Antibiotic Review: The Ins and Outs of Current Treatment Guidelines

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Disclosures

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- Melissa Murfin, PA-C
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Learning objectives

- Understand CDC antibiotic stewardship recommendations
- Prescribe current, evidence-based treatment for tick-borne illness.
- Discuss the treatment of C. difficile, according to latest IDSA/SHEA guidelines.
- Understand appropriate treatment for patients with asymptomatic bacteriuria.
- Review updated guidelines on Candida auris
- Review updated guidelines for diagnosis and treatment of CAP
- Select antibiotics that are used in the evidence-based treatment of both outpatient and inpatient CAP.

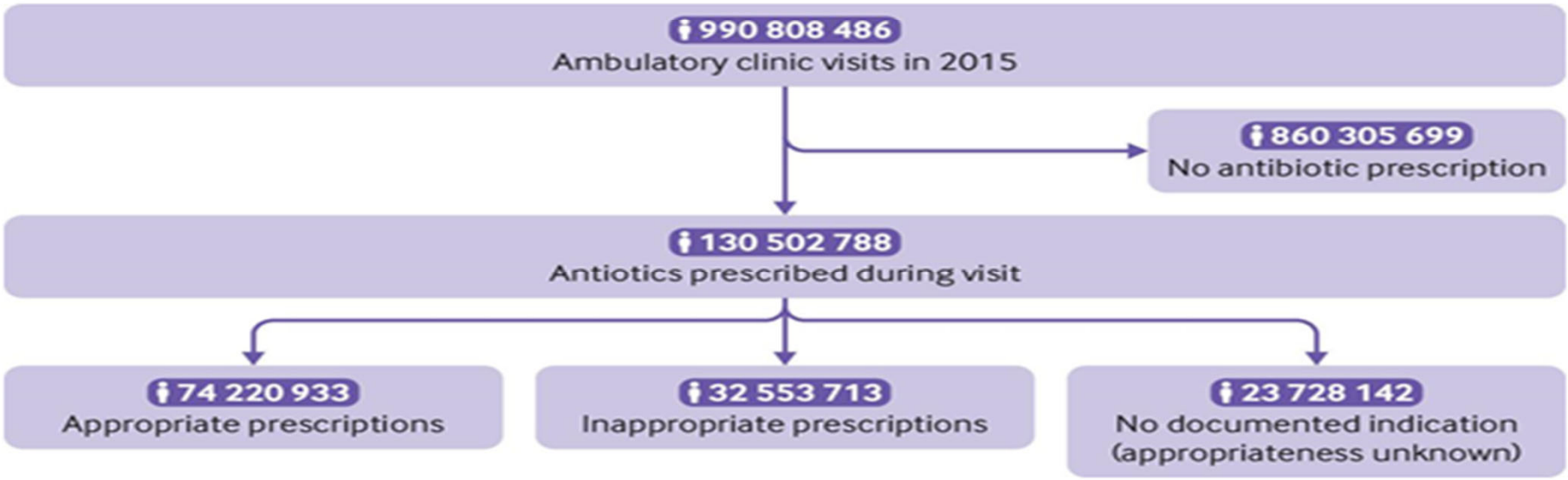
Antibiotic Stewardship: How are we doing?

January 2019 BMJ study

- 19 million privately-insured patients ages newborn to 64
- Reviewed records of filled antibiotic Rx and 91 ICD-10 diagnosis codes in 2016
- Determined if Rx was appropriate, potentially appropriate, inappropriate, or no association with recent diagnosis code
- 23% filled an inappropriate Rx
- 35% potentially inappropriate Rx
- 28% No associated diagnosis code

https://www.bmj.com/content/367/bmj.l6461

Derivation of analytic sample: weighted counts from 2015 National Ambulatory Medical Care Survey.



Michael J Ray et al. BMJ 2019;367:bmj.l6461

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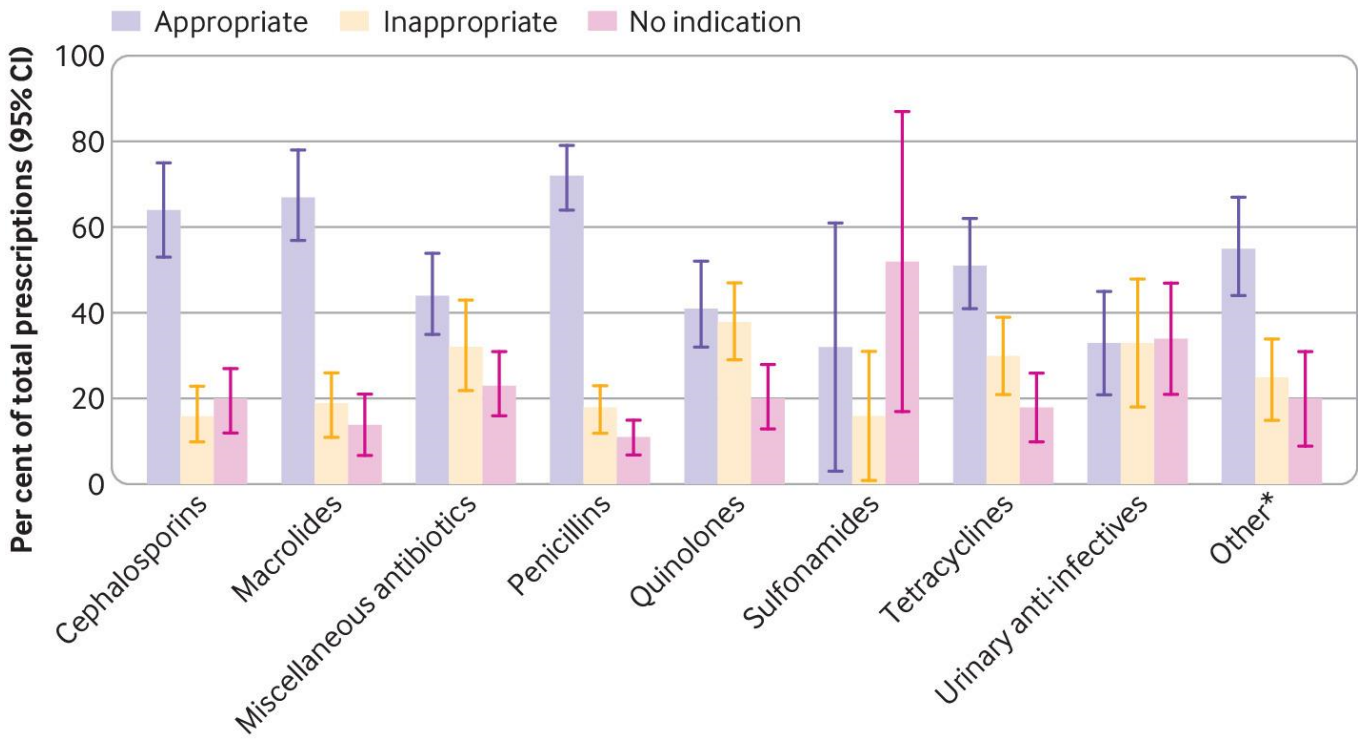
Appropriateness of prescribing by class of antibiotic. *Includes carbapenems, leprostatics, aminoglycosides, lincomycin derivatives, glycylcyclines, and glycopeptide antibiotics.



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Antibiotic Stewarship: CDC Outpatient Core Elements

- Commitment
  - accountability for optimizing antibiotic prescribing and patient safety related to antibiotics
- Action
  - Implement at least one practice to improve prescribing
- Tracking and Reporting
  - Monitor at least one aspect of prescribing
- Education and expertise
  - Provide education to patients
  - Utilize continuing education to optimize prescribing habits

https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf

Antibiotic Stewarship: CDC Inpatient Outcomes

- Commitment
  - Designated medical staff co-leaders
- Action
  - Implement at least one practice to improve prescribing
  - Infection, provider, and pharmacy based
- Tracking and Reporting
  - Monitor and report *C. diff* infections
  - Financial impact
- Education and expertise
  - Provide education to patients
  - Utilize continuing education to optimize prescribing habits

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf

Guideline Updates

C. *Diff* Guidelines 2017 update

- Case definitions
  - healthcare facility-onset (HO) CDI
    - number of cases per 10000 patient-days
  - community-onset, healthcare facility–associated (CO-HCFA) CDI
    - number of cases per 1000 patient admissions
  - community-associated (CA) CDI

C. Diff Guidelines Testing

- New-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI
  - Not on laxatives
  - No other explanation for unformed stools
- Nucleic acid amplification test (NAAT)
- Stool toxin test
- Avoid testing asymptomatic patients or within 7 days of prior test during same diarrhea episode

C. *diff* Initial Treatment

- First-line:
  - Vancomycin 125 mg po 4x daily x 10 days
  - Fidaxomicin 200 mg BID x 10 days
- Second-line:
  - Metronidazole 500 mg TID x 10 days

- Peds
  - Metronidazole 7.5 mg/kg/dose TID or QID x 10 days
  - Vancomycin 10 mg/kg/dose QID po x 10 days

Asymptomatic Bacteriuria (ASB) 2019 Guideline

- Patients without catheters with ≥10^5 colony-forming units (CFU)/mL (≥10^8 CFU/L) in a voided urine specimen
  - No UTI signs or symptoms
  - Women, 2 consecutive specimens within 2 weeks
- Benign in healthy, non-pregnant women and kids
  - prevalence healthy, premenopausal women 1% - 5%
  - healthy postmenopausal women 2.8% - 8.6%

Asymptomatic Bacteriuria (ASB) 2019 Guideline

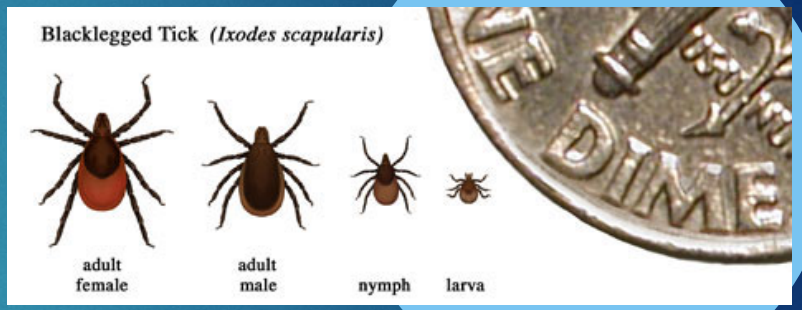
- Treatment increases antibiotic resistance and *C. diff* incidence
  - Increasing incidence of CRE urine isolates
- Stewardship programs indicate antibiotic treatment of ASB increases resistance patterns
- Recommendations for appropriate screening
  - Not recommended routinely in peds, healthy women, geriatric population, patients with diabetes, short-term catheter

Asymptomatic Bacteriuria (ASB) 2019 Guideline

- Pregnant women
  - Prevalence 2% - 7%
  - Screen at early pregnancy visit
  - Treat per culture x 4 – 7 days
    - Decreases risk of pyelonephritis
    - May decrease risk of low birth weight and preterm labor
    - Nitrofurantoin, ampicillin, or cephalexin preferred

Lyme Disease Guidelines: 2019 draft

- No treatment for low-risk bite
- High risk bite
  - Ixodes tick (deer tick)
  - Highly endemic area
  - Tick engorged and attacked for more than 36 hours
  - Offer single doxycycline dose within 72 hours of tick removal



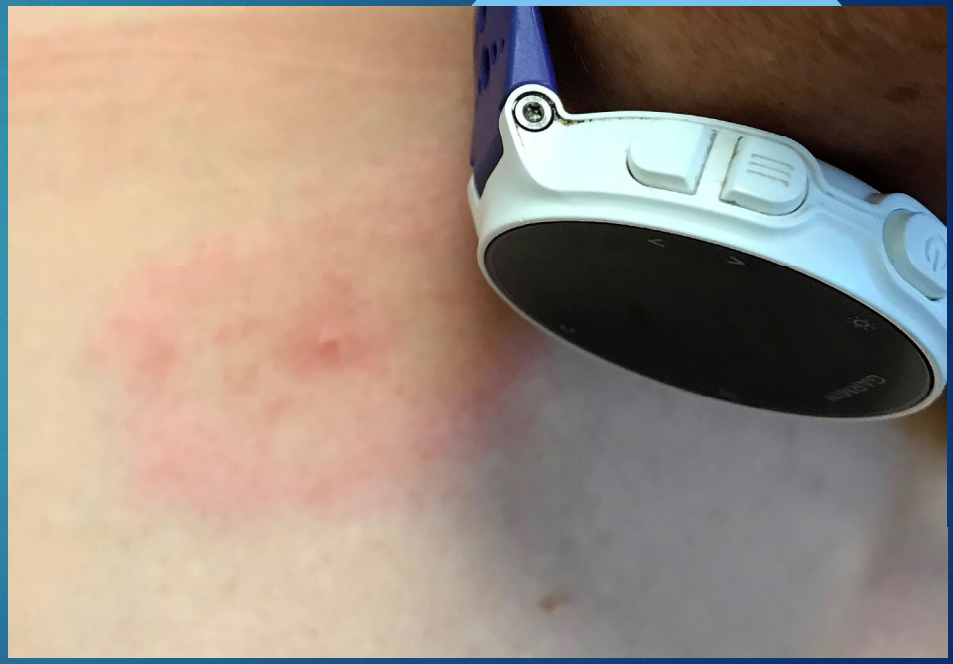
Lyme Disease Guidelines: Testing

- Recommended
  - meningitis, painful radiculoneuritis, mononeuropathy multiplex, or acute cranial neuropathies, and plausible exposure to high-risk ticks

- Not recommended with other neurological syndromes, psychiatric illnesses, children presenting with developmental, behavioral, or psychiatric disorders

Lyme Disease Guidelines: 2019 draft

- Erythema migrans Treatment
  - Doxycycline 100 mg po BID x 10 days
  - Amoxicillin 500 mg po BID x 14 days
  - Cefuroxime axetil 500 mg po BID x 14 days



STARI (Alpha Gal allergy)

- Southern Tick Associated Rash Illness
- Red meat allergy after Lone Star tick bite
- IgE response to galactose-alpha-1,3-galactose
  - Also found in gelatin, milk products
  - Not in fish, birds
- Symptoms 3 – 6 hours after eating meat products
- Antibiotics not beneficial

Candida auris: 2020 CDC Recommendations

- Systemic fungal infection
- Multi drug resistant
- Risk factors
  - hospitalized in a healthcare facility a long time
  - central venous catheter
  - Other indwelling lines
  - previously received antibiotics or antifungal medications

Candida auris: 2020 CDC Recommendations

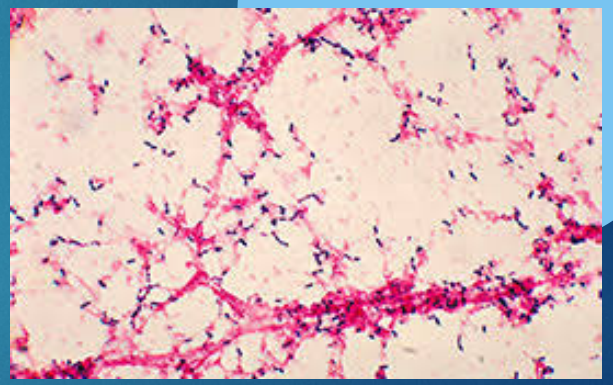
- Often misidentified on lab testing as other *Candida* species
- Must be reported to infection control and local public health
- Treatment with echinocandin antifungals
  - Caspofungin 70 mg IV x 1, then 50 mg IV daily
- Can use amphotericin if nonresponsive

2019 IDSA/ATS Update Guidelines for Diagnosis and Treatment of CAP

- Major changes:
  - "HCAP" terminology has been abandoned as rationale for broad spectrum antibiotics
  - No anaerobic coverage for suspected aspiration unless lung abscess or empyema
  - Abx duration: 5 days, guided by clinical stability

Quick Reminder about Likely Pathogens

- Most common causes of bacterial pneumonia
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Mycoplasma pneumoniae*
  - *Staphylococcus aureus*
  - *Legionella* species
  - *Chlamydia pneumoniae*
  - *Moraxella catarrhalis*



Severe vs non-severe CAP

Minor Criteria
Respiratory rate > 30/minute
PF ratio < 250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN > 20)
Leukopenia or thrombocytopenia
Hypothermia (core temp < 36 C)
Hypotension requiring aggressive IVF resuscitation

Major Criteria
Septic shock on vasopressors
Respiratory failure requiring mechanical ventilation

Either 1 major criterion or
3 or more minor criteria

Diagnosis Recommendations: Blood and Sputum Cultures

- Recommend AGAINST obtaining blood/sputum culture routinely in the outpatient setting
- Inpatient setting, send blood/sputum cx prior to antibiotics if:
  - Severe CAP
  - Empirically being treated for MRSA or pseudomonas
    - Or prior MRSA/pseudomonas PNA
  - Recent IV antibiotics in last 90 days
- Rationale
  - No evidence that routine testing improves outcomes and sputum evaluation generally is of poor yield

Legionella and Pneumococcal Urinary Antigen

- Recommend AGAINST routinely testing urine for pneumococcal antigen except in severe CAP
- No routine Legionella testing recommended except:
  - Indicated by epidemiological factors (Legionella outbreak, recent travel)
  - Severe CAP
- Rationale: No RCTs have identified benefit for urinary antigen testing and narrowing therapy due to positive urinary testing can lead to increased risk for clinical relapse

Additional testing: Influenza

- During influenza season testing for influenza is recommended in all patients with CAP (or other influenza like illness)
- Consider empiric Tamiflu while awaiting Influenza/respiratory viral panel results

Empiric Treatment of Outpatient CAP

- Based on presence of comorbidities
  - Chronic heart disease
  - Lung disease
  - Liver or renal disease
  - Diabetes mellitus
  - Alcoholism
  - Malignancy
  - Asplenia

Empiric Treatment of Outpatient CAP

- Healthy adult with no comorbidities or risk factors for resistant pathogens
  - Amoxicillin 1g TID or
  - Doxycycline 100 mg BID or
  - Macrolide such as Azithromycin 500 mg first day then 250 mg daily*

*Macrolide monotherapy is not strongly recommended unless contraindications to Amoxicillin OR documented low macrolide resistance in your area

Empiric Treatment of Outpatient CAP

- Adults with comorbidities
  - Combination therapy
    - Amoxicillin/clavulanate 500 mg TID OR Cephalosporin (Cefpodoxime 200 mg BID or Cefuroxime 500 mg BID) AND
    - Azithromycin 500 mg first day then 250 mg daily
  - Monotherapy
    - Respiratory fluoroquinolone
    - Levofloxacin 750 mg QD or Moxifloxacin 400 mg QD or Gemifloxacin 320 mg QD

Rationale for Broad Spectrum Coverage in Adults w/ Comorbidities

- These patients more likely to have poor outcome if initial abx regimen is not adequate
- Many have risk factors for antibiotic resistance due to previous contact w/ healthcare system/antibiotics
- Patients w/ COPD more likely to have *H. influenzae*, *M catarhallis* which frequently produce beta lactamase

So many options – how do I choose?

- Both sets contain multiple antibiotic options and there is no specific order of preference in the guidelines
- Choice between options based on risk/benefit assessments, local resistance patterns and presence of specific risk factors
  - B-lactam or macrolide allergy
  - Cardiac arrhythmias (macrolides can prolong QTc)
  - Vascular disease (Fluoroquinolones increase risk for aortic dissection/rupture)
  - History of C. Diff infection

Empiric Treatment of Inpatient CAP

- Inpatient adults with nonsevere CAP and no risk factors for MRSA/pseudomonas
  - Combination therapy
    - Beta-lactam (Ampicillin-Sulbactam 1.5-3g q6 or Ceftriaxone 1-2g daily or Ceftaroline 600 mg Q12) AND
    - Macrolide (Azithromycin 500 mg daily or Clarithromycin 500 mg BID)
  - Monotherapy
    - Respiratory fluoroquinolone (Levofloxacin 750 mg daily or Moxifloxacin 400 mg daily)
- If contraindications to both macrolides and fluoroquinolones recommend Beta-lactam + Doxycycline 100 mg BID

Empiric Treatment of Inpatient CAP

- Inpatient adults with severe CAP and no risk factors for MRSA/pseudomonas
  - Combination therapy
    - Beta-lactam + Macrolide OR
    - Beta-lactam + respiratory fluoroquinolone
- Rationale: No RCTs exist comparing specific regimens but in one meta-analysis of ~10,000 patients combination therapy with macrolide were associated with a significant reduction in mortality

Anaerobic Coverage for Aspiration Pneumonia

- Recommend **not** routinely adding anaerobic coverage for suspected aspiration pneumonia unless there is lung abscess or empyema
- Aspiration is common and true rate of aspiration pneumonia is difficult to quantify
- Recent studies have not shown significant isolation of anaerobic organisms in patients with aspiration
- Given increasing rates of antibiotic resistance and complications of antibiotics (like C diff) a more conservative approach is warranted

Should I cover for MRSA and pseudomonas?

- No more HCAP!
- Risk factors for MRSA and pseudomonas
  - Prior isolates in previous culture
  - IV antibiotics within last 90 days
- Recent hospitalization, living in a nursing facility etc are no longer criteria for broad spectrum coverage

Empiric Antibiotic Regimen for Patients w/ MRSA/Pseudomonas Risk

- Treatment for MRSA
  - Vancomycin 15 mg/kg q12 adjusted based on levels OR
  - Linezolid 600 mg q12
- Treatment for pseudomonas aeruginosa
  - Piperacillin-Tazobactam 4.5g q6
  - Cefepime 2g q8
  - Ceftazidime 2g q8
  - Aztreonam 2g q8
  - Meropenem (1g q8) or Imipenem (500 mg q6)

Why should we abandon HCAP?

- HCAP was first incorporated into 2007 IDSA/ATS guidelines after studies demonstrated identified higher amounts of resistant pathogens in these patients
  - Old risk factors: residence in nursing home, recent hospitalization, home infusions, chronic dialysis, family member w/ resistant pathogen
- Now multiple studies have shown that those specific risk factors do not predict higher prevalence AND
- Led to a significant increase in use of broad spectrum antibiotics without any improvements in outcomes

De-escalation: MRSA Nasal PCR

- Nasal colonization with MRSA is associated w/ clinical MRSA infection, can be detected using nasal swab PCR assay
- 2014 retrospective cohort study with 435 patients confirmed negative predictive value of **99.2%**
- Positive predictive value is poor (35.4%) so therefore positive MRSA swabs have to be interpreted with other culture data, risk factors to decide whether ongoing treatment is warranted

Take Home Point: If empiric MRSA coverage (i.e. Vancomycin) is started then a negative MRSA PCR swab can be used to de-escalate.

Cefepime and Neurotoxicity

- Cefepime can cause neurotoxicity due to its ability to cross the blood brain barrier and antagonize GABA
- Symptoms; depressed consciousness, encephalopathy/confusion, myoclonus, seizures, coma
- Can occur in up to 15% of critically ill patients treated with Cefepime
- Risk factors: renal dysfunction, excessive dosing*, pre-existing neurologic injuries
  - *can occur at normal therapeutic dosing
- Usually resolves w/ discontinuing drug

Consider choosing different pseudomonas coverage (i.e. Zosyn) in any patients w/ pre-existing seizure disorder, neurologic injury or in patients who present w/ neuro symptoms/develop evidence of neurotoxicity during treatment

Duration of Antibiotic Treatment

- Guided by clinical stability
  - Resolution of vital sign abnormalities (tachycardia, hypotension, tachypnea, hypoxia, fever)
  - Ability to eat
  - Normal mentation
- In patients with both nonsevere/severe CAP recommend 5 days total if clinically improved
- CAP due to suspected or proven MRSA/pseudomonas recommend 7 days total if clinically improved

Summary

Table 3. Initial Treatment Strategies for Outpatients with Community-acquired Pneumonia

	Standard Regimen
No comorbidities or risk factors for MRSA or *Pseudomonas aeruginosa*[*]	Amoxicillin or doxycycline or macrolide (if local pneumococcal resistance is <25%)[†]
With comorbidities[‡]	Combination therapy with amoxicillin/clavulanate or cephalosporin AND macrolide or doxycycline[§] OR monotherapy with respiratory fluoroquinolone[‖]

Definition of abbreviations: ER = extended release; MRSA = methicillin-resistant *Staphylococcus aureus*.
[*]Risk factors include prior respiratory isolation of MRSA or *P. aeruginosa* or recent hospitalization AND receipt of parenteral antibiotics (in the last 90 d).
[†]Amoxicillin 1 g three times daily, doxycycline 100 mg twice daily, azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, or clarithromycin ER 1,000 mg daily.
[‡]Comorbidities include chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia.
[§]Amoxicillin/clavulanate 500 mg/125 mg three times daily, amoxicillin/clavulanate 875 mg/125 mg twice daily, 2,000 mg/125 mg twice daily, cefpodoxime 200 mg twice daily, or cefuroxime 500 mg twice daily; AND azithromycin 500 mg on first day then 250 mg daily, clarithromycin 500 mg twice daily, clarithromycin ER 1,000 mg daily, or doxycycline 100 mg twice daily.
[‖]Levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily.

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia[*]	β-Lactam + macrolide[†] or respiratory fluroquinolone[‡]	Add MRSA coverage[§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia[*]	β-Lactam + macrolide[†] or β-lactam + fluroquinolone[‡]	Add MRSA coverage[§] and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage[§] and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*[‖] and obtain cultures to allow deescalation or confirmation of need for continued therapy

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.
[*]As defined by 2007 ATS/IDSA CAP severity criteria guidelines (*see* Table 1).
[†]Ampicillin + sulbactam 1.5–3 g every 6 hours, cefotaxime 1–2 g every 8 hours, ceftriaxone 1–2 g daily, or ceftaroline 600 mg every 12 hours AND azithromycin 500 mg daily or clarithromycin 500 mg twice daily.
[‡]Levofloxacin 750 mg daily or moxifloxacin 400 mg daily.
[§]Per the 2016 ATS/IDSA HAP/VAP guidelines: vancomycin (15 mg/kg every 12 h, adjust based on levels) or linezolid (600 mg every 12 h).
[‖]Per the 2016 ATS/IDSA HAP/VAP guidelines: piperacillin-tazobactam (4.5 g every 6 h), cefepime (2 g every 8 h), ceftazidime (2 g every 8 h), imipenem (500 mg every 6 h), meropenem (1 g every 8 h), or aztreonam (2 g every 8 h). Does not include coverage for extended-spectrum β-lactamase–producing Enterobacteriaceae, which should be considered only on the basis of patient or local microbiological data.

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Thank you!