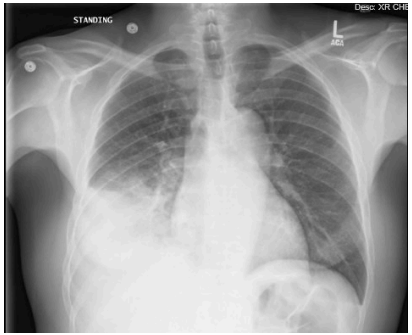

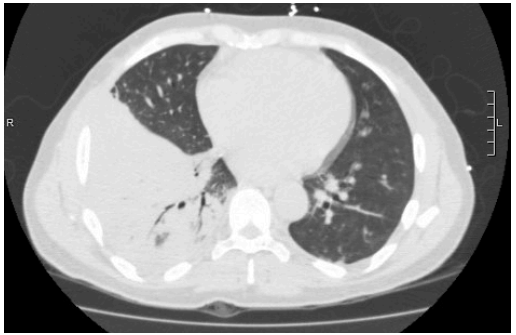

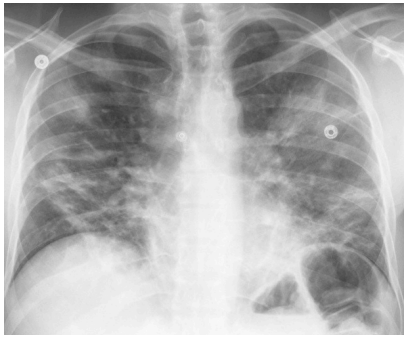

LUNG INFECTIONS IN THE HOSPITALIZED PATIENT

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23rd ANNUAL
MANAGEMENT OF THE HOSPITALIZED PATIENT
UCSF

Disclosures

- I have no disclosures.

Road Map

- Community acquired pneumonia (new IDSA guidelines!)
- Hospital acquired pneumonia (updates)
- Aspiration pneumonia (antibiotics)
- Influenza (diagnosis and treatment)

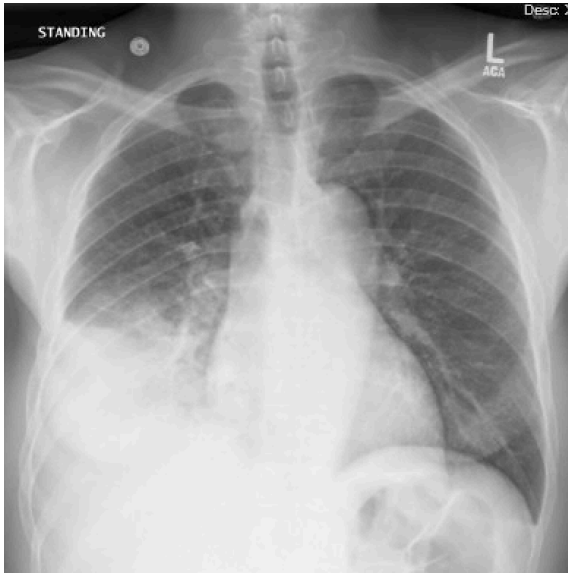
Learning Objectives

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

NEW IDSA CAP GUIDELINES – FINALLY!

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

What's New?

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

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

Metlay et al, AJRCCM 2019, 200:e45.

What's New? (1): Indications for Sputum, Blood Cultures

When should you get these?

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

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)

Metlay et al, AJRCCM 2019, 200:e45. Self et al, Clin Infect Dis 2018.

What's New? (3): Use of Steroids in CAP

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

Recommendation

NO, not for non-severe or severe CAP

(strong rec, high quality evidence for non-severe CAP; conditional rec, mod quality evidence for severe CAP)

Rationale

- Only limited data to support use in severe CAP
- Conflicting results of RCTs and meta-analyses; no consistent definition of severe CAP
- Risk of hyperglycemia, possibly ⇧ 2˚ infections
- Mortality ⇧ in influenza
- Ok if needed for shock

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)

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

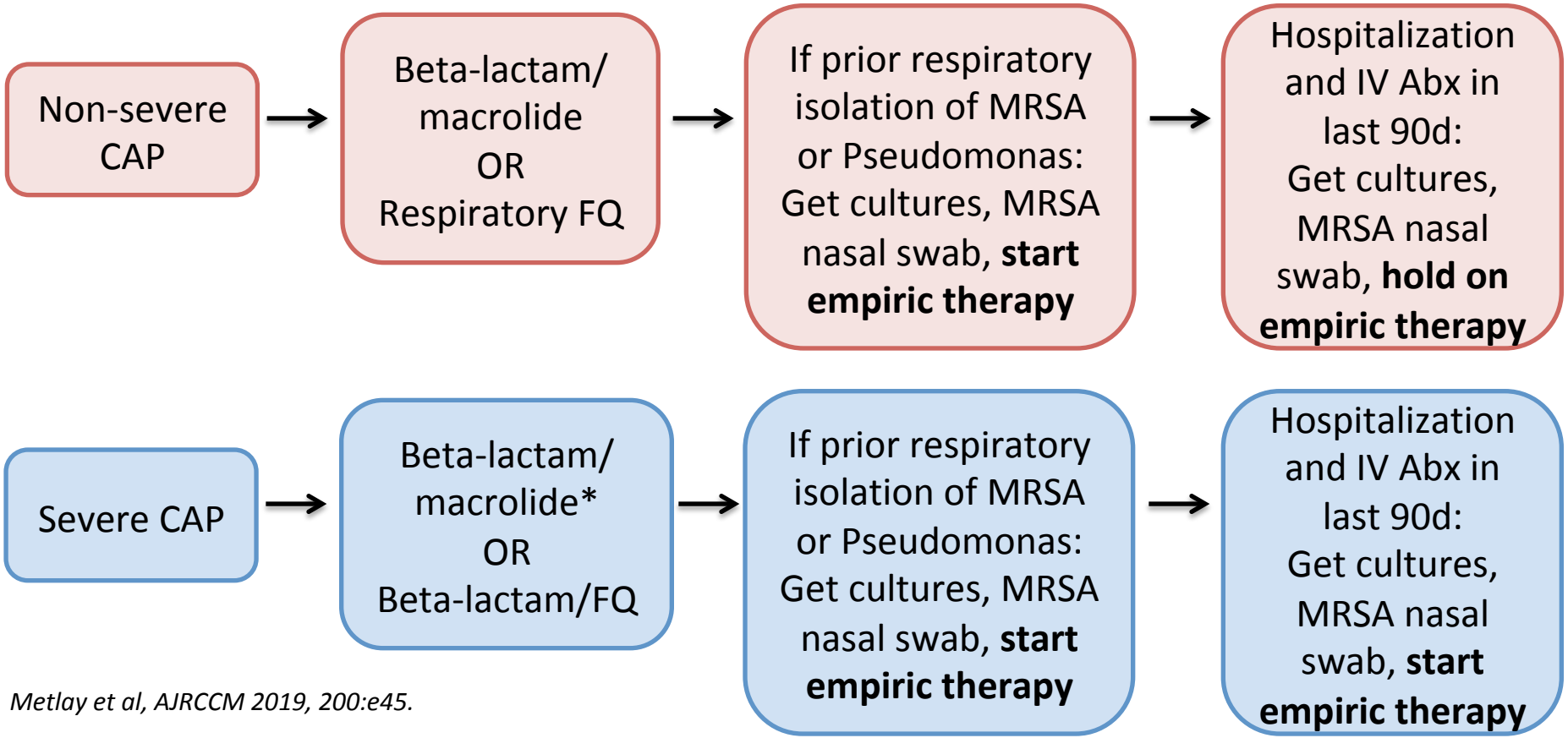
(strong rec, moderate quality evidence)

Rationale

- HCAP ≠ ⇧ MDR risk
- HCAP led to ⇧ Abx without better outcomes

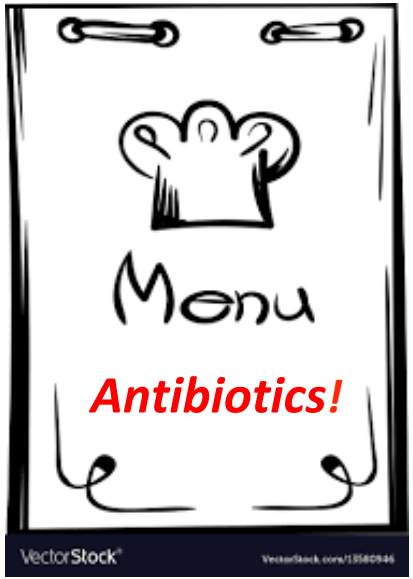
Metlay et al, AJRCCM 2019, 200:e45.

Initial Treatment Algorithm



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

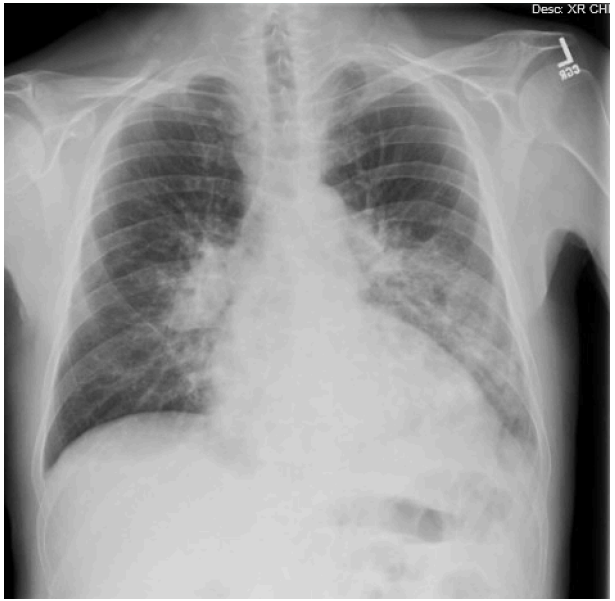
1. Get sputum culture and blood cultures for severe CAP or if risk for MRSA/Pseudomonas
2. Give empiric antibiotics in confirmed CAP irrespective of the PCT level
3. Do not use steroids for treatment of CAP (ok for other indications such as shock)
4. Use risk factors for MRSA and Pseudomonas (not HCAP)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

Metlay et al, AJRCCM 2019, 200:e45.

Case #2

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 satting 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

IDSA/ATS Guidelines, Am J Resp Crit Care Med 2005. Weber et al, ICHE 2007 Kalil et al, IDSA/ATS guidelines, CID 2016.

HAP/VAP IDSA Guidelines 2016: What Changed?

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%)

Kalil et al, IDSA/ATS Guidelines, CID 2016

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

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

Duration of Antibiotics in VAP (8 vs 15 days)

- 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

Kalil et al, IDSA/ATS Guidelines, CID 2016.

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

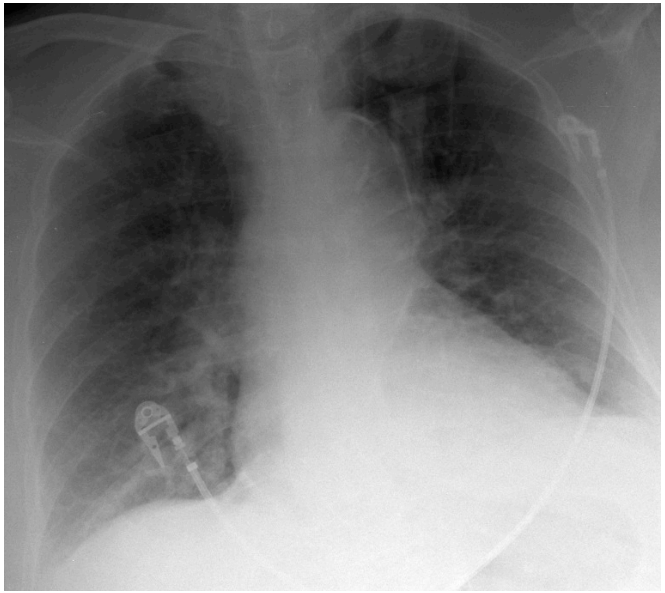
Wunderink et al, Chest 2003. Wunderink et al, Clin Infect Dis 2012; 54: 621. Kalil et al, IDSA/ATS Guidelines, CID 2016. Parente et al, Clin Infect Dis 2018, 67:1.

HAP/VAP: Take Home Points

- 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

Case #3

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.

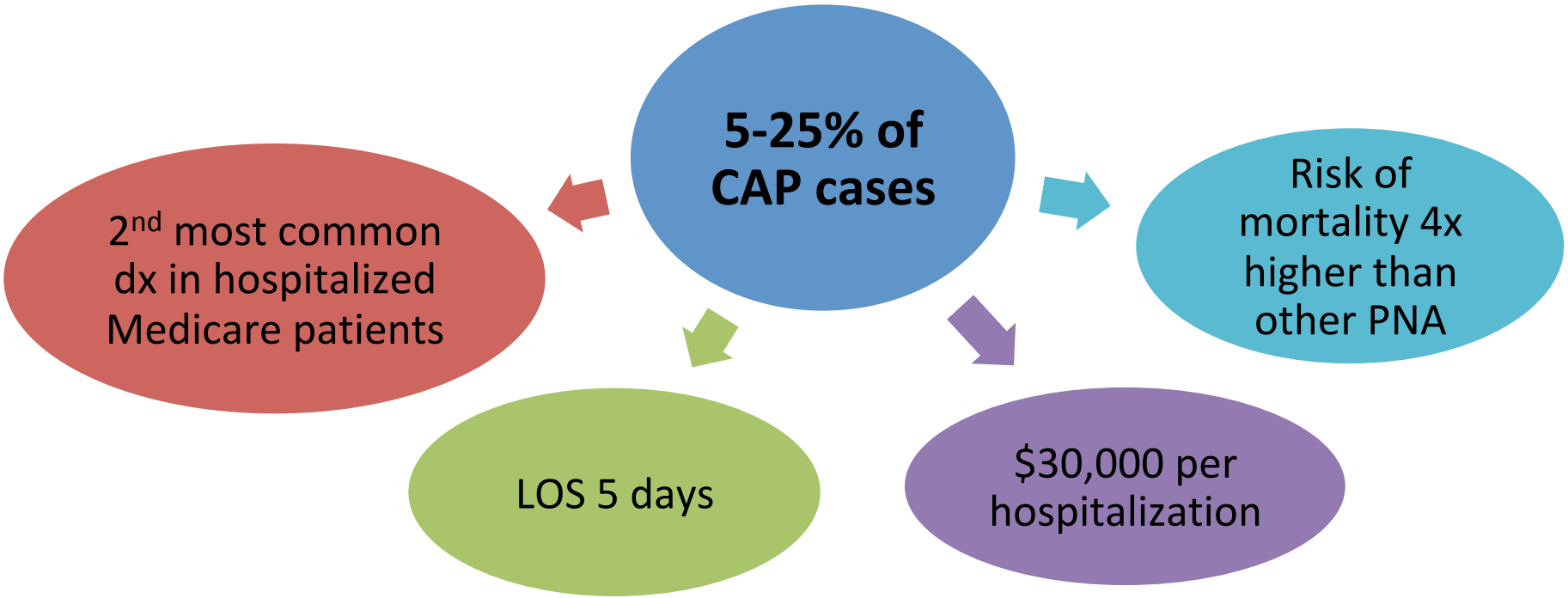
Poor dentition, bibasilar crackles.

CXR: streaky bibasilar infiltrates

What Antibiotics Would You Start?

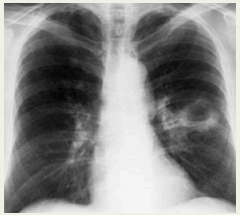
1. No antibiotics
2. Ampicillin/sulbactam
3. Piperacillin/tazobactam
4. Levofloxacin

Aspiration Pneumonia: A Major Issue in Hospital Medicine

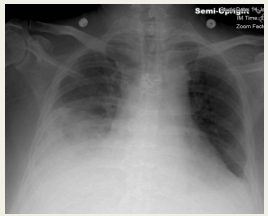


DiBardino and Wunderink, J Crit Care 2015, 30:40. Wu et al, Ann Am Thorac Soc 2017, 14:874. Rodriguez and Restrepo, Exp Rev Clin Pharm 2019.

History of Aspiration PNA



"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%**

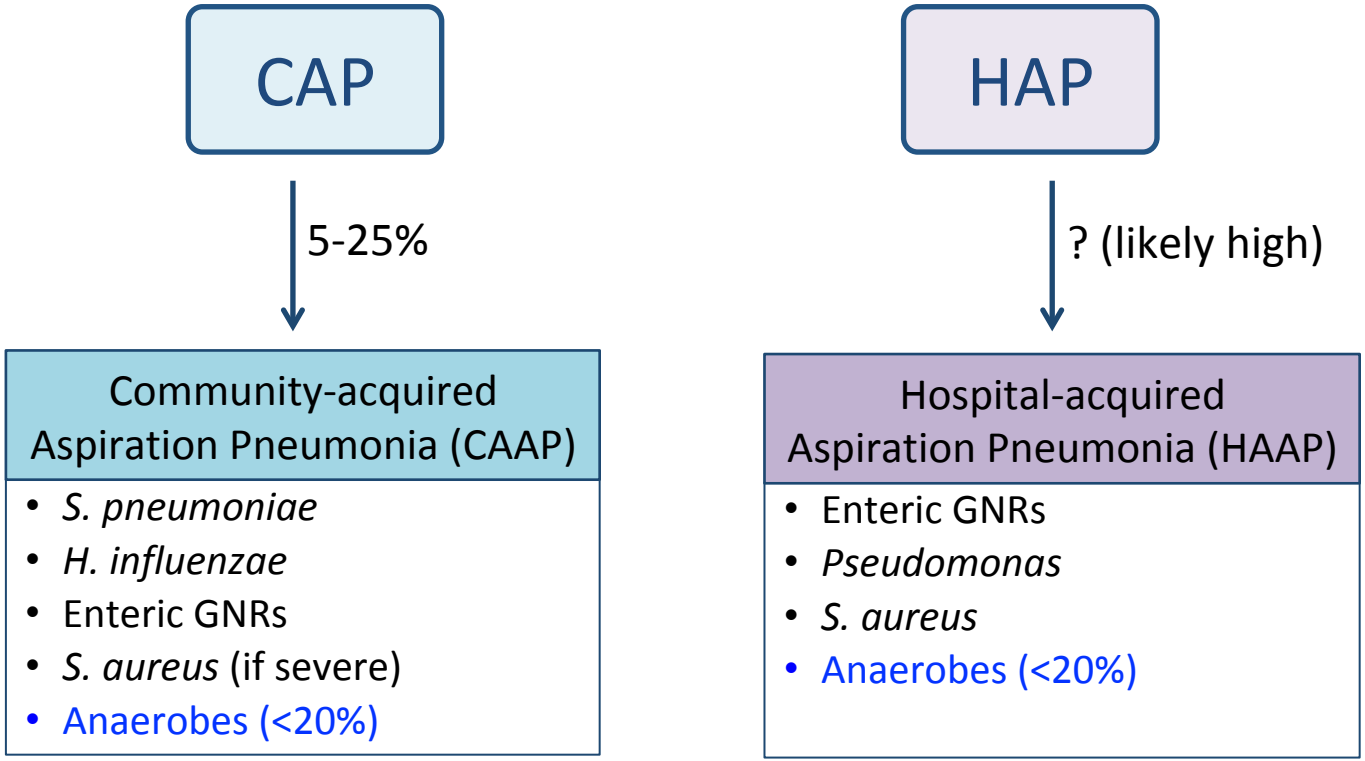
DiBardino and Wunderink, J Crit Care 2015, 30:40.

Aspiration Pneumonia vs Pneumonitis

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

Mandell and Niederman, NEJM 2019, 380:651. Rodriguez and Restrepo, Exp Rev Clin Pharm 2019.

Aspiration Pneumonia: Part of Both CAP and HAP



Mandell and Niederman, NEJM 2019, 380:651. Rodriguez and Restrepo, Exp Rev Clin Pharm 2019.

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

Metlay et al, AJRCCM 2019, 200:e45. Ott et al, Infection 2008, 36:23. Marumo et al, BMC Infect Dis 2014, 14:685, Oi et al, J Infect Chemother 2019 epub.

Empiric Rx for Aspiration PNA in Hospitalized Patients

Community-acquired Aspiration Pneumonia	Hospital-acquired Aspiration Pneumonia	Aspiration Pneumonitis

• Ceftriaxone (gets oral anaerobes)
• Amp/sulbactam
• Moxifloxacin
• Ertapenem
• Add vanco if severe
• If risk for MDR: see HAAP
	• GNR coverage as per HAP guidelines:
	  • Pip/tazo
	  • Cefepime
	  • Meropenem
	• Vanco (if +MRSA swab)
		• Supportive care
		• No benefit of prophylactic antibiotics to prevent development of PNA

Duration 5-7 days based on other PNA studies

Mandell and Niederman, NEJM 2019, 380:651. Rodriguez and Restrepo, Exp Rev Clin Pharm 2019. Dragan et al, Clin Infect Dis 2018, 67:513.

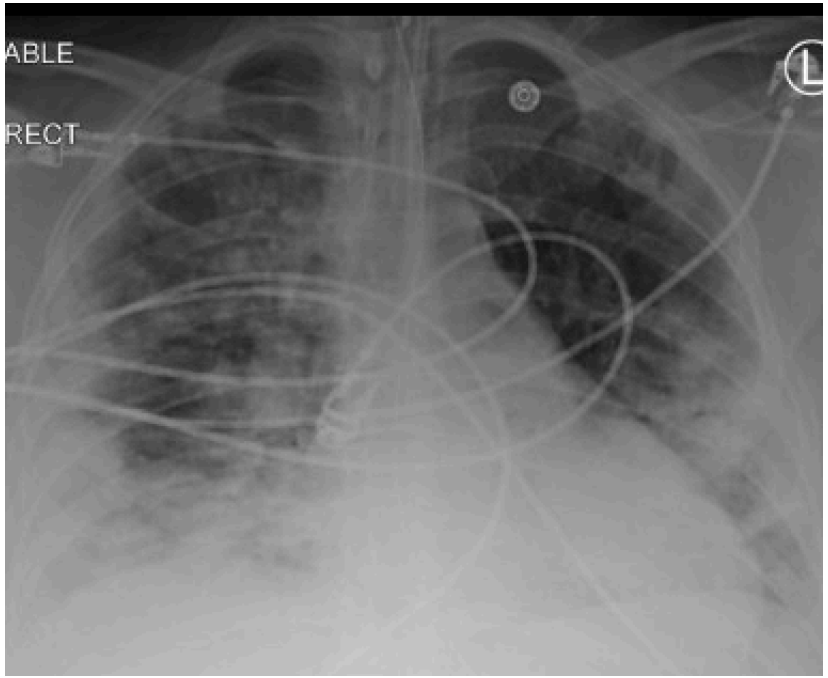
Aspiration Pneumonia: Take-Home Points

- 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

New IDSA Guidelines for Influenza

Clinical Infectious Diseases

IDSA GUIDELINE

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

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. Pavia[19]

Uyeki et al, Clin Infect Dis 2019, 68:e1.

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

	All	Elderly	Immunocompromised
Fever	75%	35%	35-70%
Cough	90%	70%	50-90%

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

Kumar et al, Clin Infect Dis 2018, 67:9 Call et al, JAMA 2005; 293:987. Apewokin et al, OFID 2014. Dugas et al, Am J Emerg Med 2015, 33:770. Miller et al, J Infect Dis 2015, 212:1604.

But She Got the Vaccine!

- 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

CDC, Seasonal Influenza Vaccine Effectiveness, 2005-2017. Belongia et al, Lancet ID 2016, 16:942. Uyeki et al, Clin Infect Dis 2018.

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)

Harper et al, Clin Infect Dis 2009, 48:1003. CDC, Influenza Symptoms and the Role of Laboratory Diagnostics, 2011. Uyeki et al, Clin Infect Dis 2018.

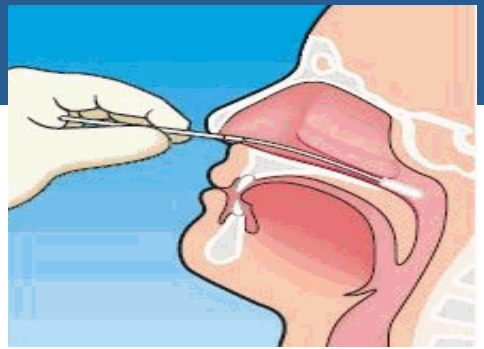
Which Inpatients Should Be Tested For Influenza? (IDSA)

- 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

Uyeki et al, Clin Infect Dis 2018.

Diagnosis: Samples



- 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)

Lopez Roa et al, Am J Crit Care Med 2012, 186:929. Reddy et al, Open Forum Infect Dis 2016. CDC, Information on Collection of Respiratory Specimens for Influenza Virus Testing, 2018. Uyeki et al, Clin Infect Dis 2018.

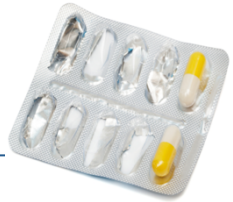
Treatment: Neurominidase Inhibitors

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

*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

Kelley and Cowling, Lancet 2015, 385:1700. Dobson et al, Lancet 2015, 385:9979. Talbird et al, Am J Health-Syst Pharm. 2009; 66:469.

Oseltamivir 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)

Lee and Ison, Clin Infect Dis 2012, 55:1205. Viasus et al, Chest 2011, 140:1025. Muthuri et al, J Infect Dis 2013, 207:553. Chaves et al, Clin Infect Dis 2015, 61:1807. Katzen et al, Clin Infect Dis 2019, 69:52.

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

Whitley et al, Antivir Ther 2014, Oct 15 Epub. Kohno et al, Antimicrob Agents Chemother 2010, 54:4568. de Jong et al, Clin Infect Dis 2014, 59:e172.

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

CDC Guidelines 2018. SFDPH guidelines 2018. Uyeki et al, Clin Infect Dis 2019.

Influenza: Take Home Points

- 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?