

**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.

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**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.

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### 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.

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### 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.

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### Guidelines

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

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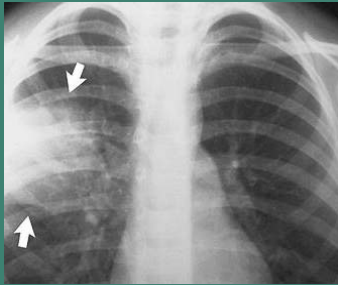
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**Introduction**  
Community-Acquired Pneumonia



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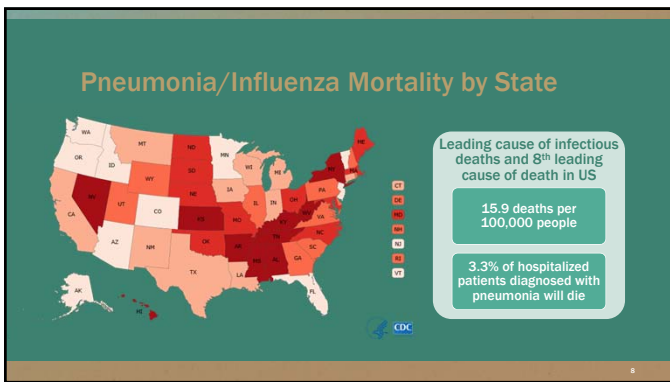
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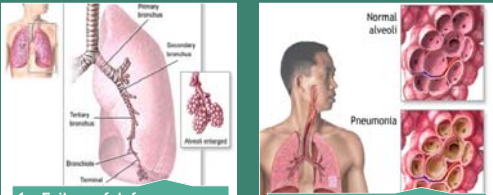
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**Pathophysiology**



1. Failure of defense mechanisms
2. Pathogen colonizes lung
3. Alveoli fill with fluid

Singh. Pathophysiology of Community Acquired Pneumonia. JAPI, 2012

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### Microbiologic Etiology

| Patient Status | Etiology   |
|----------------|--|
| Outpatient     | <b>Streptococcus pneumoniae</b><br><i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , <i>Legionella</i><br><i>Haemophilus influenzae</i> , respiratory viruses |
| Inpatient      | <b>Streptococcus pneumoniae</b><br>Atypicals<br><i>Haemophilus influenzae</i><br>Aspiration, respiratory viruses   |
| ICU            | <b>Streptococcus pneumoniae</b><br><i>Staphylococcus aureus</i><br><i>Legionella</i><br>Gram-negative bacilli, <i>Haemophilus influenzae</i>                             |

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### Risk Factors

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

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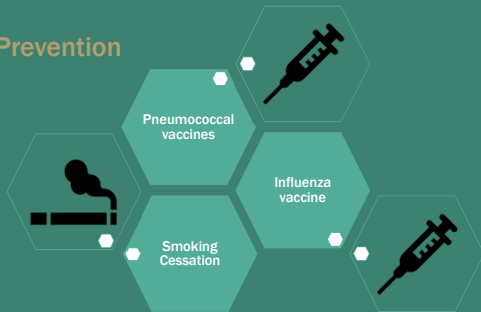
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### Prevention



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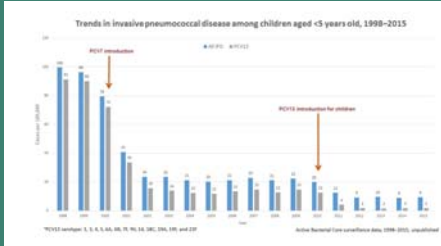
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### Pneumococcal Disease Among Children



CDC

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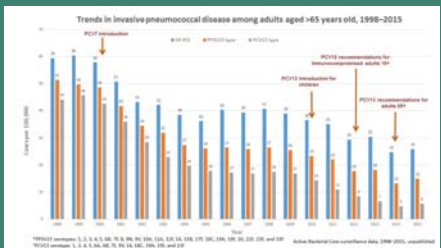
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### Pneumococcal Disease Among Elderly



CDC

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### 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

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### Clinical Presentation

A diagram with four circular icons in a row, each with a corresponding text label below it. From left to right: a person coughing (Cough), a person with a fever (Fever), a person coughing into a cup (Sputum production), and a person holding their chest (Shortness of breath & Pleuritic Chest Pain). A large double-headed arrow is positioned below the icons, spanning the width of the four boxes.

Cough

Fever

Sputum production

Shortness of breath & Pleuritic Chest Pain

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### Diagnosis

A flowchart with three boxes connected by arrows. The first box is 'Clinical presentation', the second is 'Infiltrate detected by imaging', and the third is 'Microbiological evidence'. A large arrow points from the first box to the second, and another large arrow points from the second box to the third.

Clinical presentation

Infiltrate detected by imaging

Microbiological evidence

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### Site-of-Care Decision

A diagram for site-of-care decision. On the left, a box lists criteria for hospital admission: CURB-65 2-3, Pneumonia Severity Index III-IV, Oral intake, and Social support. To the right, two arrows point from left to right. The first arrow is labeled 'CURB-65' and lists: Confusion, RR > 30, BUN > 20, SBP < 90 or DBP < 60, and Age > 65. The second arrow is labeled 'PSI' and lists: Age, Demographics, Comorbidities, Physical Exam, Labs, and Imaging. Below the 'Hospital admission' text is a green circle with a white cross.

• 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

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### Site of Care Decision

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

Minor Criteria

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

**ICU admission** 

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### 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, et al. 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. 20

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### Empirical Treatment




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### Classes of Antibiotics

| Beta-lactams  | Macrolides   | Tetracycline  | Fluoroquinolones  | Glycopeptide   |
|---|--|---|---|--|
| <ul style="list-style-type: none"> <li>amoxicillin</li> <li>ampicillin</li> <li>piperacillin</li> <li>ceftriaxone</li> <li>cefotaxime</li> <li>cefepime</li> <li>ertapenem</li> </ul> | <ul style="list-style-type: none"> <li>azithromycin</li> <li>erythromycin</li> <li>clarithromycin</li> </ul> | <ul style="list-style-type: none"> <li>doxycycline</li> </ul> | <ul style="list-style-type: none"> <li>levofloxacin</li> <li>moxifloxacin</li> <li>ciprofloxacin</li> </ul> | <ul style="list-style-type: none"> <li>vancomycin</li> </ul> |

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

Bacteria, such as *Streptococcus pneumoniae*, form in clusters in the interstitial space

(B)  $\beta$ -lactam antibiotics HYDROPHILIC & are located largely in interstitial space / blood

(M) Macrolide\* antibiotics LIPOPHILIC & Accumulate largely inside cells / tissues

\* Atypical Bacteria (Legionella, Mycobacterium, Chlamydia)

Slide courtesy of Brett Heintz, PharmD

23

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### 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, et al. 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

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### Outpatient Treatment

If Risk Factors for DRSP:

- Beta-lactam PLUS macrolide (or doxycycline)
- Anti-pneumococcal FQs: levofloxacin or moxifloxacin

Mandell LA, et al. 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 25

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### 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, et al. 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 26

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### ICU Treatment

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

Mandell LA, et al. 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 27

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**ICU Treatment**

**Special Considerations: *Pseudomonas*\***

- Antipseudomonal beta-lactam (e.g. piperacillin/tazobactam or ceftazidime)

PLUS

- Ciprofloxacin or levofloxacin

or

- Aminoglycoside and azithromycin

Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases*. 2007; 44:251-72

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**\**Pseudomonas* Risk Factors**

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

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**ICU Treatment**

**Special Considerations: Community-acquired (CA)-MRSA \***

- Add vancomycin or linezolid

Mandell LA, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clinical Infectious Diseases*. 2007; 44:251-72

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### \*MRSA Risk Factors

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

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### Special Cases

Healthcare-associated (HCA) exposure\*

- Consider enteric GNR coverage
- 3<sup>rd</sup> 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

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### 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

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Patient Case



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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.

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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

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## Pathogen-Directed Therapy

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| <i>Streptococcus pneumoniae</i>   | <i>Haemophilus influenzae</i> | Atypicals*      | <i>Staphylococcus aureus</i> |
|-----------------------------------|-------------------------------|-----------------|------------------------------|
| DRSP                              |                               |                 | MSSA                         |
| amoxicillin 1 g TID               | amoxicillin (β-lactamase neg) | macrolide       | anti-staph PCN (nafcillin)   |
| amoxicillin/clavulanate           | amoxicillin/clavulanate       | doxycycline     | cefazolin                    |
| ceftriaxone                       | ceftriaxone                   | fluoroquinolone | MRSA                         |
| anti-pneumococcal fluoroquinolone | 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 al. 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

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## De-escalation

Criteria for Clinical Stability

- Temperature ≤ 37.8°C
- Heart rate ≤ 5 BPM
- Respiratory rate ≤ 24 breaths/min
- Systolic blood pressure ≥ 90 mmHg
- Arterial oxygen saturation ≥ 90% or pO<sub>2</sub> ≥ 60 mmHg
- Ability to maintain oral intake

Intravenous to Oral Therapy

Mandell, LA, et al. 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

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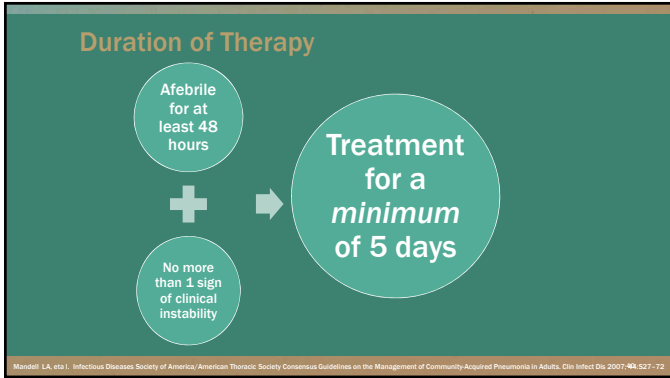
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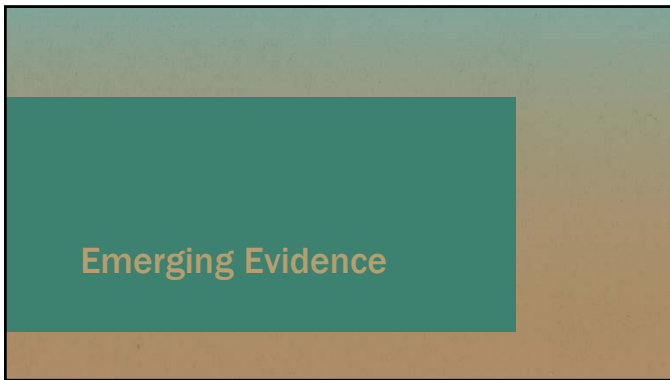
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**Rapid Diagnostics**

- 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

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**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

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**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

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### 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).<sup>1</sup>
- Elevated PCT level is associated with an increased risk of mortality<sup>2</sup>
- Cut-off of 0.5 ng/ml was not sensitive enough to identify patients at high risk of dying<sup>2</sup>

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

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### Procalcitonin

**Prognostic, not diagnostic**

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

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### Empiric Selection



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### Beta-lactams

|  |            |              |
|--|------------|--------------|
| Amoxicillin  | Ampicillin | Piperacillin |
| <b>Ceftriaxone</b><br><i>Strep. pneumoniae</i><br><i>H. influenzae</i><br><i>Staph aureus</i> (MSSA)<br>Enteric gram negative rods |            | Cefepime     |
|  |            | Ertapenem    |

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

| Study type  | Methods (n)                       | Results | Conclusions  |
|---|-----------------------------------|---------|--|
| Non-inferiority, cluster-randomized, crossover<br><br>Non-ICU<br>Legionella-neg | Beta-lactam monotherapy (656)     | 9.0%    | Beta-lactam monotherapy non-inferior with regard to 90-day mortality |
|   | Beta-lactam + macrolide (739)     | 11.1%   |  |
|   | Fluoroquinolone monotherapy (889) | 8.8%    |  |

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

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

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**Macrolides**

**Erythromycin**

**Clarithromycin**

**Azithromycin**

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

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**Azithromycin: First-Choice Macrolide**

| Study type              | Methods (n)  | Results  | Conclusion  |
|-------------------------|--|--|---|
| Open-label, prospective | Ceftriaxone + 3-day AZM (383)<br><br>Ceftriaxone + 10-day clarithromycin (220) | M: 3.6%<br>LOS: 7.4<br><br>M: 7.2%<br>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

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**Azithromycin and Cardiovascular Risk**

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

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

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### Azithromycin and Cardiovascular Risk

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

Ray, Azithromycin and the Risk of Cardiovascular Death, NEJM, 2012. 55

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### The Impact of Azithromycin's Cardiovascular Risk



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### Tetracycline

## Doxycycline

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

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### Doxycycline vs. Macrolides

| Study Type    | Methods  | Results: LOS   | Conclusion  |
|---------------|--|--|---|
| Retrospective | <ul style="list-style-type: none"> <li>BL + doxycycline</li> <li>BL + macrolide</li> </ul> | <ul style="list-style-type: none"> <li>Overall: 5</li> <li>Typical: 5</li> <li>Atypical: 3</li> <li>Overall: 6</li> <li>Typical: 6</li> <li>Atypical: 6</li> </ul> | Clinical outcomes similar between groups for typical pathogens. For atypicals, Doxycycline associated with shorter LOS (<0.001) |

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

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### Fluoroquinolones

| Levofloxacin  | Moxifloxacin   | Ciprofloxacin  |
|---|--|--|
| <ul style="list-style-type: none"> <li>Excellent <i>Strep. pneumoniae</i></li> <li><i>H. influenzae</i></li> <li>Atypicals</li> <li><i>Pseudomonas</i></li> <li>Enteric GNRs</li> </ul> | <ul style="list-style-type: none"> <li>Excellent <i>Strep. pneumoniae</i></li> <li><i>H. influenzae</i></li> <li>Atypicals</li> <li>Enteric GNRs</li> <li>Anaerobes</li> </ul> | <ul style="list-style-type: none"> <li><i>H. Influenzae</i></li> <li>Less atypical coverage</li> <li><i>Pseudomonas</i></li> <li>Enteric GNRs</li> </ul> |

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### Fluoroquinolones: The Good, the Bad, and the Ugly

| Study type                          | Methods   | Results   | Discussion   |
|-------------------------------------|---|---|--|
| Systematic review and meta-analysis | <ul style="list-style-type: none"> <li>Macrolide vs. BL + macrolide</li> <li>FQ vs. BL + FQ</li> <li>FQ vs. BL + macrolide</li> </ul> | <ul style="list-style-type: none"> <li>No difference in clinical failure or other efficacy outcomes</li> <li>No differences in all outcomes</li> <li>No difference in mortality. Clinical failure less common in FQ arm.</li> </ul> | FQ or macrolide monotherapy as effective as combination therapy. No difference in mortality. Higher rates of diarrhea in combination arms. |

Ho Poster. Fluoroquinolones or macrolides alone versus combined with beta-lactams for adults with community-acquired pneumonia. International Journal of Antimicrobial Agents, 2016. 60

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### 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>
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### Fluoroquinolones: The Good, the Bad, and the Ugly

| Musculoskeletal & Peripheral nervous system  | Central nervous system/ Psychiatric | Other                                  |
|--|-------------------------------------|--|
| Tendonitis / tendon rupture  | Psychosis                           | <i>Clostridium difficile</i> 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<br>– GI tract structural instability | Hallucinations                      | Pneumonitis / nephritis                |
|  | Suicidal Ideations                  | Blood glucose disturbances             |
|  | Confusion                           | Drug-drug interactions                 |

Sehlmann R, Lode H. Safety Considerations of Fluoroquinolones in the Elderly An Update Drugs Aging 2010; 27 (3): 193-209. Tillston GS. FDA and the safe and appropriate antibiotic use of Fluoroquinolones. Lancet Infectious Diseases 2016;16(3):e11-12.
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### 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. LaPointe, PharmD. "Antimicrobial Stewardship in Geriatric Populations Including Long-term Care and Extended Care Facilities"
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### 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. Am J Allergy Immunol 2010; 35(4):269-73. 2. Allergy Clin Immunol Pract 2013;3(3):208-13. 3. J Allergy Immunol 2015; 139(4):772-76. 4. Allergy 2013;68(12):1618-21. 5. Pharmacotherapy 2011;31:742-47. 6. Allergy Immunol Pract 2013;3(3):208-13. 7. QJ 2014;68(1):140-6. 8. J Gen Intern Med 2010; 25:209-211. 9. Jones BM. Report on Penicillin Skin Testing as an Antimicrobial Stewardship Initiative. 64

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### 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. McDonald. Screening for Beta-Lactam Allergy in Joint Arthroplasty Patients to Improve Surgical Prophylaxis Practice. J Arthroplasty. 2017. 65

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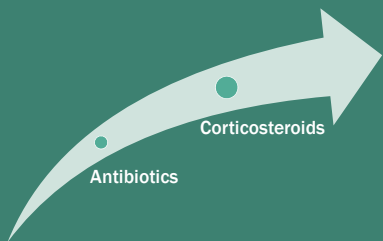
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### Adjunctive Therapy



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### Corticosteroids: What is the evidence?

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

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

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### Corticosteroids: What is the evidence?

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

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

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### 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

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### Corticosteroids: What is the evidence?

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

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

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### 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

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### De-escalation/ Definitive Therapy



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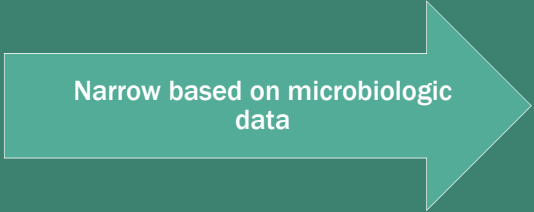
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Definitive Therapy



Narrow based on microbiologic data

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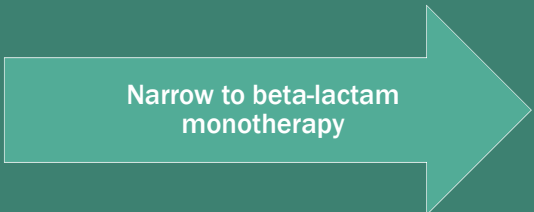
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De-escalation



Narrow to beta-lactam monotherapy

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Azithromycin: When to Discontinue



Clinically responding

No culture results

*Legionella* negative

Received 1500mg total

OR

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

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### Azithromycin: When to Discontinue

| Study type                        | Methods                                      | Results  | Conclusion  |
|-----------------------------------|--|--|---|
| Open-label, randomized, crossover | AZM 1500mg single dose<br>AZM 500mg x 3 days | C <sub>max</sub> : 1.46 AUC: 13.1<br>C <sub>max</sub> : 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

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### De-escalation

Narrow to fluoroquinolone monotherapy

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### 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)

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### De-escalation

Utilize MRSA nasal swab results to guide therapy

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### 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 |

Parents. The Clinical Utility of MRSA Nasal Screening: A Diagnostic Meta-analysis. Oxford University Press; 2018. Prediction of MRSA Involvement in Disease Sites by Contaminant Nasal Sampling. J of Clin Micro. 2008; Designated. Predictive Value of MRSA Nasal Swab PCR for MRSA Pneumonia. Antimicrob Agents and Chemother. 2008; 52(12):3511-3516.

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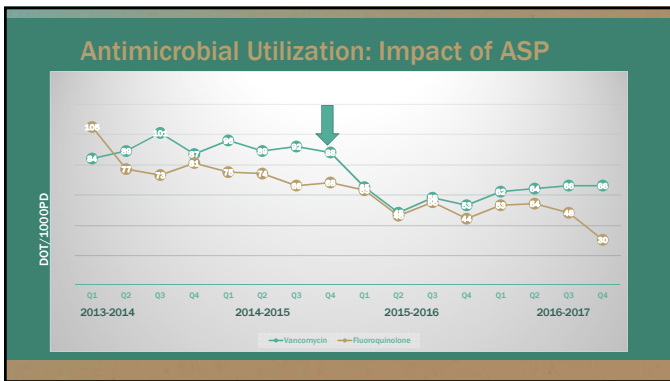
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Patient Case



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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.

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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

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**Duration of Therapy**




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**Duration of Therapy**

Current guidelines recommend a minimum of 5-day courses

Numerous studies support 5-day courses as equally effective to longer courses

⑩ Most treated with fluoroquinolones<sup>1-4</sup>

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 MOCIV Study—A Randomized Clinical Trial. Clinical Infectious Diseases 2006; 45:1469-1509

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**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%<br>30-d: 91.9% | 5-day courses trended towards higher clinical success rates. |
|                             | Control (150)            | 10-d: 48.6%<br>30-d: 88.6% |  |

Uranga. Duration of Antibiotic Treatment in CAP. JAMA. 2016. 87

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**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

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**Patient Case**



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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?

- 6 more days for 10 days total
- 10 more days for 14 days total
- 1 more day for 5 days total
- No more – his inpatient treatment was adequate

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### 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

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