Pneumonia in Hospitalized Patients

Update in Hospital Medicine
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- Grant funding
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
  - Massachusetts Department of Public Health

- Royalties
  - UpToDate for chapters on pneumonia

Outline

- How accurate are clinical signs for pneumonia?
- Is pneumonia in hospitalized patients viral or bacterial?
- What kind of imaging should we get?
- Is there a role for procalcitonin?
- Do we need to get cultures?
- Do we need to start antibiotics right away?
- What should we treat with?
- Do we need to include atypical coverage?
- How long should we treat for?
A 72-year old gentleman with a history of coronary disease, atrial fibrillation, and obstructive lung disease is admitted to hospital with shortness of breath x 2 days. He notes poor appetite, feeling weak, and intermittent non-productive cough but denies fever.

Went to his grandchild’s birthday party the week before (pizza!) but none were sick and he wore a mask at all times.

On exam, he is lethargic but easily arousable. Temperature 100.1, HR 120 irregular, BP 98/64, RR 28, SaO2 90% RA. JVP difficult to see. Crackles in the bases. Mild bilateral lower extremity edema.

Labs are notable for WBC count of 10.2, hct 32, plt 240, Na 130, creatinine 1.4, liver function tests mildly elevated.

Portable chest x-ray with edema +/- LLL infiltrate

SARS-CoV-2 anterior nares rapid PCR negative
Does this patient have pneumonia?
Would you start antibiotics?

Why is Pneumonia So Difficult to Diagnose?

- Many medical conditions in hospitalized patients present with the same clinical signs as pneumonia
  - Radiographic opacities
  - Fever
  - Abnormal white blood cell count
  - Impaired oxygenation
  - Increased pulmonary secretions
Accuracy of Clinical Diagnosis of Pneumonia
Relative to 253 autopsies

- **Sensitivity / Positive Predictive Value**
  - Loose definition: Infiltrate and 2 of temp / wbc / purulence
  - Strict definition: Infiltrate and 3 of temp / wbc / purulence

Tejerina et al., J Critical Care 2010;25:62

Accuracy of Bronchoalveolar Lavage Cultures for Pneumonia
Relative to histology

Kirtland, Chest 1997;112:445
Fabregas, Thorax 1999;54:867
Chastre, Am Rev Respir Dis 1984;130:924
Torres, Am J Resp Crit Care Med 1994;149:324
If the patient does have pneumonia, is it more likely bacterial or viral?

Etiology of Community-Acquired Pneumonia

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

- No pathogen isolated 62%
- Viruses 23%
- Bacteria 11%
- Bacteria + Virus 3%
- Fungus or AFB 1%

Etiology of Community-Acquired Pneumonia
2,259 adults admitted to 5 hospitals in Chicago and Nashville

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Rhinovirus</td>
<td>8.6%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.8%</td>
</tr>
<tr>
<td><em>Strep. pneumoniae</em></td>
<td>5.1%</td>
</tr>
<tr>
<td>Metapneumovirus</td>
<td>3.9%</td>
</tr>
<tr>
<td>RSV</td>
<td>3.0%</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>3.0%</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>2.3%</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>1.9%</td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>1.6%</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1.4%</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>1.4%</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>1.4%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>0.5%</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>0.4%</td>
</tr>
<tr>
<td>Other</td>
<td>2.3%</td>
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</tbody>
</table>

Prevalence of Viruses in CAP

Pooled Prevalence 24%
...and so too in hospital-acquired pneumonia

174 Patients with Non-Ventilator HAP
Barnes-Jewish Hospital, St Louis

Virus alone
22%
Virus + Bacteria
14%
Bacteria
63%
No pathogen
12%

99 Patients with HAP Admitted to ICU
Bichat-Claude Bernard Hospital, Paris

Virus
18%
Virus & Bacteria
14%
Bacteria
63%
No pathogen
22%

viruses in 22% of patients

18% with virus alone
14% with virus + bacteria

Shorr, Respiratory Medicine 2017;122:76-80
Loubet, J Clinical Virology 2017;91:52-57

...and so too in severe pneumonia

364 patients with pneumonia (CAP/HAP/VAP) requiring mechanical ventilation, Barnes-Jewish Hospital, St. Louis

viruses in 22% of patients

Rhinovirus/ enterovirus 29%
Influenza 19%
RSV 16%
CMV 7%
Adenovirus 8%
Parainfluenza 10%
HMPV 11%

Chest 2018; 154:84-90.
Lower Tract Specimens Increase Diagnostic Yield

1,407 patients requiring mechanical ventilation admitted to 5 Dutch ICUs. Nasopharyngeal swabs and tracheal aspirates sent for respiratory virus PCRs in all patients, regardless of reason for admission.

- 20% of viruses isolated exclusively from nasopharyngeal swab
- 51% of viruses found in both NP swab and tracheal aspirate
- 29% of viruses isolated from tracheal aspirates alone

If it is viral, do we have to worry about coinfection with bacteria?
Prevalence of Antibiotic Prescribing for Covid-19

Meta-analysis of 154 studies including 30,623 patients

Langford, Clin Micro Infection 2021;27:520-531
Prevalence of Co-Infection in Covid-19

Prospective cohort study amongst 260 hospitals in the United Kingdom including 48,902 patients

- Cultures obtained in: 18%
- Present on Admission: 29%
- Hospital-Onset: 71%
- Bacterial co-Infection documented in: 2.2%

Russell, Lancet Microbe 2021; doi.org/10.1016/S2666-5247(21)00090-2

Do we have to start antibiotics right away?
Clinical Signs in Patients Starting Antibiotics for Pneumonia

9,540 patients admitted to 4 Boston hospitals & started on antibiotics for pneumonia, 2015-2018

- 79% had a temperature <38°C
- 82% had a median respiratory rate <22 breaths/min
- 55% had a WBC count >4,000 and <12,000 cells/mm³
- 39% had O₂ sat > 95% on ambient air

All signs normal in 19% !!!

Klompas, JAMA Network Open 2020;3(7):e2010700

In Septic Shock, Time Matters...

Crit Care Med 2006;34:1589-1596
But are antibiotics equally urgent for sepsis without shock?

Association between each hour of delay until broad-spectrum antibiotics and in-hospital death amongst 49,331 patients in New York State

New York State

<table>
<thead>
<tr>
<th>Vasopressors</th>
<th>OR 1.07 (1.05-1.09)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vasopressors</td>
<td>OR 1.01 (0.99-1.04)</td>
</tr>
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</table>

Adjusted Odds Ratio for Death

Tailor Immediacy of Treatment to Certainty of Infection and Severity of Illness

Give Antibiotics & Get More Data
(stop antibiotics if the data do not support infection)

Hold Antibiotics & Get More Data
(treat expeditiously if/when the data suggest infection)
Could further imaging help?
Chest X-Ray vs CT Scan
319 patients with clinically suspected pneumonia

Initial pneumonia classification following chest x-ray

Chest X-Ray vs CT Scan
319 patients with clinically suspected pneumonia

Revised pneumonia classification following CT chest

Claessens, AJRCCM 2015;192:974-982
Chest X-Ray vs CT Scan
319 patients with clinically suspected pneumonia

Final Pneumonia Classification:
- Definite
- Probable
- Possible
- Excluded

Claessens, AJRCCM 2015;192:974-982

Intensive Care Med 2016;42:1159-63
Could procalcitonin help?

Procalcitonin and Pneumonia Etiology
1,735 adults admitted to 5 U.S. hospitals with pneumonia

Procalcitonin Level

No pathogen isolated

Bacteria

Virus

<0.1 0.1-0.24 0.25-0.49 ≥0.5

Self, Clin Infect Dis 2017;65:183-90
Procalcitonin for Pneumonia

1656 patients with possible pneumonia randomized to procalcitonin vs routine care

Antibiotic Starts in the ED

Percent of Patients

Usual Care Procalcitonin

Duration of Antibiotics

Days of Antibiotics

Usual Care Procalcitonin

NS


Should we culture for bacteria and test for viruses?
**Impact of Multiplex Respiratory PCR on Outcomes: RCT 1**

496 patients with respiratory symptoms presenting to a Finnish ED randomized to multiplex PCR with immediate results vs results a week later

4. No difference in overall antibiotic days but more patients randomized to PCR received <48h antibiotics (17% vs 9%) and hospital length-of-stay was one day shorter
Impact of Viral Testing on Antibiotic Utilization
166,273 patients admitted to 179 U.S. hospitals with pneumonia

Klompas, ICHE 2021;42:817-825

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

Inpatients: we suggest performing NAAT testing for respiratory viruses other than influenza in patients with severe CAP or immunocompromised state.
### ATS/IDSA Guidelines

Obtain sputum gram stain & culture in inpatients if:

- Any of the following:
  - The patient has severe pneumonia
  - You believe empiric coverage for MRSA or Pseudomonas is necessary
  - The patient has a prior history of MRSA or Pseudomonas infection
  - The patient was been hospitalized and received IV antibiotics within the preceding 90 days

- Test for influenza if influenza is circulating in the community. Test for other respiratory viruses if severe pneumonia or immunocompromised.

### My Opinion

Obtain sputum gram stain & culture + viral studies in all inpatients

My reasons:

- Risk factors for resistant organisms are ill defined
- Positive cultures can help you tailor treatment
- Negative cultures can facilitate stopping antibiotics early
- Culture data is critical to generate hospital antibiograms to inform future empiric treatment choices
- Many viruses cause pneumonia & they circulate year-round (Covid!)
- Viral diagnosis has infection control implications

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**Which antibiotics should we use?**
**Treatment Strategy for Inpatients with CAP**

<table>
<thead>
<tr>
<th></th>
<th>Standard Regimen</th>
<th>MRSA coverage?</th>
<th>Pseudomonas coverage?</th>
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<tbody>
<tr>
<td><strong>Mild disease</strong></td>
<td>B-lactam + macrolide or Fluoroquinolone</td>
<td>If prior history of respiratory MRSA then cover for MRSA</td>
<td>If prior history of respiratory Pseudomonas then cover for Pseudomonas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If risk factors alone, get cultures &amp; nasal PCR. Only cover MRSA if cultures or nasal PCR positive</td>
<td>If risk factors alone, get cultures. Only cover for Pseudomonas if cultures positive</td>
</tr>
<tr>
<td><strong>Severe disease</strong></td>
<td>B-lactam + (macrolide or fluoroquinolone)</td>
<td>If prior history of respiratory MRSA or risk factors for MRSA then get cultures and cover MRSA upfront</td>
<td>If prior history of respiratory Pseudomonas or risk factors for Pseudomonas get cultures and cover for Pseudomonas upfront</td>
</tr>
</tbody>
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**Nasal MRSA Culture/PCR**

- Can a nasal swab screen MRSA predict the presence or absence of MRSA pneumonia?
- Meta-analysis of 22 studies, 5163 patients

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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>85%</td>
</tr>
<tr>
<td><strong>Positive predictive value</strong></td>
<td>57%</td>
</tr>
<tr>
<td><strong>Negative predictive value</strong></td>
<td>98%</td>
</tr>
</tbody>
</table>
Overtreatment is Very Common

Frequency of treatment for resistant organisms vs frequency of presence of organisms amongst 17,430 patients with culture-positive sepsis on admission, 136 U.S. hospitals, 2009-2015

1 in 6 treated for MRSA had MRSA
1 in 6 treated for CTX Resistance had CTX Resistance
1 in 16 treated for VRE had VRE
1 in 70 treated for ESBL had an ESBL


...and Potentially as Harmful as Undertreating

17,430 patients with culture-positive sepsis on admission, 136 U.S. hospitals, 2009-2015

Hospital Death
Acute Kidney Injury
C. difficile

Antibiotics Too Narrow

Antibiotics Too Broad

Odds Ratio

Do we need to cover for atypicals?

β-lactam vs β-lactam+macrolide vs β-lactam+quinolone
Cluster randomized trial of 2,283 non-ICU patients with CAP in the Netherlands

90-day Mortality

- Beta lactam: NS
- Beta lactam + macrolide: NS
- Beta lactam + quinolone: NS

**β-lactam vs β-lactam+macrolide vs β-lactam+quinolone**
Cluster randomized trial of 2,283 non-ICU patients with CAP in the Netherlands

- Median Hospital Length of Stay

- Beta lactam
- Beta lactam + macrolide
- Beta lactam + quinolone

**β-lactam alone vs β-lactam+macrolide**
Randomized controlled trial of 580 patients with CAP in Switzerland

- 30-day readmissions
- ICU admissions
- 30-day mortality
- 90-day mortality


JAMA Internal Med 2014;174:1894-1901
β-lactam alone vs β-lactam+macrolide
Randomized controlled trial of 580 patients with CAP in Switzerland

Mild Illness

Moderate-Severe Illness

Do patients who aspirate need antibiotics?
Aspiration Pneumonitis: Do Antibiotics Help?

- Retrospective analysis of antibiotics (N=76) versus supportive care alone (N=124) for patients with aspiration pneumonitis.

- Groups similar in demographics, comorbidities, and risk factors for aspiration.

- Antibiotic treatment associated with:
  - No difference in hospital mortality (odds ratio 0.9, 95% CI 0.4-1.7).
  - No difference in ICU transfers (5% vs 6%).
  - More antibiotic escalations (8% vs 1%).

No!

How long should we treat for?
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Jean Chastre, MD
Michel Wolff, MD
Jean-Yves Fagon, MD
Sylvie Chevret, MD
Franc Thibault, MD

Context The optimal duration of antimicrobial treatment for ventilator-associated pneumonia (VAP) is unknown. Shortening the length of treatment may help to contain the emergence of multiresistant bacteria in the intensive care unit (ICU).

Objective To determine whether 8 days is as effective as 15 days of antibiotic treatment of patients with microbiologically proven VAP.

Ventilator Associated Pneumonia

401 patients with ventilator-associated pneumonia randomized to 8 vs 15 days of antibiotics

Mortality % or No. of Days

All Cause Mortality
Ventilator-Free Days
Organ Failure Free Days
ICU Length-of-Stay

8 Days
15 Days

NS
NS
NS
NS
Is less than 8 days feasible?

5 vs 10 Days for Community Acquired Pneumonia
Randomized controlled trial, 312 patients, 4 hospitals in Spain

Clinical Success Rate

All Patients
- 5-Day Rx
- 10-Day Rx

PORT Score IV or V
- 5-Day Rx
- 10-Day Rx

JAMA Internal Medicine 2016;176:1257-1265
Is less than 5 days feasible?

3 vs 8 Days of Amoxicillin for Patients Hospitalized with Pneumonia

- Clinical Cure
- Bacteriological success
- Radiologic Success

BMJ 2006;332:1355-61
3 vs 8 Days for Community Acquired Pneumonia
Randomized double-blind multicenter trial, 310 patients, 20 hospitals in France

Clinical Cure on Day 15

<table>
<thead>
<tr>
<th></th>
<th>3-Day Rx</th>
<th>8-Day Rx</th>
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</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Per Protocol</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS NS

Dinh et al. Lancet 2021;397:1195-1203

Do we need any antibiotics at all?
3 vs 0 Days for Community Acquired Pneumonia in Children*

Randomized double-blind multicenter trial, 4002 kids with nonsevere pneumonia, Pakistan

*age range 2-59 months

<table>
<thead>
<tr>
<th>Treatment Failure d.3</th>
<th>Relapse</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Days Amoxicillin</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Event Rates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0%</td>
<td>7.5%</td>
<td>5.0%</td>
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<tr>
<td>7.5%</td>
<td>5.0%</td>
<td>2.5%</td>
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<tr>
<td>0.0%</td>
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Antibiotics associated with less clinical failure!

OR 0.52
95% CI, 0.37 to 0.74

NS NS

Jehan, NEJM 2020;383:24-34

Could procalcitonin help?
Procalcitonin Surveillance: SAPS
1575 critically ill patients, open label RCT, 15 ICUs, Netherlands

![Bar chart showing comparison between Procalcitonin Arm and Control Arm for median duration of antibiotics, ICU length-of-stay, and mortality (28-day)].

**Median Duration of Antibiotics**
- Procalcitonin Arm: 5.5 days (IQR: 3-8)
- Control Arm: 7.0 days (IQR: 4-10)

**ICU Length-of-Stay**
- Procalcitonin Arm: 15 days (IQR: 10-20)
- Control Arm: 20 days (IQR: 15-25)

**Mortality (28-day)**
- Procalcitonin Arm: 10%
- Control Arm: 15%

**CAP Subgroup (N=440)**
- Procalcitonin Arm: 5.5 days (IQR: 3-8)
- Control Arm: 7.0 days (IQR: 4-10)

i.e. 25% of PCT patients treated for ≤3 days!

ATS/IDSA Guidelines
Treat all patients for a minimum of 5 days

My Opinion
If patient is immunocompetent, hemodynamically stable, and clearly improving then <5 days is fine.

My reasons:
- Diagnosis of pneumonia is often questionable. Even when the diagnosis is correct, a third or more are caused by viruses
- 2 RCTs showing 3 days as good as 8 days for both mild and severe CAP
How many days of antibiotics does the patient need after discharge?

Typical Treatment Durations at Discharge

6,481 patients treated for pneumonia in 43 Michigan hospitals

68% Overtreated. Discharge antibiotics accounted for 93% of unnecessary antibiotic days
Each additional day of treatment associated with 5% increase in risk of adverse events
Diagnosing pneumonia is challenging. *We’re often wrong.* CT may help.

Many (?most) pneumonias are caused by *viruses.* Test for them.

Tailor the *urgency of treatment* to *severity of illness* and *certainty of infection.* If you’re on the fence and the patient is stable, *get more data* before starting antibiotics.

Know your antibiogram. *Vancomycin not necessary* for most patients. If you start it, stop if MRSA not found. *Atypical coverage most important* for patients with severe disease or compromised immune systems.

*Short course regimens (3-5 days) usually adequate.* Serial procalcitonin measures may enable shorter courses. *Don’t reset the clock at discharge!*