

Is it Influenza or Pneumonia . . .or Both?

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Objectives

Discuss the health impacts of pneumonia and influenza in the United States

Discuss the diagnostic options available for influenza and pneumonia

Discuss the biology of how an influenza infection can predispose a person to pneumococcal pneumonia

Infectious Disease in the US

1970: William Stewart, the Surgeon General of the United States declared the U.S. was “ready to close the book on infectious disease as a major health threat”; modern antibiotics, vaccination, and sanitation methods had done the job.

1995: Infectious disease had again become the third leading cause of death, and its incidence is still growing!

Current Number of Pneumonia Cases (US)

37 million ambulatory care visits per year for acute respiratory infections (physician and ER visits combined)

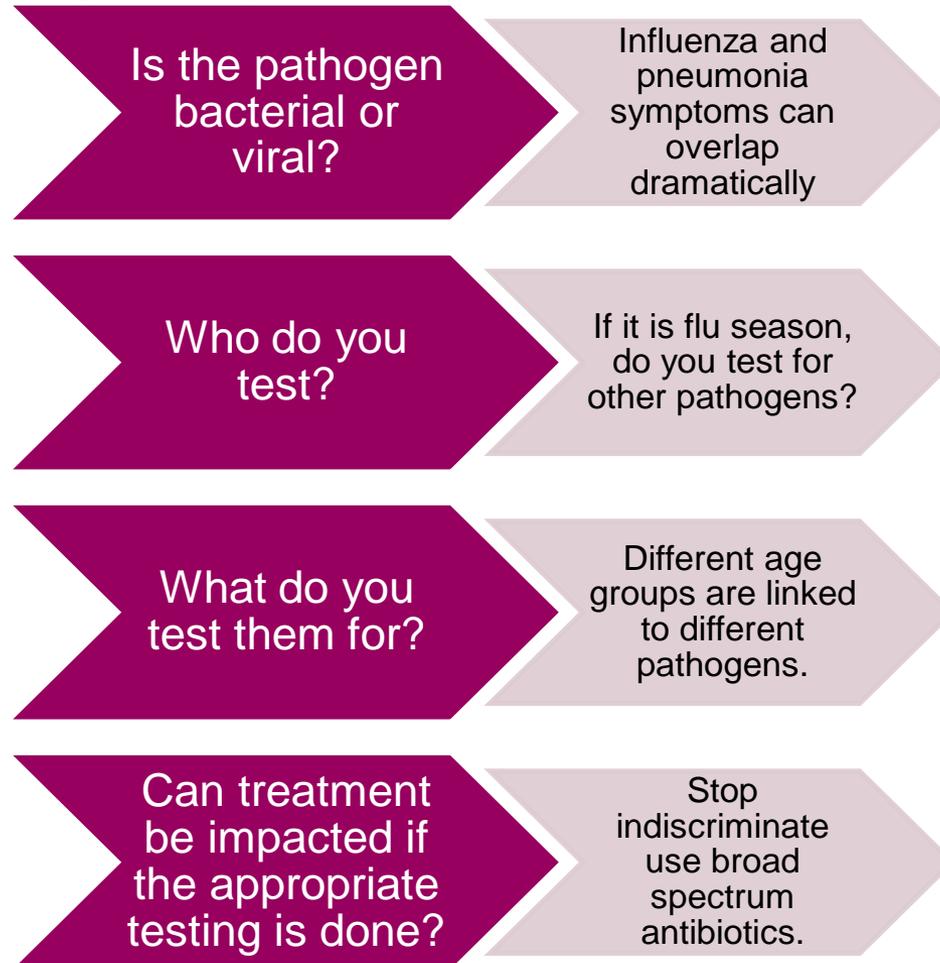
Community-Acquired Pneumonia (CAP)

- Each year 2 - 3 million cases of CAP result in ~ 10 million physician visits & 500,000 hospitalizations in the US
- Average mortality is 10-25% in hospitalized patients with CAP

Hospital-Acquired Pneumonia

- Standard definition: onset of symptoms occurs approx 3 days after admission
- 250,000 - 350,000 cases of nosocomial pneumonia per year
- 25 - 50% mortality rate

Treating Respiratory Diseases in the Emergency Department



Misuse of Antibiotics Can Lead to Other Medical Issues



Pneumonia may be treated with fluoroquinolone

Disrupts normal intestinal flora

O27 strain of *C. difficile* is specifically resistant to fluoroquinolone

Etiological Agents

Newborns (0 to 30 days)

- Group B *Streptococcus*, *Listeria monocytogenes*, or Gram negative rods are common
- RSV in premature babies

Infants and toddlers

- 90% of lower respiratory tract infections are viral with the most common being RSV, Influenza A&B, and parainfluenza. Bacterial infections are rare, but could be *S. pneumoniae*, Hib, or *S. aureus*.

Etiological Agents

Outpatient

- *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, and respiratory viruses

Inpatient (non-ICU)

- With the above agents, add *L. pneumophila*

Inpatient (ICU)

- *S. pneumoniae*, *S. aureus*, *L. pneumophila*, Gram-negative bacteria, and *H. influenzae*

Streptococcus pneumoniae

Types – Over 90 serotypes exist, with 88% of disease covered in the 23-valent vaccine

Incidence – 100,000 to 135,000 cases of pneumonia requiring hospitalization up to the year 2000

- Around 80% of CAP
- Cases are dropping due to the *S. pneumoniae* vaccine

Transmission – Person to person

Risk groups – The young and elderly

Most common identification – Blood culture and sputum culture

The Future of Pneumococcal Pneumonia

Between 2004 and 2040, the US population is expected to increase 38%

Pneumococcal pneumonia cases may increase 96%

- Roughly 400,000 cases to 790,000

Absent intervention, the cost of pneumococcal pneumonia will increase \$2.5 billion annually

Influenza A&B

Impact of influenza in the US

- Hospitalizations up from 114,000 to 226,000
- 36,000 deaths annually
- Influenza target population: 188MM in US

5-20% of US population affected by influenza each year

Most deaths affect elderly and young children

- Also affects otherwise healthy individuals

A bit of history

There are flu epidemics every 1 to 3 years for at least the last 400 years.

Pandemics (worldwide) occur around every 10 to 20 years.

History

Hippocrates described flu back in the 5th century.

Columbus brought a devastating flu on his second voyage to the new world.

Spanish flu of 1918-1919 was the single greatest epidemic in history.

- 50 to 100 million people were killed (3-6% of the world's population!)
- Another 500 million were infected (1/3rd of the world's population)

WWI Army Soldiers



Aren't you supposed to build immunity to influenza?

The problem with influenza, like the common cold, is that there are many different strains.

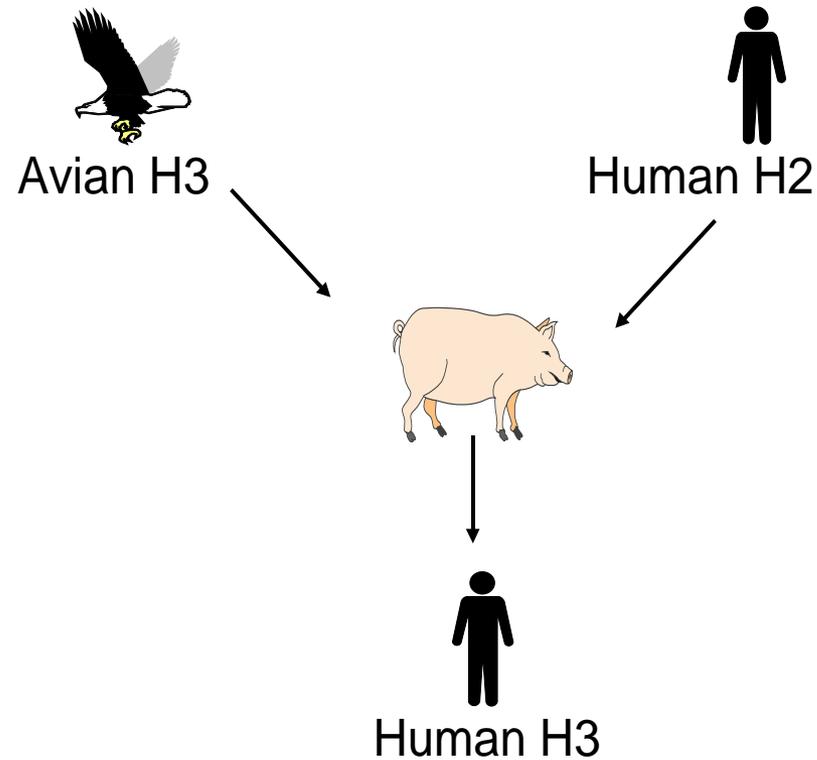
That is also why the performance of rapid tests are different every year!

How the virus changes – Shift vs. Drift

Antigenic drift – small changes in the virus that happen over time. It allows new strains that can evade the body's immune system.

Antigenic shift – an abrupt, major change that results in a new hemagglutinin and/or new hemagglutinin and neuraminidase protein.

How do you make a pandemic flu?



Influenza Treatment

Antiviral drugs are available

- Must be administered within 48 hr of onset of symptoms
- Generally reduce duration of symptoms by one day
- First generation drugs (amantidine, rimantidine) are cheaper but only treat influenza A
- Second generation drugs (Tamiflu[®], Relenza[®]) are more expensive but treat both influenza A and B
- Reason to differentiate between influenza A and B

Specimen Collection for Bacterial Pneumonia

Sputum Collection

Quality of specimen

- Care should be taken in collection since a lower respiratory tract sample can be contaminated with upper unless collected by an invasive technique

Collection

- Patient is instructed to give a deep coughed specimen
 - Put into sterile container, trying to minimize saliva
 - Transport to lab immediately
- Patient unable to give specimen can be given an aerosol-induced specimen

Blood culture

Usually done with fever spike

Standard is to take two sets of blood cultures one hour apart

Urine

Urine can be used for *Legionella* and *Streptococcus pneumoniae*

- Antigen test
- Non-invasive sample
- Does not need to be qualified like a sputum sample

Influenza Sample Collection

Appropriate specimens

- Nasal wash/aspirate, nasopharyngeal swab, or nasal swab
- Throat swabs have dramatically reduced sensitivity

Samples should be collected within first 24 to 48 hours of symptoms since that is when viral titers are highest and antiviral therapy is effective

Testing can be done immediately with rapids or sample placed in transport media

- Infectivity is maintained up to 5 days when stored @ 4-8°C
- If the sample cannot be evaluated in this time period, the sample should be frozen @ -70°C.

Diagnostic Methods Available

Infectious Disease Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)

Diagnostic Testing

- Suggestive clinical features combined with a chest radiograph or other imaging technique is required for the diagnosis of pneumonia
- It is recommended that “patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues.”

Blood Culture

Pros:

- Inexpensive
- Allows for antibiotic susceptibility testing
- High specificity

Cons:

- Requires live bacteria – antibiotics can affect results
- Requires dedicated tech time / experienced personnel
- Results take 24 hours to >1 week
- Many bacterial infections don't progress to bacteremia



Infectious Disease Society of America/American Thoracic Society CAP Guidelines 2007

When to apply diagnostic tests

- Optional for outpatients with CAP
- Blood culture and sputum culture for inpatients with productive cough*
- All adult patients with severe CAP, should have blood culture, sputum culture, *Legionella* urinary antigen and *S. pneumoniae* urinary antigen tests*

Common Diagnostic Tests

Gram stain

Sputum culture

Blood culture

Latex agglutination assays

DFA/IFA

PCR

Serology

Urinary antigen

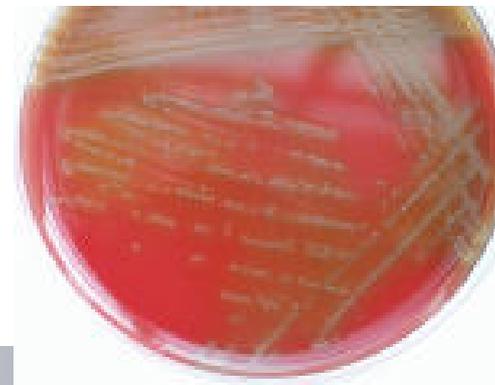
Sputum Culture – Bacterial Culture

Pros: Inexpensive

- - Standard media for most – Sheep blood agar, MacConkey agar, and chocolate agar, BCYE for *Legionella*
- - Allows for antibiotic susceptibility testing

Cons: Requires live bacteria – antibiotics can affect results

- - Difficult to get good sample
- - Requires dedicated tech time / experienced personnel
- - Results take 24 hours to >1 week



Urinary antigen

Tests are available for *S. pneumoniae* and *L. pneumophila* serogroup 1

With *Legionella*, antigen appears in the urine 1 to 3 days after infection

Noninvasive sample

Easy-to-use



Diagnostic Methods for Influenza

Culture

DFA

PCR

Rapid Tests

Molecular Assays

Pro

- For respiratory specimens, high performance
- Same day results

Con

- Turn around time from lab is extensive, especially if batching specimens
- Expensive
- Requires experienced technicians, labs, dedicated equipment, etc.

Rapid Tests

Pro

- Tests take minimal time
- Some tests are so simple that they can be CLIA-waived
- Can be used to triage patients
- Positive results can be used to rule out other issues like pneumonia so don't give unnecessary chest x-ray, antibiotics, etc.

Con

- Performance is not as good as culture, PCR, and DFA

Rapid Molecular Tests

Can be done in the same time as traditional rapid tests with molecular sensitivity

Can be brought to point-of-care

Attempts to CLIA-waive

Results – Cost Savings Associated with using a Rapid Test

	Flu positive			Flu negative		
	MD aware N=96	MD unaware N=106	<i>P</i> value	MD aware N=97	MD unaware N=92	<i>P</i> value
CBC	0	13	<0.001	13	7	0.196
Blood Culture	0	11	<0.001	12	6	0.172
Urine dipstick	4	7	0.543	7	7	0.918
Urinalysis	2	12	0.011	10	8	0.706
Urine culture	3	14	0.011	12	5	0.096
CSF studies/culture	0	2	0.499	3	2	0.695
Chest X-ray	7	26	0.001	22	23	0.708
Lab/radiology charges per patient	\$15.65	\$92.37	<0.001	\$93.07	\$68.91	0.871
Antibiotics	7	26	<0.001	27	27	0.818
Antivirals	18	7	0.02	0	2	0.236
Time (min. from exam to discharge)	25	49	<0.001	45	42	0.549

Sensitivity vs Specificity vs PPV vs NPV

Sensitivity:

Probability test=positive if patient=positive

Specificity:

Probability test=negative if patient=negative

PPV: Probability patient=positive if test=positive

NPV: Probability patient=negative if test=negative

- Flu is seasonal. Prevalence of the disease is different in June than in January.
- This will impact the perceived performance of the test

Test 1,000 persons

Test Specificity = 99.6% (4/1000)

Prevalence = 10%

True positive: 100

False positive: 4

Positive predictive value:

100/104 = 96%

Test 1,000 persons

Test Specificity = 99.6% (4/1000) Prevalence = 10%

True positive: 100

False positive: 4

Positive predictive value: $100/104 = 96\%$

Prevalence = 0.4%

True positive: 4

False positive: 4

Positive predictive value:

$4/8 = 50\%$

The Connection Between Influenza and *S. pneumoniae*

Statistics of influenza and pneumonia

Influenza pandemics of 1957 and 1968

- Bacterial etiology in roughly 70% of patients with severe pneumonia (life threatening or fatal)^{1,2}

Influenza hospitalizations rates (non pandemic)

- 44-57% bacterial pneumonia³⁻⁶

Approximately 25% of influenza-related deaths have a secondary bacterial pneumonia⁷

EID - Predictors of Pneumococcal Co-infection with Pandemic (H1N1)

Study
in
Spain
July
2009-
March
2010.

- Looked at adults who had influenza-like illness and sought medical attention and had ≥ 1 risk factor for contracting influenza-related complications

EID Study- Data Collection

Samples

- Oropharyngeal and nasopharyngeal swab samples
- Urine sample
- Sputum and 2 blood cultures

Assays

- PCR for the detection of influenza
- Blood, urinary antigen, or qualified sputum for *S. pneumoniae*

EID Study - Results

418
patients
were
evaluated

- 179 were confirmed H1N1
- In PCR H1N1 negative, 25.1% had pneumococcal disease

Of 100
patients
with
influenza

- 14% had pneumococcal infection
- “Infection in more than half these patients would not have been diagnosed if a pneumococcal urinary antigen test had not been performed.”

EID Study

When Coinfection Found. . .

Patients more frequently admitted to the hospital and to the intensive care unit

Had lower oxygen saturation

Had higher axillary temperature

EID Study - Conclusions

Concurrent infection significantly increased risk of patient complications

If only looking for influenza, pneumococcal pneumonia may be missed or only looking for pneumonia, influenza may be missed.

H1N1 Pandemic with *S. pneumoniae* in Argentina¹

May 2009 –
pandemic
H1N1 had
estimated
fatality rate of
0.6%

- Similar to seasonal influenza

July 2009 –
Argentina
reported fatality
rate of 4.5%
(137 deaths out
of 3056 cases)

- No genetic difference in virus
- *S. pneumoniae* associated with 56.4% of severe disease

Influenza and MRSA

MRSA infrequently causes CAP

In 2007 season, the CDC received reports of 10 cases of severe MRSA CAP in Louisiana and Georgia

- Two month period
- Ten cases of severe CAP MRSA in previously healthy children
 - Six of the ten children died
- Additional note – Respiratory symptoms began an average of 3 days before recovery of MRSA so short duration suggests infections may be concomitant

Proposed Mechanisms

Bacterial adherence after epithelial destruction

- Autopsy evidence in 1918 outbreak with *S. aureus*¹

Neutrophil apoptosis in presence of influenza and *S. pneumoniae*²

Upregulation of molecules that *S. pneumoniae* can use as receptors

- Incubation with cytokines from viral infections³

Environmental factors

Mechanism of Influenza Leading to Pneumococcal Pneumonia

Influenza has two surface glycoproteins

- Hemagglutinin (HA) binds to sialic acid on host cells
 - Aids in internalization and fusion
- Neuraminidase (NA) helps the virus release from host cells by cleaving sialic acid during budding
 - Also prevents influenza particle clumping

Synergistic Effect of Neuraminidase

Some cellular structures that bacteria use as receptors can be covered by sialic acid

Bacteria such as *S. pneumoniae* can use its own neuraminidase activity to expose these receptors

- **Mutant strains of pneumococcal pneumonia lacking the gene were found to be attenuated in mice, but could cause disease if mice were pre-infected with influenza¹**

In vitro Studies

After exposure of influenza or rhinovirus to cultured cells, increased adhesion of *S. pneumoniae* can be seen¹

McCullers Study²

- Incubate cells for 30 minutes with influenza (no viral replication)
- Adherence of pneumococcus increases 2 to 4-fold
- Action is reversed with addition of neuraminidase inhibitor

Animal Models

Mice initially challenged with influenza and seven days later, *S. pneumoniae*.

- Pre-exposure had greater bacterial counts and levels of inflammatory cytokines¹

Mortality rates in pre-exposure of influenza then *S. pneumoniae*

- Low doses gave 100% mortality from pneumonia in 3-7 days while little to no mortality in control mice infected individually.²

Experimentation on Neuraminidase

Recombinant influenza viruses were made with neuraminidase from representative strains of past 50 years¹

- Viral strains associated with higher mortality were able to prime animals better for subsequent pneumococcal invasion
- Mortality was reduced when neuraminidase inhibitor was added

Type 1 Interferon As Mechanism

Mice were infected with influenza¹

- Deficient in type 1 IFN- α/β receptor signaling vs. wild type

Mutants were better at clearing *S. pneumoniae* from lungs/blood and had improved chances of survival

- Wild type had impaired production of some neutrophil chemoattractants
- Early phase of disease in wild type was inadequate with less neutrophils

S. pneumoniae in Biofilm

Provides a safe haven

Allows transmission of person-to-person

10-40% of health individuals can carry *S. pneumoniae*

Pneumococci in biofilm are hyper-adhesive and show attenuated virulence in animal models

Viral infections in children gives 15-fold increase in pneumococci in nasal cultures

Pneumococcal Biofilm Dispersion

Environmental factors can lead *S. pneumoniae* to convert from passive colonizing agent in biofilm to virulent free-form pathogen

Environmental factors include

- High temperature
- ATP
- Norepinephrine
- Increased nutrient availability

Mouse model – Intranasal application can lead from carriage to pneumonia

Conclusions

Diagnostic technologies for respiratory infections allow more directed therapy

Biological mechanisms do exist which predispose patients with influenza to pathogens such as *S. pneumoniae*

A superinfection with bacterial pneumonia has been shown to increase morbidity/mortality in influenza infections

Testing for both influenza and bacterial pneumonia in select populations can help predict how well patients do