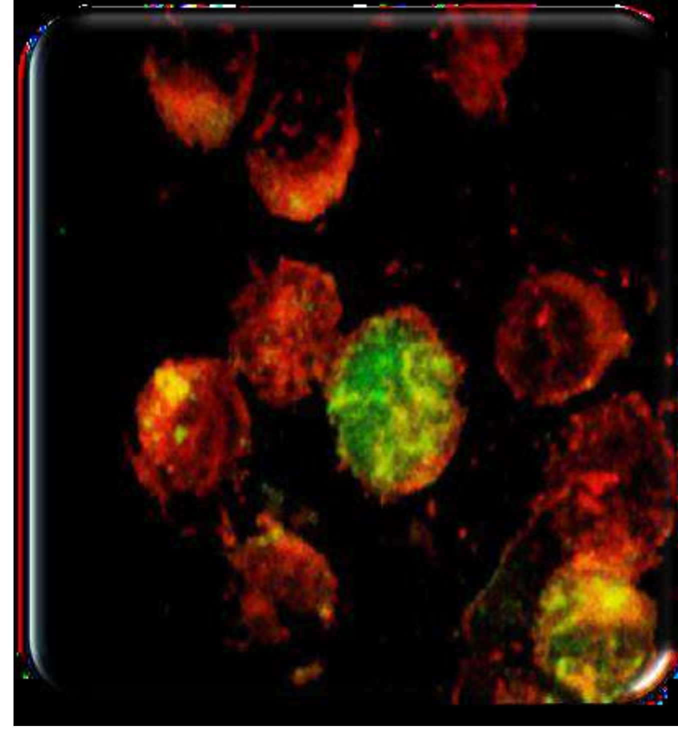
Culture Based tests:

- Viral Culture
  - Shell Vial (Rapid Centrifugation)
  - Impractical for modern medicine!

- Bacterial Culture
  - Still the gold standard for major bacterial pathogens
    - Gives a higher level information
    - Provides relative proportions
    - Susceptibility information

Others Tests

- DFA (obsolete?)
  - Laborious
  - Costly
  - Low sensitivity, specificity
- Antigen test (soon to-be obsolete?)
  - Easy to use, Cost effective
  - Low Sensitivity, specificity
  - Needs Reflex!



Molecular Tests

- No molecular expertise needed!!
- Built-in controls (IQCP eligible)
- Accurate results
- Can replace rapid antigen testing
  - Generally slower
  - Could be Costly $$

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Molecular Tests (cont'd)

- Targeted, single or multiplex tests
  - BD-Max, Cepheid, DiaSorin Simplexa, Luminex,…
- Point-of-Care (POC)
- Large Respiratory Syndromic panels
  - BioFire , GenMark (e-Plex), Luminex (Verigene)
- Lower-Respiratory Panels
  - BioFire Pneumonia, Curetis LRT

Molecular: Targeted tests

- Usually 1-4 pathogens
- Less costly than the larger panels
- In line with Diagnostic tests Stewardship
- Recommended approach by insurance companies

Molecular: Point-of-Care

Close to care, Rapid, and Easy-to-Perform approach to testing.

	Device	Company	Accuracy: %Agreements (95% CI)							
			Influenza				RSV		Group A Strep.	
			A		B					
	Alere-i®	Abbott®	30	**100%** (90.1%-100%)	29	**97.7%** (81.9%-99.9%)	29	**97.7%** (81.9%-99.9%)	30	**100%** (90.1%-100%)
	Cobas Liat®	Roche®	30	**100%** (90.1%-100%)	30	**100%** (90.1%-100%)	30	**100%** (90.1%-100%)	30	**100%** (90.1%-100%)
	GeneXpert	Cepheid®	30	**100%** (90.1%-100%)	30	**100%** (90.1%-100%)	29	**97.7%** (81.9%-99.9%)	30	**100%** (90.1%-100%)
	Solana®	Quidel®	30	**100%** (90.1%-100%)	29	**97.7%** (81.9%-99.9%)	29	**97.7%** (81.9%-99.9%)	30	**100%** (90.1%-100%)

Noorbash MH, Gsmalsed BA, 2018 ASM Microbe - Atlanta, GA

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Molecular: Point-of-Care (Cont'd)

	Device	Level of Detection: Influenza, only		Sample Volume (µL)	Unit#/device	Interface able	Dimensions (L"xW"xH")	Turn-Around	Ease of use
		A	B						
	Alere-i®	1:10	1:100	200	1	Yes	8x8x5.5	17'	14
	Cobas Liat®	1:10,000	1:10,000	200	1	Yes *	9.5x4.5x7.5	20'	12
	GeneXpert	1:1,000	1:1,000	50	4	Yes *	11.7x11x12	32'	20
	Solana®	1:1	1:1	50	2	Yes *	9x825x5	40'	16

Noorbash MH, Gsmalsed BA, 2018 ASM Microbe - Atlanta, GA

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Molecular: Comprehensive Panels

- For clinically indistinguishable syndromes
- Upper respiratory specimens
- Costly $$$

Examples:

- BioFire Respiratory panel - 21-targets
- Verigene (Luminex) RP-*Flex* - 16 targets
- NxTAG RPP (Luminex) – 18 targets
- e-Plex Respiratory Panel (GenMark) – 17 targets

Molecular: Lower Respiratory - Curetis

- Designed for critically ill patient, and for Bronchial and Sputum specimens

- **Curetis: Unyvero LRT**
  - **21** Microbial targets

Acinetobacter baumanii, C. pneumoniae, C. freundii, E. coli, E. cloacae, H. influenzae, K oxytoca, K pneumoniae, M. morganii, M. pneumoniae, P. jirovecii, Proteus, P. aeruginosa, S. marcescens, S. aureus, S. maltophilia, S. pneumoniae.

  - **17** resistance Markers

*erm*B, *mec*A, *mec*C, *tem*, *shv, ctx*-M, *imp, kpc, ndm, oxa*-23, *oxa*-24/40, *oxa*-48, *oxa*-58, *vim*, *sul-1, gyr*A83, *gyr*A87,

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Molecular: Lower Respiratory - BioFire

BACTERIA:
Semi-Quantitative Bacteria
- *A. baumannii*
- *Enterobacter cloacae*
- *E. coli*
- *Haemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *K. pneumoniae*
- *Moraxella catarrhalis*
- *Proteus* spp.
- *P. aeruginosa*
- *Serratia marcescens*
- *S. aureus*
- *S. agalactiae*
- *S. pneumoniae*
- *S. pyogenes*

VIRUSES:
- Adenovirus
- Coronavirus
- Metapneumovirus
- Rhinovirus/Enterovirus
- Influenza A
- Influenza B
- Parainfluenza Virus
- RSV

ATYPICAL BACTERIA:
- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

RESISTANCE GENES:
- *mec*A/C and MREJ
- KPC
- NDM
- Oxa-48-like
- VIM
- IMP
- CTX-M

Pneumonia Panel – 33 targets

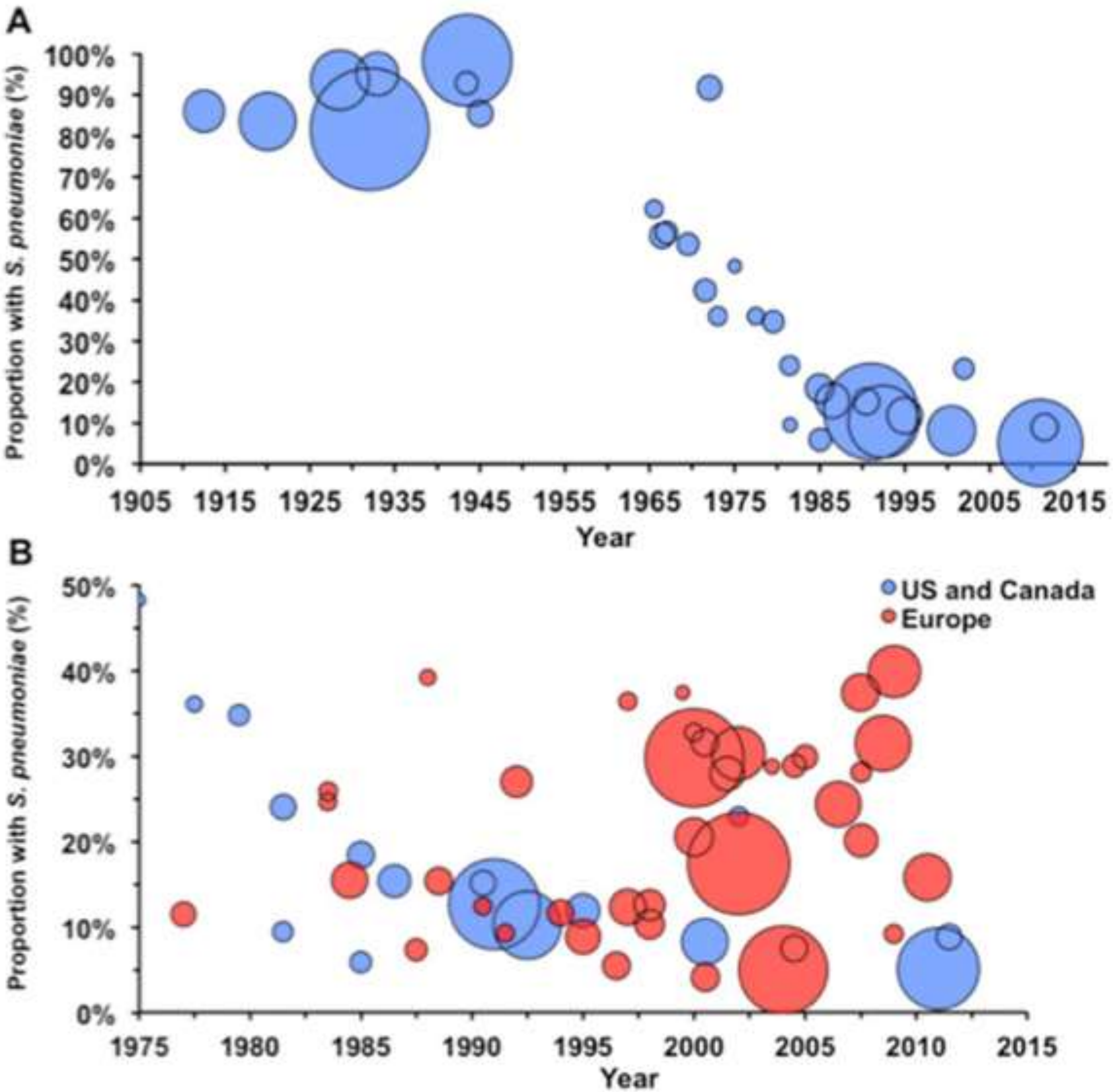
Testing Considerations

- Many primary care practices do not have rapid testing for respiratory viruses.
  - Diagnostic tests would be sent to a reference laboratory.
  - Time to result could be over 24 hours.
- CLIA-waived testing available in this setting:
  - Rapid influenza antigen testing
  - Pediatrics: RSV antigen testing
  - Now there are CLIA-waived molecular tests for influenza, RSV, Group A Strep, and a respiratory pathogen panel

Clinical Case (Part-3)

- She continued to improve over the next 3 days.
- Then her <u>cough</u> worsened, accompanied by chest pain and return of <u>fever</u>.
- Exam is notable for <u>respiratory distress</u> and evidence of <u>sepsis</u>.
- A CXR revealed bibasilar reticular infiltrates.
- She is admitted for treatment of community-acquired pneumonia.

Bacterial Culture: main Pathogens
Streptococcus pneumoniae



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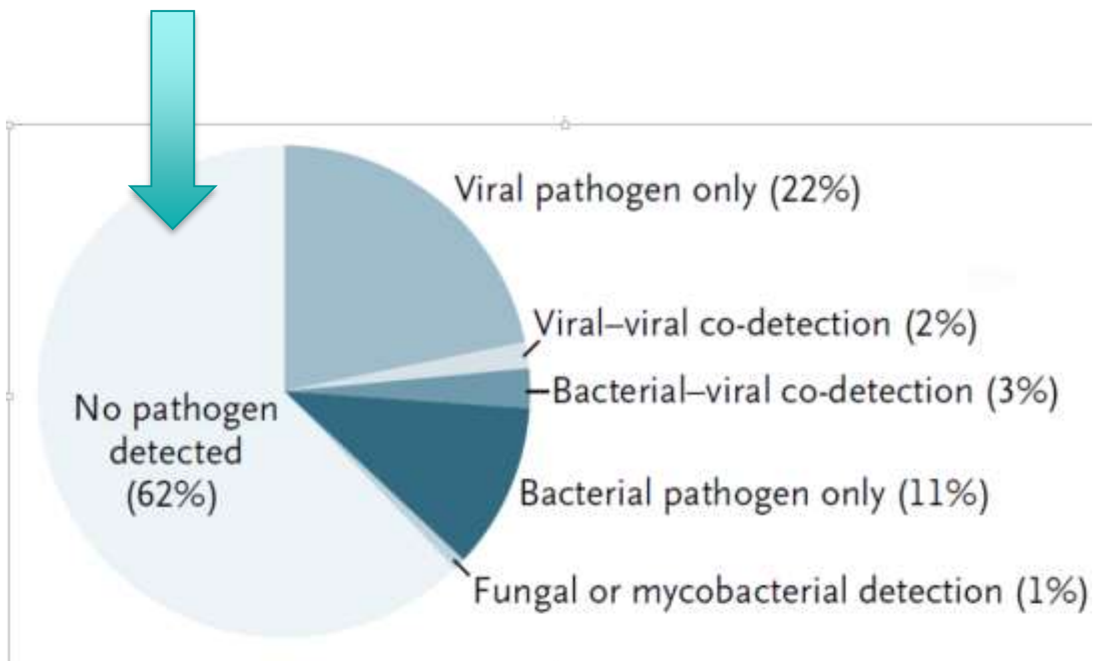
Reduction trend in pneumococci

- Widespread use of pneumococcal polysaccharide vaccine by US adults vs. none in Europe
- Substantial reduction in cigarette smoking by US adults
- Conjugate pneumococcal vaccine in kids

Etiology= Unknown?

- What is the cause of all those unknowns?
- Is there testing issue?
  - The Specimen? or
  - The test?



Sputum

- A product of lung inflammation: Cells, bugs, fluids
- Need "correct" collection (or it's spit)
- Antibiotics destroy organisms in[1]:
  - Direct Exam ~ 18 hours
  - Cultures ~ 24 hours
- It contains "Normal Respiratory Flora"
  - Usually the main cause of pneumonia

1- (Musher, Montoya, Clin Infect Dis 39:165, 2004)

FACTS

- Most CAP with unknown etiology still bacterial
- Current guidelines recommends antibiotic to even viral PCR positive patients!
- $>10^6$ CFU/mL bacterial pathogens are in pneumonia
- Systematic microscopic and quant-culture indicates the crucial role of normal flora.

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Lorber, Ann Intern Med 81:329, 1974;Musher et al JAMA 233:894, 1975

How to distinguish?
Normal-Flora or Pathogen?

- Acute onset of ≥2 of the symptoms:
  - New or Increasing Cough, or Productive-Cough
  - Fever
  - Sepsis
  - Confusion
  - Leukocytosis

AND

  - **Good Quality Sputum** (WBC/Ep Cell >10)

Rejected!

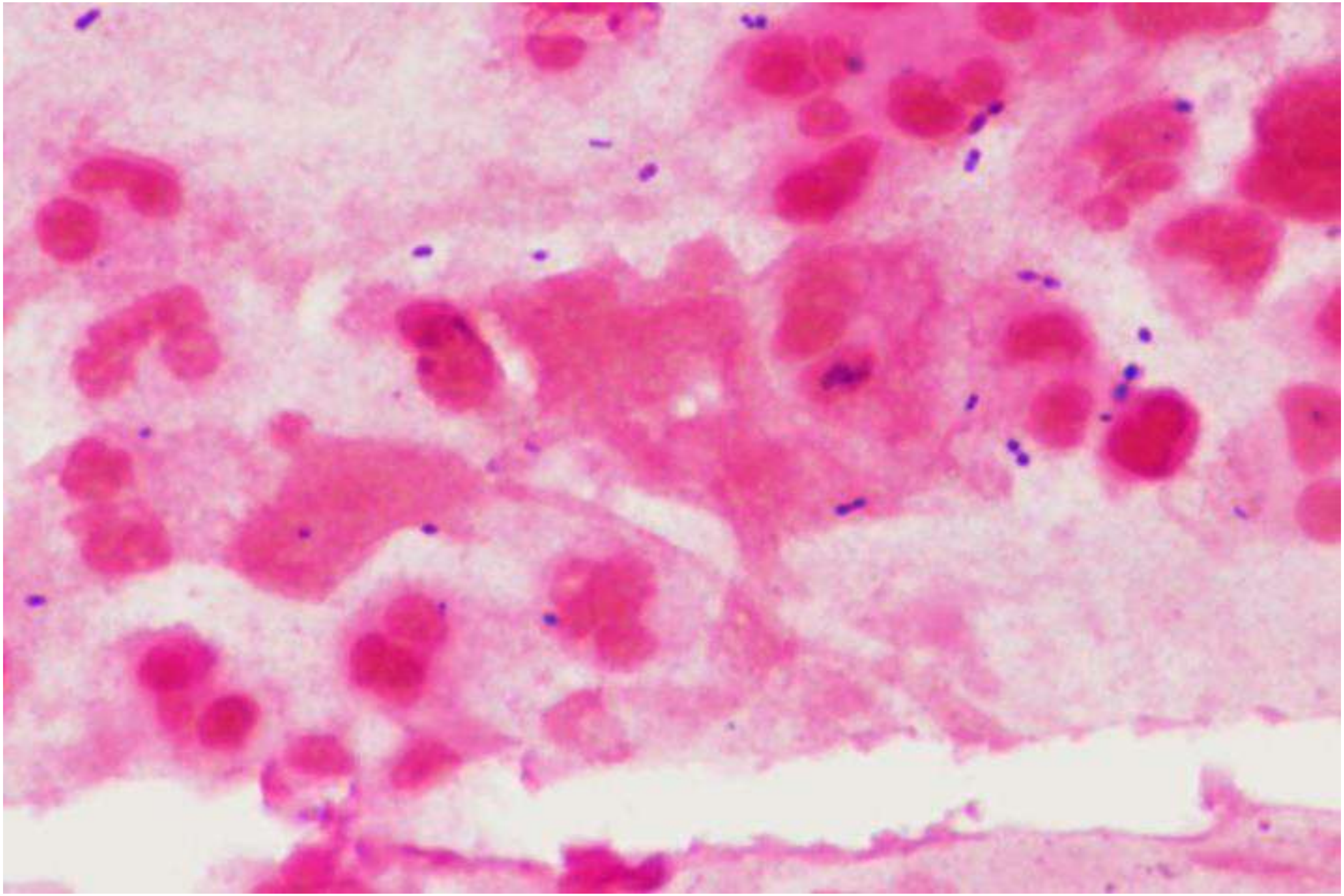
- SHSL rejection criteria>10 Epi/LPF
  - >30% of sputum!
- WBC/Ep Cell >10 will increase the rejection rate
- SHSL do not reject based on antimicrobial use >18 hours.

Optimized sputum culture

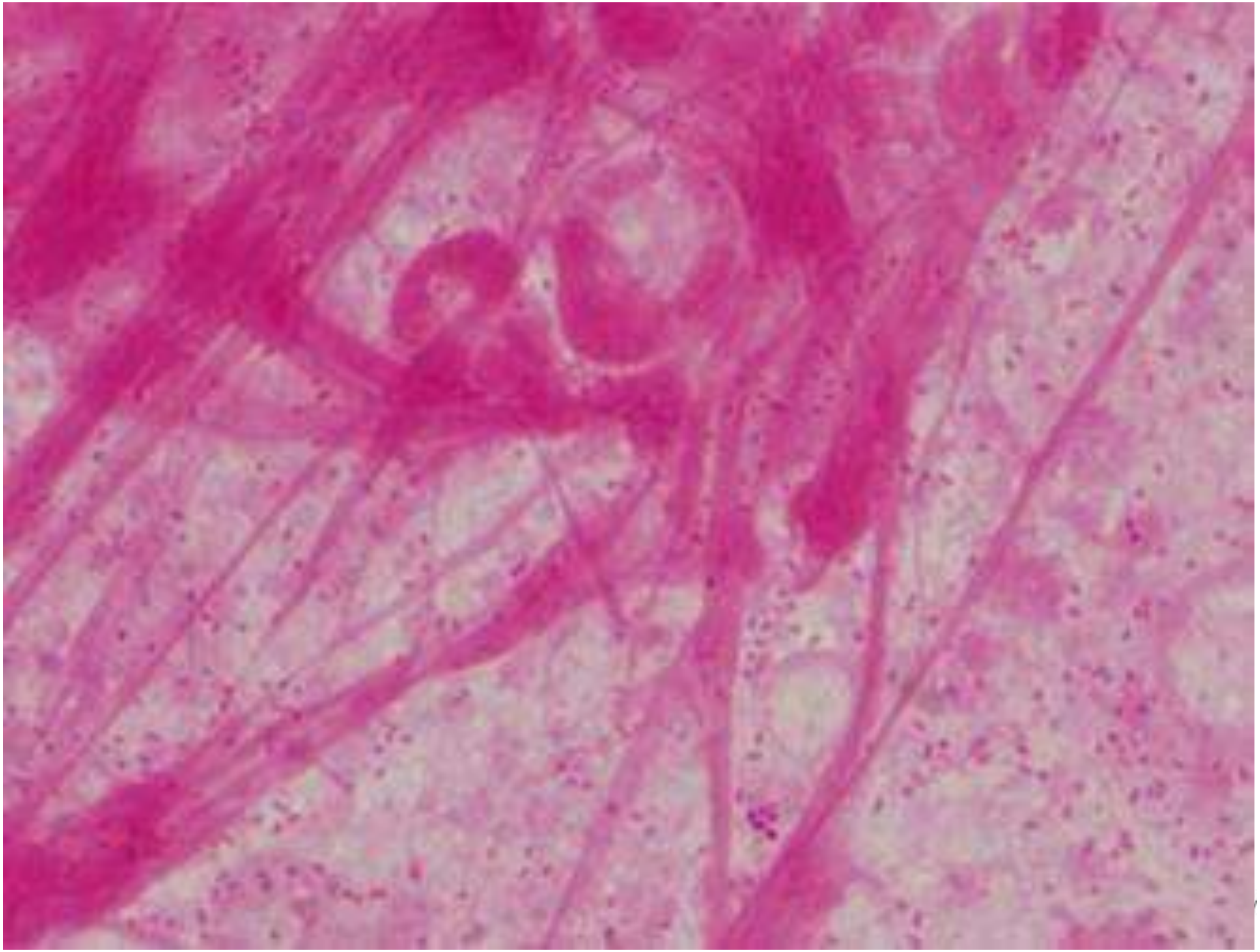
(FDA guidelines: Musher D. et al 2018)

- Assist and educate for proper collection
- Reject if WBC/Ep Cell >10
- Reject if on antimicrobial > 18 hours
- Use mucolytic (N-Acetyl Cyst.) and quantitate
- Studied other criteria
  - Blood cult., Urine Ag, Procalcitonin, BNP, Targeted PCR
- Bacteria=41% Pos; 13% mix

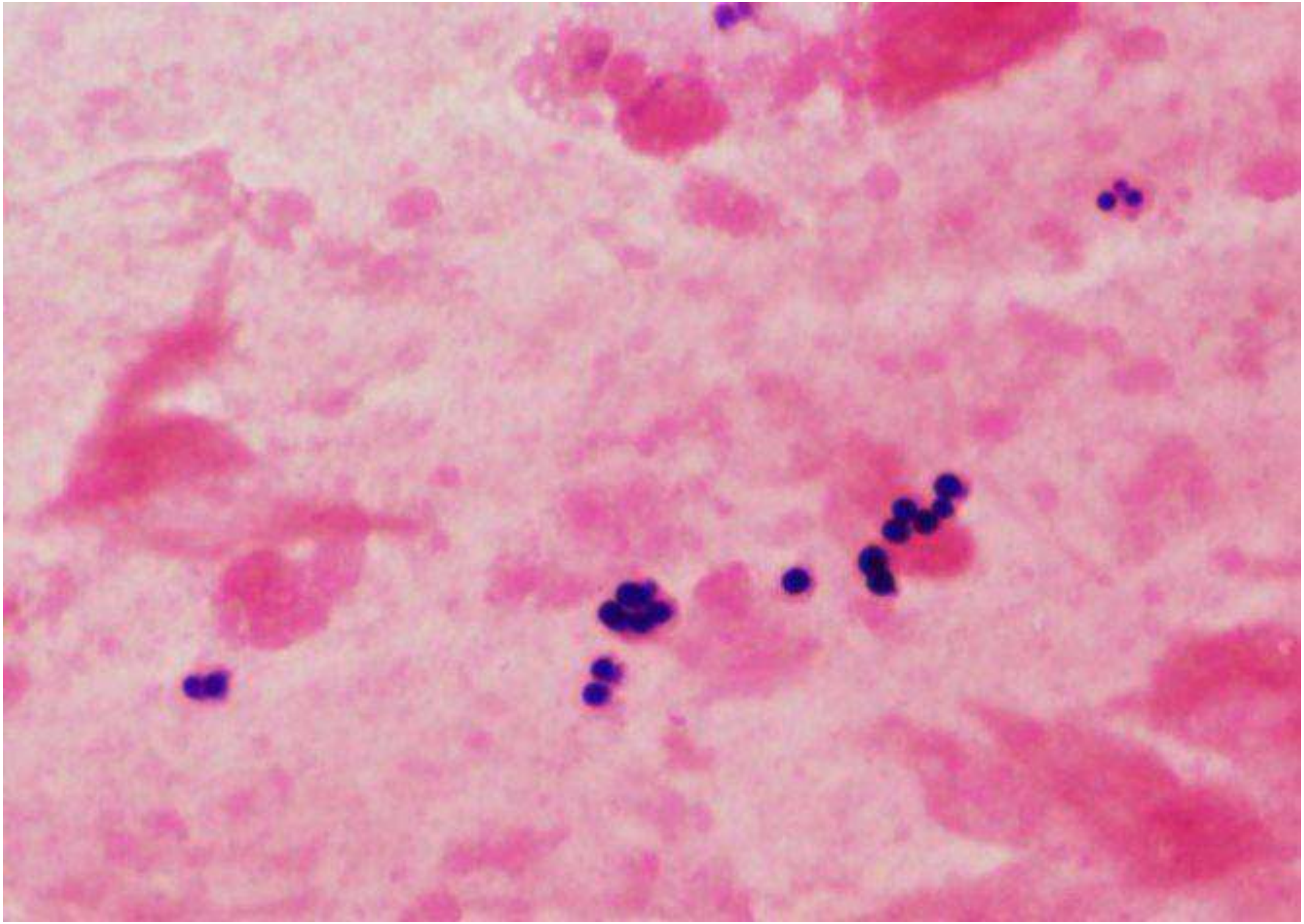
S. pneumoniae



H. influenzae



S. aureus



Pathogen isolation rate

Pathogens	#	Rate
Bacterial	49	41%
Viral	27	23%
Co-infected	13	11%
No pathogen detected	26*	22%
Non-infectious	4	3%
Total	119	100%

- Requirements for high quality sputum samples resulted in 75% pathogen ID

* 19/26 (16%) show pure bacteria, however they are deemed as a part of Normal flora, such as Corynebacteria, and Viridans group Strep.

Clinical Case (Part-4)

- The sputum Gram stain showed 2+ neutrophils and Gram-positive-cocci in pairs indicating a well-collected specimen that should be cultured for bacteria.
  - grow *Streptococcus pneumoniae*
- RVP was positive for human metapneumovirus
- The patient most likely had a post-viral bacterial pneumonia, though she may also have a concomitant viral pneumonia with hMPV.

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New CAP Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Treatment of Adults with Community-acquired Pneumonia

An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Joshua P. Metlay*, Grant W. Waterer*, Ann C. Long, Antonio Anzueto, Jan Brozek, Kristina Crothers, Laura A. Cooley, Nathan C. Dean, Michael J. Fine, Scott A. Flanders, Marie R. Griffin, Mark L. Metersky, Daniel M. Musher, Marcos I. Restrepo, and Cynthia G. Whitney; on behalf of the American Thoracic Society and Infectious Diseases Society of America

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY MAY 2019 AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA AUGUST 2019

New CAP Guidelines criteria

- X-ray base diagnosis
- US focused
- Excluded patients:
  - Immunocompromised, Cancer, Transplant
- Treatment recommendation for select bacterial pathogens:
  - *S. pneumoniae, H. influenzae, M. pneumoniae, S. aureus, Legionella, C. pneumoniae,* and *M. catarrhalis*

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

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New CAP Guidelines criteria

- Declining role of *S. pneumoniae* (vaccine)
- Increased role of viral pathogens
- Role of bacterial & viral co-infections
- Emergence of multidrug resistant pathogens
  - MRSA
  - *P. aeruginosa*

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

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New CAP Guidelines criteria

- Gram Stain & Culture
- Obtaining valid specimens are challenging
  - Out Patient: Not recommended
  - In-Patient recommended only for:
    - **Severe CAP class**, or intubated
    - Targeting MRSA or *P. aeruginosa*
    - History of MRSA or *P. aeruginosa* infections
    - History of hospitalization in the last 90 days

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

Severe CAP criteria

Defines by Three minor or One major criteria

- **Minor criteria**
  - Respiratory rate>30 breaths/min
  - PaO2/FIO2 ratio<250
  - Multilobar infiltrates
  - Confusion/disorientation
  - Uremia (blood urea nitrogen level >20 mg/dl)
  - Leukopenia (white blood cell count,4,000 cells/ml)
  - Thrombocytopenia (plateletcount,100,000/ml)
  - Hypothermia (core temperature,368C)
  - Hypotension requiring aggressive fluid resuscitation
- **Major criteria**
  - Septic shock with need for vasopressors
  - Respiratory failure requiring mechanical ventilation

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

New CAP Guidelines

- No empiric anaerobic coverage for aspiration pneumonia
- Macrolide is preferred over doxy for atypical pneumonia.
- Minimum duration of antibiotics: 5 days
- MRSA by PCR and/or sputum cultures are recommended to allow de-escalation or confirmation of need for continued therapy.

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

New CAP Guidelines (Cont'd)

- Use Pneumococcal urinary antigen
- Limit *Legionella* urine antigen to severe cases or epidemic links.
- Influenza testing should be performed by NAAT, when the virus is circulating rather than the antigen assays.

Metlay, et al, 2019 American Journal of Respiratory and Critical Care Medicine

Summary

- Molecular detection become and integral part of the diagnosis, & should not be ignored.
- Micro-aspiration of "Normal Resp. Flora" is the major cause of pneumonia.
- Right sputum specimen is key to diagnosis
- Bacterial Pneumonia is under-detected
- Co-infection is a real thing, especially with virus

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