LUNG INFECTIONS IN THE HOSPITALIZED PATIENT

Jennifer Babik, MD, PhD
Associate Clinical Professor
Division of Infectious Diseases
University of California, San Francisco
I have no disclosures.
Community acquired pneumonia (new IDSA guidelines!)
Hospital acquired pneumonia (updates)
Aspiration pneumonia (antibiotics)
Influenza (diagnosis and treatment)
LEARNING OBJECTIVES

By the end of this talk, you will be able to:

1. List the major updates to the new IDSA CAP guidelines

2. Recognize the appropriate antibiotic regimens and duration of therapy for hospital-acquired pneumonia

3. Construct an antibiotic plan to treat aspiration pneumonia

4. Describe the key principles in diagnosing and managing influenza in hospitalized patients
CASE #1

75 year old man with diabetes, CAD, COPD, and ESRD on hemodialysis is admitted from an assisted living facility in June for fever and cough. His last hospitalization was for a hip fracture 6 months ago.

Temp 38.4°C, RR 20, SaO2 92% 2L. WBC 18, other labs normal. CXR shows RLL consolidation.
WHAT ANTIBIOTICS WOULD YOU START?

1. Ceftriaxone + levofloxacin
2. Ceftriaxone + azithromycin
3. Vancomycin + ceftriaxone
4. Vancomycin + pip/tazo
What was the Key Factor in Choosing his Antibiotics?

1. Lives in an assisted living facility
2. On dialysis
3. Hip fracture 6 months ago
4. Lack of risk factors for MRSA or Pseudomonas
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

Am J Respir Crit Care Med Vol 200, Iss 7, pp e45–e67, Oct 1, 2019
4 major changes from 2007 Guidelines:

1. Indication for sputum culture and blood cultures
2. Use of procalcitonin
3. Use of corticosteroids
4. HCAP classification

Metlay et al, AJRCCM 2019, 200:e45.
### First, Some Definitions

**CAP**

PNA acquired outside of the hospital

- NO immunocompromise
- NO recent foreign travel

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**Severe CAP**

1 major or ≥3 minor criteria:

**Major:**
- Septic shock requiring pressors
- Resp failure requiring intubation

**Minor**
- Vitals: RR ≥ 30, T<36°C, low BP requiring aggressive fluids, P/F ratio ≤ 250
- Multilobar infiltrates
- Confusion
- Labs: BUN ≥ 20, WBC <4,000, Plts <100,000

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Metlay et al, AJRCCM 2019, 200:e45.
**Recommendation**

(1) Severe CAP

(2) New: Empiric Rx/risk factors for MRSA or Pseudomonas
   - Prior infection
   - Hospitalization and IV Abx <90d

*(strong rec, very low quality of evidence)*

**Rationale**

Recognize cultures are:
- Low yield
- Don’t change outcomes
- Risk of false (+)

So why recommend?
- Improve Abx use (↓ or ↑)
- Delay in appropriate Abx in severe CAP can be bad
- Understand local epi

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*Metlay et al, AJRCCM 2019, 200:e45.*
**What’s New? (2): Use of Procalcitonin in CAP**

Should PCT be used to decide if it is safe to withhold empiric antibiotics in a patient with CAP (i.e., can it distinguish viral vs bacterial CAP)?

**Recommendation**

NO, if a patient has confirmed CAP you should start antibiotics irrespective of the PCT result  
*(strong rec, moderate quality of evidence)*

**Rationale**

- Many of the PCT studies looked at CAP vs URI (not viral vs bacterial CAP)
- No PCT cut-off can sufficiently distinguish viral vs bacterial (cut-off of ≥0.1, PCT only ~80% sensitive for bacteria)

Should steroids be used in any subset of patients with CAP?

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO, not for non-severe or severe CAP</strong>&lt;br&gt;(strong rec, high quality evidence for non-severe CAP; conditional rec, mod quality evidence for severe CAP)</td>
<td>• Only limited data to support use in severe CAP&lt;br&gt;• Conflicting results of RCTs and meta-analyses; no consistent definition of severe CAP&lt;br&gt;• Risk of hyperglycemia, possibly 2° infections&lt;br&gt;• Mortality in influenza&lt;br&gt;• Ok if needed for shock</td>
</tr>
</tbody>
</table>

*Metlay et al, AJRCCM 2019, 200:e45.*
**What’s New? (4): How to Decide to Expand Coverage?**

Should HCAP guide decisions to expand antibiotic coverage?

**Recommendation**

No More HCAP!

(Strong rec, moderate quality evidence)

**Rationale**

• HCAP ≠ ↑ MDR risk
• HCAP led to ↑ Abx without better outcomes

**Recommendation**

Instead, use risk factors for MRSA, Pseudomonas

Empiric Rx if:

• **Prior respiratory infection (1yr)**
• Hospitalized and IV Abx in last 90d (empiric Rx in severe CAP only)
• Use local data

(Strong rec, moderate quality evidence)

*Metlay et al, AJRCCM 2019, 200:e45.*
In the initial treatment algorithm, non-severe CAP cases are treated with either Beta-lactam/macrolide or Respiratory FQ. If prior respiratory isolation of MRSA or Pseudomonas is noted, cultures should be obtained, MRSA nasal swab taken, and empiric therapy started. If hospitalization and IV antibiotics were administered in the last 90 days, cultures should be obtained and MRSA nasal swab taken, with empiric therapy held on.

Severe CAP cases are treated with Beta-lactam/macrolide* or Beta-lactam/FQ. If prior respiratory isolation of MRSA or Pseudomonas is noted, cultures should be obtained, MRSA nasal swab taken, and empiric therapy started. If hospitalization and IV antibiotics were administered in the last 90 days, cultures should be obtained and MRSA nasal swab taken, with empiric therapy started.

*Beta-lactam/macrolide may be adjusted based on susceptibility testing.

Metlay et al, AJRCCM 2019, 200:e45.
**ANTIBIOTIC OPTIONS**

- **Beta-lactams**
  - Amp/sulbactam
  - Cefotaxime
  - Ceftriaxone (Ceftaroline)

- **Macrolides**
  - Azithro
  - Clarithro

- **Respiratory FQ**
  - Levofloxacin
  - Moxifloxacin

- **MRSA**
  - Linezolid
  - Vancomycin

- **Pseudomonas**
  - Pip/tazo
  - Cefepime
  - Ceftazidime
  - Meropenem
  - Imipenem
  - Aztreonam

*Metlay et al, AJRCCM 2019, 200:e45.*
NEW CAP GUIDELINES: TAKE HOME POINTS

1. Get sputum culture and blood cultures for severe CAP or if risk for MRSA/Pseudomonas
2. Give empiric antibiotics in confirmed CAP irrespective of the PCT level
3. Do not use steroids for treatment of CAP (ok for other indications such as shock)
4. Use risk factors for MRSA and Pseudomonas (not HCAP) to guide when to expand empiric antibiotic coverage

Metlay et al, AJRCCM 2019, 200:e45.
65 y/o man with cirrhosis is admitted for SBP and is slowly improving. Over the last few days he begins to have fevers to 38.4 with new production of thick secretions. He has had no recent antibiotics. He is sitting well on RA.

- Blood cultures: negative
- CXR: new LLL infiltrate
- MRSA nasal swab from admission: negative
What empiric antibiotics would you start?

1. Pip/tazo
2. Pip/tazo plus vancomycin
3. Pip/tazo plus ciprofloxacin
4. Amp/sulbactam
**Pneumonia in the Hospital**

- **Hospital-Acquired PNA (HAP)** = PNA acquired after 48h in the hospital and not incubating at admission

- **Ventilator-Associated PNA (VAP)** = PNA acquired after 48h of intubation (subset of HAP)

- Microbiology overall is similar:
  - Gram (+): *S. aureus*, particularly MRSA
  - Gram (-): *Pseudomonas, E. coli, Klebsiella*
  - *Pseudomonas, Stenotrophomonas, Acinetobacter* more common in VAP

1. HCAP no longer included (not at high risk for MDR)

2. Recommendation for semi-quantitative endotrachaeal aspirate over invasive methods for VAP (BAL, mini-BAL)

3. Slightly less emphasis on using 2 antibiotics against *Pseudomonas* for empiric coverage

4. Duration of therapy = 7 days for all pathogens

*Kalil et al, IDSA/ATS Guidelines, CID 2016*
VAP: MICROBIOLOGIC DIAGNOSTICS

- Get blood cultures (~15% are positive)
- 2016 guidelines recommend semi-quantitative endotracheal aspirate over invasive sampling (mini-BAL, BAL) (weak recommendation, low quality evidence)

Why?
- No difference in outcomes (mortality, ICU days, ventilation)
- Requires less resources
- Both ~75% sensitive but mini-BAL/BAL more specific (80% vs 50%)
HAP/VAP: EMPIRIC ABX

- Cover for *S. aureus*, *Pseudomonas*, GNRs

- **Do you need MRSA coverage?**
  - Yes if MDR risk, >20% local *S. aureus* isolates are MRSA, high risk of mortality

- **Do you need 2 drugs for *Pseudomonas***?
  - Yes if MDR risk, >10% local GNRs resistant to monotherapy Abx, high risk mortality
  - But use clinical judgment

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**Risk of MDR VAP**
- Prior IV Abx in 90 d
- Septic shock
- ARDS
- ≥5 d in hospital
- Acute HD/CRRT

**Risk of MDR HAP**
- Prior IV Abx in 90 d

Kalil et al, IDSA/ATS Guidelines, CID 2016
HAP/VAP: ABx Menu

MRSA
Vancomycin
Linezolid

Anti-pseudomonal β-lactam
Piperacillin/tazobactam
Cefepime/ceftazidime
Meropenem/imipenem
Aztreonam
HAP only: levo/ciprofloxacin

2nd Anti-pseudomonal
Levo/ciprofloxacin
Aminoglycosides

*Use local resistance patterns to help guide therapy

Kalil et al, IDSA/ATS Guidelines, CID 2016
RTC of 400 patients with VAP randomized to 8 vs. 15 days of ABx

- 8-day group had:
  - No difference in mortality, recurrent infections, ICU LOS
  - More ABx-free days and less MDR organisms if recurrent
  - But...higher pulmonary reinfection rate (41 vs 25%) if had a glucose nonfermenter (*Pseudomonas, Acinetobacter, or Stenotrophomonas*)

- This led to the recommendation for 15 days for glucose nonfermenters and 8 days for everyone else

*Chastre et al, JAMA 2003, 290:2588.*
NEW IDSA GUIDELINES: DURATION OF ABx IN VAP

- Systematic reviews of 6 RCTs comparing short (7-8 days) vs long (10-15 days) course therapy:
  - Confirmed benefit of short course Rx (more Abx free days, less recurrences with MDRO) and no difference in cure, mortality
  - Glucose-nonfermenter subgroup: no difference in recurrence, mortality

- Bottom line:
  - 7d treatment course, even for glucose non-fermenters
  - Extrapolate data to HAP
  - Note MRSA IDSA guidelines recommend 7-21d for MRSA PNA

HAP/VAP: When to Stop Empiric Vanco?

- Clinical factors which make MRSA less likely:
  - Low clinical suspicion based on disease severity
  - Negative respiratory cultures (before antibiotics)
  - Note: negative blood cultures alone are not sufficient as these are positive in only 5-10% of MRSA PNA

The MRSA nasal swab:
- A negative MRSA nasal swab with a low prevalence of MRSA PNA has a NPV of 95% for VAP, 98% for CAP
- Can also avoid starting vanco in the first place in stable patients if you have a negative nasal swab within the last 7 days

Think about risk factors for MDR pathogens and local resistance patterns to guide empiric therapy

Duration of therapy = 7 days in most cases

MRSA nasal swab can be helpful to avoid starting or for stopping vancomycin
An 89 year-old man with dementia is admitted from home with 2 days of SOB, productive cough. Family reports he has been coughing a lot while eating. He has not been hospitalized or received antibiotics recently.

Afebrile, SaO2 94% on RA, WBC 10.
Poor dentition, bibasilar crackles.
CXR: streaky bibasilar infiltrates
What Antibiotics Would You Start?

1. No antibiotics
2. Ampicillin/sulbactam
3. Piperacillin/tazobactam
4. Levofloxacin
ASPIRATION PNEUMONIA: A MAJOR ISSUE IN HOSPITAL MEDICINE

2\textsuperscript{nd} most common dx in hospitalized Medicare patients

5-25\% of CAP cases

LOS 5 days

Risk of mortality 4x higher than other PNA

$30,000 per hospitalization

“Aspiration PNA” likely originally referred to **anaerobic pleuropneumonia** (cavitary PNA, empyema)

Subacute cough, purulent foul-smelling sputum, recent LOC, gingivitis

Micro studies in the 1970s via invasive procedures: >90% involved anaerobes

This syndrome is now rare

Anaerobes are now isolated in aspiration PNA in <20%

*DiBardino and Wunderink, J Crit Care 2015, 30:40.*
### Aspiration Pneumonia vs Pneumonitis

<table>
<thead>
<tr>
<th>Aspiration Pneumonia</th>
<th>Aspiration Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequent aspiration of oral/upper GI contents (colonized w/bacteria), rarely witnessed</strong></td>
<td><strong>Aspiration of large volume, low pH gastric contents (sterile), usually witnessed</strong></td>
</tr>
<tr>
<td><strong>Aspiration risk (age, dysphagia, tube feeds,↓consciousness), poor dental health</strong></td>
<td><strong>Anesthesia, reduced LOC, usually younger patients</strong></td>
</tr>
<tr>
<td><strong>Acute onset, normal signs/symptoms of PNA, (classic findings of anaerobic PNA are rare)</strong></td>
<td><strong>Sudden onset (within hours) of SOB, hypoxia, diffuse wheeze/crackles, +/- ARDS</strong></td>
</tr>
<tr>
<td><strong>CXR: infiltrates in gravity-dependent areas, more commonly on right</strong></td>
<td><strong>+/- Abnormal CXR</strong></td>
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**Aspiration Pneumonia: Part of Both CAP and HAP**

**CAP**
- 5-25%
- Community-acquired Aspiration Pneumonia (CAAP)
  - *S. pneumoniae*
  - *H. influenzae*
  - Enteric GNRs
  - *S. aureus* (if severe)
  - Anaerobes (<20%)

**HAP**
- ? (likely high)
- Hospital-acquired Aspiration Pneumonia (HAAP)
  - Enteric GNRs
  - *Pseudomonas*
  - *S. aureus*
  - Anaerobes (<20%)

TREATMENT: IS ANAEROBIC COVERAGE NEEDED?

- Expert opinion: varies
- New IDSA CAP guidelines: only if suspect lung abscess, empyema
- IDSA HAP guidelines: not discussed
- Most studies compare anaerobic Abx: no diff (eg moxi vs amp/sulb)
- Studies suggesting broad anaerobic coverage not needed:
  - Small prospective study of azithro (n=36) vs amp/sulb (n=81): no difference
  - Recent RCT of cefepime (n=101) vs meropenem (n=86): no difference
  - Both azithro and cefepime cover oral but not gut anaerobes

Bottom line: Choose antibiotics with oral anaerobic coverage → escalate to cover gut anaerobes if ↑ suspicion for anaerobic PNA or severe illness

### Empiric Rx for Aspiration PNA in Hospitalized Patients

#### Community-acquired Aspiration Pneumonia
- Ceftriaxone (gets oral anaerobes)
- Amp/sulbactam
- Moxifloxacin
- Ertapenem
- Add vanco if severe
- If risk for MDR: see HAAP

#### Hospital-acquired Aspiration Pneumonia
- GNR coverage as per HAP guidelines:
  - Pip/tazo
  - Cefepime
  - Meropenem
- Vanco (if +MRSA swab)

#### Aspiration Pneumonitis
- Supportive care
- No benefit of prophylactic antibiotics to prevent development of PNA

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**Duration 5-7 days based on other PNA studies**

Aspiration Pneumonia: Take-Home Points

- Aspiration PNA is common, especially in the elderly
- Anaerobes are not a major pathogen in most cases
- For CAAP: can use regular CAP antibiotics with oral anaerobic coverage → escalate to cover gut anaerobes if high suspicion for anaerobic PNA or severe illness
- Treat HAAP as per normal HAP guidelines
CASE #4

A 75 year old woman is admitted in January with 5 days of fever, cough, SOB and now has hypoxemic respiratory failure requiring intubation. She had received the influenza vaccine.

- 37.6°C, WBC 15
- Nasopharyngeal swab for influenza PCR is negative
WOULD YOU START EMPIRIC OSELTAMIVIR?

1. No

2. Yes
Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza

Timothy M. Uyeki,1 Henry H. Bernstein,2 John S. Bradley,3,4 Janet A. Englund,5 Thomas M. File Jr,6 Alicia M. Fry,1 Stefan Gravenstein,7 Frederick G. Hayden,8 Scott A. Harper,9 Jon Mark Hirshon,10 Michael G. Ison,11 B. Lynn Johnston,12 Shandra L. Knight,13 Allison McGeer,14 Laura E. Riley,15 Cameron R. Wolfe,16 Paul E. Alexander,17,18 and Andrew T. Pavia19
MAKING A CLINICAL DIAGNOSIS IS HARD!

- Abrupt onset of fever + cough is >70% sensitive for flu but signs/sx of flu are variable in different populations

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Elderly</th>
<th>Immunocompromised</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>75%</td>
<td>35%</td>
<td>35-70%</td>
</tr>
<tr>
<td>Cough</td>
<td>90%</td>
<td>70%</td>
<td>50-90%</td>
</tr>
</tbody>
</table>

- In ER/inpatient, sensitivity of a provider’s clinical diagnosis for flu is only 30-35%

Vaccine effectiveness usually 40-50%, varies based on predominant subtype
- Influenza B 54%
- Seasonal H1N1 67%
- Pandemic H1N1 61%
- H3N2 33% (good match), 23% (poor match)

CDC/IDSA: a history of vaccination should not be used in decision-making about diagnostics or empiric Rx

## Diagnostic Tests for Influenza

### Rapid Antigen Testing
- POCT in clinics, ERs
- ~50-70% sensitive, >90% specific
- Cannot rule out influenza during flu season

### Molecular Assays
- Most are ~95% sensitive, specific
- Some assays can determine influenza subtypes
- Test of choice (IDSA)

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All patients admitted with:
- Acute respiratory illness incl. PNA (with or without fever)
- Acute worsening of a chronic cardiopulmonary disease (COPD, asthma, CAD, CHF)
- Immunocompromised with undifferentiated fever

All inpatients who develop an acute respiratory illness while hospitalized without an alternative diagnosis

Upper tract samples:
- NP swab is optimal method
- Note that shedding after 3-4 days
- Can be negative in up to 40% of critically ill patients with positive lower tract samples for influenza

If critically ill: collect upper and lower tract samples and do not stop empiric therapy until a lower tract sample is negative (IDSA)

### Treatment: Neurominidase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dosage</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td>75mg PO bid x 5 d (renally dose)</td>
<td>None</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>10mg INH bid x 5 d</td>
<td>Respiratory disease (asthma, COPD)</td>
<td>Bronchospasm Cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cannot use if intubated</td>
<td></td>
</tr>
<tr>
<td>Peramivir</td>
<td>600mg IV x 1 (renally dose)</td>
<td>None</td>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

*All given same recommendation in IDSA Guidelines but oseltamivir is the drug of choice*
**OSELTAMIVIR IN OUTPATIENTS**

**Efficacy**
- Decrease in symptom duration by ~24h
- Decrease in PNA, hospitalizations

**Timing**
- RCT patients all have symptom duration ≤ 48h
- The earlier Rx is started → the greater the effect

**Cost**
Cost-effective assuming a benefit in preventing complications, hospitalizations

OSEL TAMIVIR IN INPATIENTS

- Treatment of inpatients at <48hrs of symptoms:
  - ↓ mortality by 50-65%
  - But almost 70% of patients hospitalized with influenza present at >48h

- Multiple studies: mortality benefit at >48hrs, even up to 5-7 days

- But earlier is better (emphasis on empiric therapy):
  - Earlier treatment → lower mortality
  - Earlier treatment → shorter LOS
    (2.8d if antivirals given <6h from admission vs 3.9d if 6-24h, 5.6d if >24h)

**PERAMIVIR (IV)**

- FDA approved 2014 for adults with uncomplicated influenza and symptoms <48hrs

- **When to use?**
  - Any concerns for GI absorption of oseltamivir
  - Note: limited data that oseltamivir is well absorbed in obese and critically ill patients including those on CRRT and ECMO

- **How to dose?**
  - FDA approved for a single dose in uncomplicated influenza
  - UCSF guidelines: 1-5 days

**Which Inpatients to Treat? (IDSA/CDC)**

- **All inpatients** with influenza irrespective of duration of symptoms

- For suspected cases, **treat as early as possible** - do not delay while awaiting lab confirmation

Not all patients with influenza have fever - especially elderly, immunocompromised

PCR testing is the diagnostic method of choice

In critically ill patients, do not stop empiric therapy until a lower respiratory tract sample is negative

Treat all inpatients with influenza – treat early, irrespective of symptom duration

Oseltamivir is the drug of choice for most patients, but remember peramivir is an IV option if needed
ROAD MAP REVISITED: TAKE-HOME POINTS

- CAP: Use risk factors for MRSA and Pseudomonas (rather than HCAP) to guide decisions around expanded Abx
- Hospital acquired pneumonia: treat for 7 days, use the MRSA nasal swab (has high NPV)
- Aspiration pneumonia: usually don’t need gut anaerobic coverage
- Influenza: treat all inpatients and treat early and empirically
Thank You!

- Questions?