Community-Acquired Pneumonia: A Re-CAP

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Disclosure

Meghan Griebel does not have any actual or potential conflicts of interest to disclose.

Goal

At the end of the presentation, attendees will be able to discuss the IDSA guidelines for community-acquired pneumonia and evaluate the potential impact of recent literature articles on future guideline updates.

Objectives for Pharmacists

1. Summarize the IDSA guidelines for community-acquired pneumonia.
2. Explain to a pharmacy student 3 risks associated with use of fluoroquinolones.
3. Compare published data regarding beta-lactam monotherapy vs. combination therapy for empiric treatment.
4. Identify the role of corticosteroids in adjunctive therapy for community-acquired pneumonia.
5. Given a patient case, choose appropriate treatment options and duration for community-acquired pneumonia.

Objectives for Pharmacy Technicians

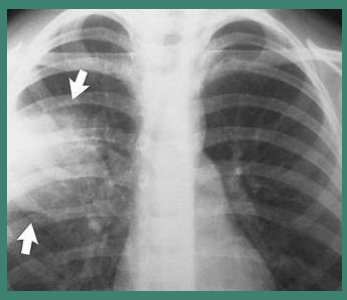
1. Restate the definition of community-acquired pneumonia.
2. Given a list of antibiotics, classify as beta-lactam, macrolide, or fluoroquinolone.
3. Identify the role of corticosteroids in adjunctive therapy of community-acquired pneumonia.
4. Recommend an appropriate duration of therapy for community-acquired pneumonia.
5. Describe two known adverse drug events associated with fluoroquinolones.

Guidelines

Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS)

Introduction

Community-Acquired Pneumonia



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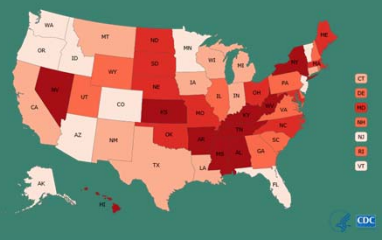
Pneumonia/Influenza Mortality by State



Leading cause of infectious deaths and 8th leading cause of death in US

15.9 deaths per 100,000 people

3.3% of hospitalized patients diagnosed with pneumonia will die

8

Pathophysiology

1. Failure of defense mechanisms
2. Pathogen colonizes lung

3. Alveoli fill with fluid

Singh. Pathophysiology of Community Acquired Pneumonia. JAPI. 2012

9

Microbiologic Etiology

Patient Status	Etiology
Outpatient	***Streptococcus pneumoniae*** *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella* *Haemophilus influenza*, respiratory viruses
Inpatient	***Streptococcus pneumoniae*** Atypicals *Haemophilus influenza* Aspiration, respiratory viruses
ICU	***Streptococcus pneumoniae*** *Staphylococcus aureus* *Legionella* *Gram-negative bacilli, Haemophilus influenza*

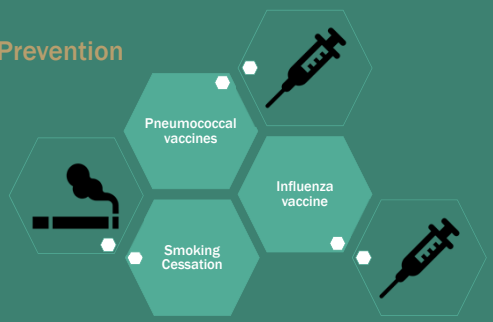
10

Risk Factors

- Age > 65
- Smoking
- Immunocompromised
- Multiple chronic conditions
- Structural lung disease

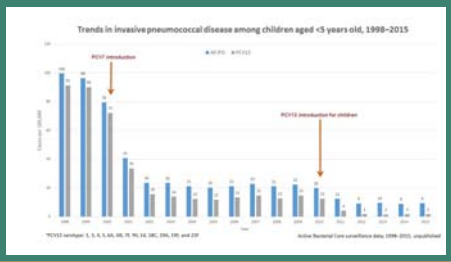
11

Prevention



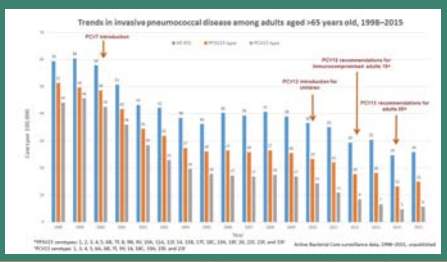
12

Pneumococcal Disease Among Children



CDC 13

Pneumococcal Disease Among Elderly



CDC 14

Impact of Pneumococcal Vaccine on CAP

Population-Based Ecological Study in Canada 2017:

- Pneumonia hospitalizations declined by 45% after public funding for PCV13
- Hospitalization-related costs declined by 46%
- Declines also seen in PCV-ineligible older children and elderly patients

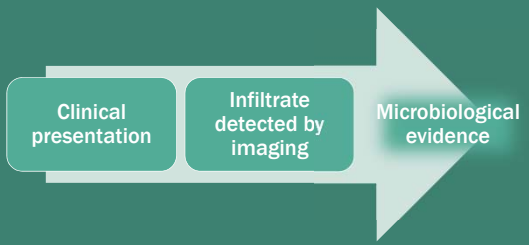
➢ Herd Immunity

Luca DL. Impact of Pneumococcal Vaccination on Pneumonia Hospitalizations and Related Costs in Ontario: A Population-Based Ecological Study. Clin Infect Dis 2017 15

Clinical Presentation

16

Diagnosis



17

Site-of-Care Decision

- CURB-65 2-3
- Pneumonia Severity Index III-IV
- Oral intake
- Social support

Hospital admission

CURB-65

- Confusion
- RR > 30
- BUN >20
- SBP < 90 or DBP < 60
- Age > 65

PSI

- Age
- Demographics
- Comorbidities
- Physical Exam
- Labs
- Imaging

18

Site of Care Decision

- One Major Criteria
  - Septic shock requiring vasopressors
  - Mechanical ventilation
- OR 3 minor criteria

ICU admission

Minor Criteria

- Tachypnea
- Hypoxemia
- Multi-lobar infiltrates
- Confusion
- Uremia
- Leukopenia
- Thrombocytopenia
- Hypothermia
- Hypotension

19

Clinical Indications for More Extensive Diagnostic Testing

Indication	Blood culture	Sputum culture	Legionella UAT	Pneumococcal UAT
ICU admission	X	X	X	X
Failure of outpatient antibiotic therapy		X	X	X
Cavitary infiltrates	X	X		
Leukopenia	X			X
Alcohol abuse	X	X	X	X
Severe liver disease	X			X
Severe COPD		X		
Asplenia	X			X
Recent travel			X	
+ Legionella UAT		X		
+ pneumococcal UAT	X	X		
Pleural effusion	X	X	X	X

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72

20

Empirical Treatment

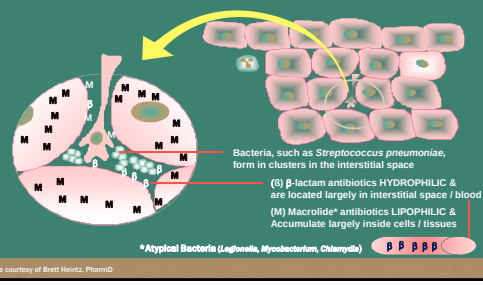
21

Classes of Antibiotics

Beta-lactams	Macrolides	Tetracycline	Fluoroquinolones	Glycopeptide
amoxicillin	azithromycin	doxycycline	levofloxacin	vancomycin
ampicillin	erythromycin		moxifloxacin	
piperacillin	clarithromycin		ciprofloxacin	
ceftriaxone				
cefotaxime				
cefepime				
ertapenem				

22

Link between Microbiologic and PK/PD: Why do we often use two antibiotics for CAP?



Slide courtesy of Brett Heintz, PharmD

23

Outpatient Treatment

Previously healthy with no risk of drug-resistant *Streptococcus pneumoniae* (DRSP)*
- Macrolide
- Doxycycline

DRSP Risk Factors

- Age < 2 or > 65
- Recent antibiotics
- Immunosuppression
- Multiple comorbidities
- Exposure to daycare
- Alcoholism

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72

24

Outpatient Treatment

If Risk Factors for DRSP:
- Beta-lactam PLUS macrolide (or doxycycline)
- Anti-pneumococcal FQs: levofloxacin or moxifloxacin

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72 25

Inpatient Treatment

- Beta-lactam* (ceftriaxone preferred) PLUS macrolide (or doxycycline)
- Levofloxacin or moxifloxacin

* Ceftriaxone preferred; consider amp/sulb if concerned for anaerobes (aspiration); reserve ertapenem if suspect/history of MDR GNRs

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72 26

ICU Treatment

- Beta-lactam PLUS azithromycin
- Beta-lactam PLUS anti-pneumococcal fluoroquinolone

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72 27

ICU Treatment

Special Considerations: *Pseudomonas**
- Antipseudomonal beta-lactam (e.g. pip/tazo or cefepime)

PLUS
- Ciprofloxacin or levofloxacin

or
- Aminoglycoside and azithromycin

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72 28

**Pseudomonas* Risk Factors*

- Structural lung disease
  - Cystic fibrosis
  - Bronchiectasis
- Known colonization
- Recent broad spectrum antibiotics

29

ICU Treatment

Special Considerations: Community-acquired (CA)-MRSA*
- Add vancomycin or linezolid

Mandell LA, eta l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:S27–72 30

*MRSA Risk Factors

- Colonization of MRSA in nares
- Evidence of MRSA on gram stain
- Critically ill

31

Special Cases

Healthcare-associated (HCA) exposure*

- Consider enteric GNR coverage
  - 3rd generation cephalosporin OR amp/sulb (amox/clav)
  - Levofloxacin or moxifloxacin if severe beta-lactam allergy

Healthcare Exposure

- Broad spectrum antibiotic infusion therapy
- Wound care or dialysis within 30 days
- Hospitalization > 2 days in last 90 days
- Skilled nursing facility

32

Special Cases

Aspiration Event

- Consider anaerobic ± enteric GNR coverage (alcoholic or HCA exposure)
  - Clindamycin if no suspicion of enteric GNRs
  - Metronidazole ± amp/sulb (amox/clav) OR ceftriaxone
  - Moxifloxacin if severe beta-lactam allergy

33

Patient Case

34

JW is 60 YOM who presented to the ED with symptoms of cough, increased purulent sputum, and fever, but denies any shortness of breath. Chest x-ray revealed a consolidation on his left lung, leading to a diagnosis of community-acquired pneumonia. He has no other health conditions or allergies, and has not used antibiotics in the last year. Which of the following would be most appropriate for treatment of his CAP as an outpatient?

1. Amoxicillin + azithromycin
2. Doxycycline
3. Levofloxacin
4. He should be admitted to the hospital and given appropriate inpatient therapy.

35

The following year, JW develops symptoms for CAP and presents to the ED again. This time, he complains of shortness of breath and his pneumonia is considered moderate based on his PSI score of III. The ED provider decides to admit him. Which of the following is appropriate empirical therapy for his CAP as an inpatient (non-ICU)? NKDA.

1. Piperacillin/tazobactam and vancomycin
2. Azithromycin
3. Ceftriaxone and azithromycin
4. Ceftriaxone and levofloxacin

36

Pathogen-Directed Therapy

37

Streptococcus pneumoniae	*Haemophilus influenzae*	*Atypicals**	*Staphylococcus aureus*
DRSP	amoxicillin (β-lactamase neg)	macrolide	MSSA
amoxicillin 1 g TID	amoxicillin/ clavulanate	doxycycline	anti-staph PCN (nafcillin)
amoxicillin/ clavulanate	ceftriaxone	fluoroquinolone	cefazolin
ceftriaxone	fluoroquinolone		MRSA
anti-pneumococcal fluoroquinolone			vancomycin or linezolid
			TMP/SMX or doxycycline

* If *Legionella* identified or suspected (ICU) use macrolide or fluoroquinolone as superior to doxycycline

Mandell LA, et a l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:527–72

38

De-escalation

Criteria for Clinical Stability:
- Temperature ≤ 37.8˚C
- Heart rate ≤ BPM
- Respiratory rate ≤ 24 breaths/min
- Systolic blood pressure ≥ 90 mmHg
- Arterial oxygen saturation ≥ 90% or pO_2 ≥ 60 mmHg
- Ability to maintain oral intake

→ Intravenous to Oral Therapy

Mandell LA, et a l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:527–72

39

Duration of Therapy

Afebrile for at least 48 hours

+

No more than 1 sign of clinical instability

→ Treatment for a *minimum* of 5 days

Mandell LA, et a l. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. Clin Infect Dis 2007; 44:527–72

40

Emerging Evidence

Diagnostics

Rapid Diagnostics

- Rapid PCR detection of usual CAP pathogens
- MRSA nasal swab and *Legionella* urinary antigen

Gadsby. Comprehensive Molecular Testing for Respiratory Pathogens in CAP. Clinical Infectious Diseases, 2016. 43

Procalcitonin

- Inflammatory marker similar to CRP
- Acute-phase reactant
- Correlation with prognosis and CAP severity

Berg. The role of procalcitonin in adult patients with CAP. Danish Med Journal, 2012 44

Procalcitonin: What is the evidence?

Procalcitonin

- Bacteremic patients had significantly higher concentrations of PCT (p=0.0002)
- PCT levels significantly higher in *pneumococcal* infections than in those with *Mycoplasma* (p=0.009), other bacteria (p=0.038), or viral infections (p=0.017)
- Median PCT concentration higher in severe patients with PSI 4-5 (p=0.03)

Johansson. Procalcitonin levels in CAP – correlation with aetiology and severity. Scandinavian Journal of Infectious Diseases, 2014. 45

Procalcitonin: What is the evidence?

Systematic reviews and meta-analyses

- Complications during admission, severity of disease, and to a lesser extent, death within a month all tended to correlate with higher PCT levels (> 0.5).[1]
- Elevated PCT level is associated with an increased risk of mortality[2]
- Cut-off of 0.5 ng/ml was not sensitive enough to identify patients at high risk of dying[2]

1. Berg. The role of procalcitonin in adult patients with CAP. Danish Med Journal, 2012.
2. Liu. Prognostic value of procalcitonin in pneumonia. Respirology, 2016.

46

Procalcitonin

Prognostic, not diagnostic

Berg. The role of procalcitonin in adult patients with CAP. Danish Med Journal, 2012 47

Empiric Selection

Beta-lactams

- Amoxicillin
- Ampicillin
- Piperacillin
- **Ceftriaxone**
  - *Strep. pneumoniae*
  - *H. influenzae*
  - *Staph aureus* (MSSA)
  - Enteric gram negative rods
- Cefepime
- Ertapenem

49

Beta-lactam monotherapy vs. combination therapy: What is the evidence?

Study type	Methods (n)	Results	Conclusions
Non-inferiority, cluster-randomized, crossover Non-ICU Legionella-neg	Beta-lactam monotherapy (656) Beta-lactam + macrolide (739) Fluoroquinolone monotherapy (888)	9.0% 11.1% 8.8%	Beta-lactam monotherapy non-inferior with regard to 90-day mortality

Postma. Antibiotic Treatment Strategies for CAP in Adults. NEJM. 2015.

50

Beta-lactam monotherapy vs. combination therapy: What is the evidence?

Study Type	Methods (n)	Results	Conclusion
Randomized, non-inferiority trial	Beta-lactam monotherapy (291) Beta-lactam + macrolide (289)	41.2% 33.6%	Patient infected with atypicals or with PSI IV had delayed clinical stability with monotherapy

Garin. Beta-lactam Monotherapy vs. Beta-lactam-Macrolide Combination Treatment in Moderately Severe CAP. JAMA. 2014

51

Macrolides

- Erythromycin
- Clarithromycin
- **Azithromycin**
  - Increasing resistance for *Strep. pneumoniae*
  - *H. influenzae*
  - Atypicals
  - Anti-inflammatory properties

52

Azithromycin: First-Choice Macrolide

Study type	Methods (n)	Results	Conclusion
Open-label, prospective	Ceftriaxone + 3-day AZM (383) Ceftriaxone + 10-day clarithromycin (220)	M: 3.6% LOS: 7.4 M: 7.2% LOS: 9.8	AZM better outcomes than clarithromycin, with benefit of shorter course of therapy.

Sanchez. Is Azithromycin the First-Choice Macrolide for Treatment of CAP? CID. 2003

53

Azithromycin and Cardiovascular Risk

Study type	Methods (n)	Results	Conclusion
Retrospective cohort	Azithromycin (31,863) Matched; no exposure (31,863)	90-d M: 17.4% (P<.001) MI: 5.1% 90-d M: 22.3% MI: 4.4% (P<.001)	Patients treated with PNA treated with AZM had lower risk of 90-d mortality and increased risk of MI.

Mortensen. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. JAMA. 2014.

54

Azithromycin and Cardiovascular Risk

Study type	Methods	Results	Conclusion
Cohort	Azithromycin	Incidence: 85.2 HR: 2.88	5-day course of AZM was associated with an increased risk of CV death.
	No antibiotics	Incidence: 31.5 HR: 0.95	
	Amoxicillin	Incidence: 29.8 HR: 1	

Ray. Azithromycin and the Risk of Cardiovascular Death. NEJM. 2012.

55

The Impact of Azithromycin's Cardiovascular Risk

56

Tetracycline

Doxycycline

Strep. pneumoniae
Atypicals (inferior coverage of *Legionella*)
H. Influenzae
Staph. aureus
Anti-inflammatory properties

57

Doxycycline vs. Macrolides

Study Type	Methods	Results: LOS	Conclusion
Retrospective	BL + doxycycline	Overall: 5 Typical: 5 Atypical: 3	Clinical outcomes similar between groups for typical pathogens. For atypicals, Doxycycline associated with shorter LOS (<0.001)
	BL + macrolide	Overall: 6 Typical: 6 Atypical: 6	

Teh et al. Doxycycline vs macrolides in combination therapy for treatment of community-acquired pneumonia. European Society of Clinical Microbiology and Infectious Diseases. 2011.

58

Fluoroquinolones

Levofloxacin	Moxifloxacin	Ciprofloxacin
Excellent *Strep. pneumoniae*	Excellent *Strep. pneumoniae*	*H. Influenzae*
H. influenzae	*H. influenzae*	Less atypical coverage
Atypicals	Atypicals	*Pseudomonas*
Pseudomonas	Enteric GNRs	Enteric GNRs
Enteric GNRs	Anaerobes	

Fluoroquinolones: The Good, the Bad, and the Ugly

Study type	Methods	Results	Discussion
Systematic review and meta-analysis	Macrolide vs. BL + macrolide	No difference in clinical failure or other efficacy outcomes	FQ or macrolide monotherapy as effective as combination therapy. No difference in mortality. Higher rates of diarrhea in combination arms.
	FQ vs. BL + FQ	No differences in all outcomes	
	FQ vs. BL + macrolide	No difference in mortality. Clinical failure less common in FQ arm.	

Raz-Pasteur. Fluoroquinolones or macrolides alone versus combined with beta-lactams for adults with community-acquired pneumonia. International Journal of Antimicrobial Agents. 2013.

60

Fluoroquinolones: The Good, the Bad, and the Ugly

Black Box Warning

- Serious adverse reactions: Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including: **tendinitis and tendon rupture, peripheral neuropathy, and CNS effects.** Discontinue the fluoroquinolone immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. **Because fluoroquinolones have been associated with serious adverse reactions, reserve their use in patients who have no alternative treatment options for the following indications: acute exacerbation of chronic bronchitis, acute sinusitis, and acute uncomplicated cystitis.**

http://www.fda.gov/Drugs/DrugSafety/ucm511530.htm

Fluoroquinolones: The Good, the Bad, and the Ugly

Musculoskeletal & Peripheral nervous system	Central nervous system/Psychiatric	Other
Tendonitis / tendon rupture	Psychosis	*Clostridium difficile* infection
Muscle pain / weakness	Anxiety	Cardiotoxicity, QTc
Joint pain / swelling	Insomnia	Antimicrobial resistance
Peripheral neuropathy	Depression	Myelosuppression
GI perforation: collagen degradation (chelation) & necrosis of chondrocytes resulting in cartilage damage – *GI tract structural instability*	Hallucinations	Pneumonitis / nephritis
	Suicidal Ideations	Blood glucose disturbances
	Confusion	Drug-drug interactions

Stahlmann R, Lode H. Safety Considerations of Fluoroquinolones in the Elderly An Update Drugs Aging 2010; 27 (3): 193-209; Tillotson GS. FDA and the safe and appropriate antibiotic use of fluoroquinolones. Lancet Infectious Diseases 2016;16(3):e11-12

Drivers of Fluoroquinolones Use

In a recent VA survey, PCPs were asked, "What's the single biggest factor driving the decision to use fluoroquinolones in the outpatient setting?" [n=81]

Beta-lactam allergy: 46%	More effective than other oral options: 22%	More convenient than other oral options: 16%	Safer than other oral options: 11%	Other combination of factors: 5%

Slide courtesy of Kerry L. LaPlante, PharmD. "Antimicrobial Stewardship in Geriatric Populations Including Long-term Care and Extended Care Facilities" [illegible]

Antibiotic Allergies

10% patients report a penicillin allergy, but often unreliable

- > 90% of "allergies" can be ruled out
- > 95% of patients with an "penicillin allergy" tolerate a penicillin\
- Often over reported, poorly documented & subjective
- Sensitivity can be lost over time, especially > 10 years

Beta-lactam allergies have been associated with worse outcomes

1. Ann Allergy Immul 2010; 105(4):269-73; 2. Allergy Clinic Immunol Pract 2013;1(3):258-63; 3. J allergy Imunol 2015;135(4):972-76. 4. Allergy 2013;68(12):1618-21; 5. Pharmacotherapy 2011;31:742-47; 6. J Adv Pharm Technol Res. 2010;1(1):11-17. 7. CID 2014;58(8):1140–8. 8. Curr. Opin allergy imm 2015. 15:308-313 . 9. Jones BM, Bland CM. Penicillin Skin Testing as an Antimicrobial Stewardship [illegible]

Consider Penicillin Skin Testing

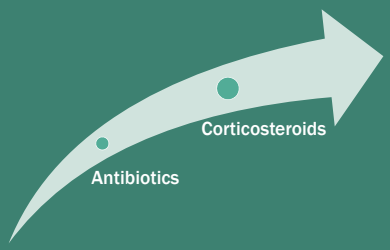
90% sensitivity, ~ 99% NPV for type 1 mediated reactions

PST may reduce broad spectrum therapy and drug costs

Local study at UIHC ruled out >99% of penicillin allergies with use of skin testing

Jones BM, Bland CM. Penicillin Skin Testing as an Antimicrobial Stewardship Initiative. Am J Health-Syst Pharm 2017;74:232-237.
McDonnel. Screening for Beta-Lactam Allergy in Joint Arthroplasty Patients to Improve Surgical Prophylaxis Practice. J Arthroplasty. 2017.

Adjunctive Therapy



Corticosteroids: What is the evidence?

Study type	Methods	Results	Conclusion
Systematic review and meta-analysis	Corticosteroids	Mortality: 5.3% RR: 0.67 CI (0.45-1.01)	Corticosteroids may reduce mortality (severe CAP), mechanical ventilation by 5%, and LOS by 1 day.
	Control	Mortality: 7.9%	

Siemieniuk. Corticosteroid Therapy for Patients Hospitalized With CAP. Annals of Internal Medicine, 2015. 67

Corticosteroids: What is the evidence?

Study type	Methods	Results	Conclusion
Systematic review and meta-analysis	Corticosteroids	Mortality: 5.1% RR: 0.72 CI (0.43-1.21)	Steroids were not associated with a reduction in mortality, but were with a decreased risk of ARDS. They may reduce LOS, duration of IV abx, & time to clinical stability.
	Control	Mortality: 6.5%	

Wan. Efficacy and Safety of Corticosteroids for CAP. CHEST. 2016. 68

Corticosteroids: What is the evidence?

Torres and Ferrer: What's new in severe CAP? Corticosteroids as adjunctive treatment to antibiotics. Intensive Care Med, 2016.

- SCAP not well-defined in systematic reviews
- Inclusion of low-severity patients
- Inclusion regardless of level of inflammation (CRP)
- Performed RCT

Torres and Ferrer. What's new in severe community-acquired pneumonia? Corticosteroids as adjunctive treatment to antibiotics. Intensive Care med. 2016. 69

Corticosteroids: What is the evidence?

Study type	Methods (n)	Results	Conclusion
Randomized, double-blind, placebo-controlled	IV methyl-prednisolone (61)	Treatment failure: 13% P = 0.02	In SCAP and high CRP, use of corticosteroids decreased treatment failure significantly.
	Placebo (59)	Treatment failure: 31%	

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients with Severe CAP and High Inflammatory Response. JAMA. 2015. 70

Steps for Administration of Corticosteroids in Severe CAP

Select patients with criteria for SCAP (PSI IV & V)

- Exclude patients with influenza or contraindications to steroids

Select patients with serum CRP > 15mg/dL

Standard of care
+ start corticosteroids ASAP

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients with Severe CAP and High Inflammatory Response. JAMA. 2015. 71

De-escalation/ Definitive Therapy

Definitive Therapy

Narrow based on microbiologic data

73

De-escalation

Narrow to beta-lactam monotherapy

74

Azithromycin: When to Discontinue

Clinically responding → No culture results → *Legionella* negative → Received 1500mg total

OR

Identified pathogen susceptible to beta-lactam (e.g. pneumococcus)

75

Azithromycin: When to Discontinue

Study type	Methods	Results	Conclusion
Open-label, randomized, crossover	AZM 1500mg single dose AZM 500mg x 3 days	C_{max}: 1.46 AUC: 13.1 C_{max}: 0.54 AUC: 11.2	Single 1500mg doses of azithromycin provide equal exposure as 500mg x 3 days with biologic half life ≥ 7 days

Amsden. Serum and WBC pharmacokinetics of 1500mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers. Journal of Antimicrobial Chemotherapy, 2004.

76

De-escalation

Narrow to fluoroquinolone monotherapy

77

Fluoroquinolone Monotherapy

- Utilization of fluoroquinolone monotherapy may be appropriate in select cases
  - Desire single agent that covers all likely pathogens, including atypicals and/or IV equivalent agent for more severe cases of CAP
  - *Legionella* on culture or urinary antigen test positive
  - Severe beta-lactam allergy
- When utilizing a fluoroquinolone based regimen utilize the shortest course as clinically appropriate (5 days in most cases: more later)

78

De-escalation

Utilize MRSA nasal swab results to guide therapy

79

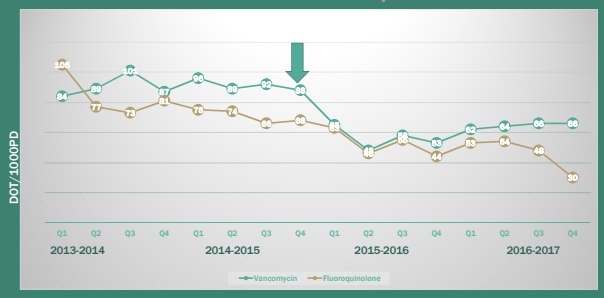
MRSA nasal swab to guide therapy: What is the evidence?

Type of Pneumonia	Results of meta-analysis to predict a MRSA-positive culture for patients tested for nasal colonization			
	Sensitivity	Specificity	PPV	NPV
All	70.9 (58.8-80.6)	90.3(86.1-93.3)	44.8	96.5
CAP/HCAP	85.0(59.7-95.6)	92.1(81.5-96.9)	56.8	98.1
VAP	40.3(17.4-68.4)	93.7(77.1-98.4)	35.7	94.8

Parente. The Clinical Utility of MRSA Nasal Screening: A Diagnostic Meta-analysis. Oxford University Press, 2018. Prediction of MRSA Involvement in Disease Sites by Concomitant Nasal Sampling. J of Clin Micro. 2008; Dangerfield. Predictive Value of MRSA Nasal Swab PCR for MRSA Pneumonia. Antimicrobial Agents and

80

Antimicrobial Utilization: Impact of ASP



Patient Case

82

JW is feeling drastically better on day 3 when his *Legionella* test comes back negative. His sputum culture is still pending. At this point, JW has received 3 days of therapy of ceftriaxone and azithromycin (1500mg total). What is the best option for de-escalation?

1. Discontinue azithromycin and continue ceftriaxone IV while cultures are pending.
2. Discontinue azithromycin and change ceftriaxone to amoxicillin/clavulanate.
3. Discontinue both antibiotics and change to moxifloxacin PO.
4. Do not de-escalate. Continue ceftriaxone and azithromycin for 5 days total.

83

Later that day his sputum culture comes back positive as *Streptococcus pneumoniae,* susceptible to penicillins, ceftriaxone, levofloxacin, and moxifloxacin. Which agent is the best option for de-escalation at this time?

1. Amoxicillin PO
2. Levofloxacin PO
3. Moxifloxacin PO
4. Continue amoxicillin/clavulanate PO

84

Duration of Therapy

Duration of Therapy

- Current guidelines recommend a minimum of 5-day courses
- Numerous studies support 5-day courses as equally effective to longer courses
  - Most treated with fluoroquinolones[1-4]

1. Dunbar LM. High-dose, short-course levofloxacin CAP. Clin Infect Dis 2003; 37: 752-60; 2. Dunbar LM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of CAP caused by atypical pathogens. Curr Med Res Opin 2004;20:555-63; 3. File TM, et al. Clinical implications of 750 mg, 5-day levofloxacin for the treatment of CAP. Current Medical Research and Opinion. 2004;20:9, 1473-148; 4. Torres A. Moxifloxacin Monotherapy Is Effective in Hospitalized Patients with CAP: The MOTIV Study—A Randomized Clinical Trial Clinical Infectious Diseases 2008; 46:1499–1509

86

Short courses (5 days of therapy): What is the evidence?

Study type	Methods (n)	Results (ITT)	Conclusion
Non-inferiority, randomized	5-day intervention (162)	10-d: 56.3% 30-d: 91.9%	5-day courses trended towards higher clinical success rates.
	Control (150)	10-d: 48.6% 30-d: 88.6%	

Uranga. Duration of Antibiotic Treatment in CAP. JAMA. 2016.

87

Relevant exclusions to short course studies

- Immunocompromised patients
- Healthcare exposure
  - SNF, recent hospitalization, recent antibiotics
- Complications
  - *Pseudomonas, S. aureus, Legionella*, chest tube, pleural effusion requiring drainage, extrapulmonary infection

Uranga. Duration of Antibiotic Treatment in CAP. JAMA. 2016.

88

Patient Case

89

The next day, JW is ready for discharge. He has received 4 days of antibiotics so far. How many additional days of therapy will JW need upon discharge?

1. 6 more days for 10 days total
2. 10 more days for 14 days total
3. 1 more day for 5 days total
4. No more – his inpatient treatment was adequate

90

Summary

- Reserve fluoroquinolones when possible
- Corticosteroids may be used as adjunctive therapy in SCAP
- Utilize microbiologic data to guide therapy if available
- Discontinue vancomycin if the MRSA nasal swab is negative
- If Legionella negative, discontinue azithromycin after 1500mg
- Treat for 5 days in most cases

91