The Up To Date APP Pharmacology Update

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Objectives

- Discuss updates to the IDSA/ATS guidelines for the diagnosis and treatment of adults with community-acquired pneumonia
- Formulate empiric and definitive antimicrobial treatment plans for patients with community-acquired pneumonia
- Analyze novel therapeutic options for the treatment of multidrug-resistant pathogens

Community-Acquired Pneumonia Update

Community-Acquired Pneumonia

- IDSA/ATS Guidelines published in October 2019
  - Long awaited update to 2007 guidelines
- Defined as the clinical entity of pneumonia that is acquired outside the hospital setting
- In-hospital mortality: 2.2%
  - Risk factors for death
    - Age ≥ 65 years old
    - 2 or more chronic comorbidities
- Long-term outcomes
  - ICU admission
    - 30 day mortality: 11%
    - One year mortality: 27%

Chest. 2018: 154 (3):628.
Chest. 2011: 139(1):88.
Am J Respir Crit Care Med. 2019; 200(7):e45.

Clinical Prediction Tools

Pneumonia Severity Index

- Components
  - Sex, demographics (age/nursing home), comorbidities, exam/lab findings
- 0-405 points
  - Classifies patients in risk classes from I-V

CURB-65

- Components
  - Confusion, uremia, respiratory rate, blood pressure, age ≥ 65
- 0-5 points
  - Low risk: 0-1
  - Higher risk: 2-5

N Engl J Med. 1997; 336:243-250.
Am J Respir Crit Care Med. 2019; 200(7):e45.

Clinical Prediction Tools

- PSI is the preferred clinical prediction tool over CURB-65
  - PSI is better able to accurately predict mortality
- Determination on inpatient placement(ICU vs. general floor) should utilize clinical judgement with IDSA/ATS 2007 severe CAP criteria

- PSI Interpretation

Class	Points	Mortality (%)
I		0.1
II	0-70	0.6
III	71-90	2.8
IV	91-130	8.2
V	131+	29.2

- Class II-III are candidates for outpatient treatment

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2007 IDSA/ATS Severe CAP Criteria

- Site of care (ICU vs. general floor) serves as surrogate for disease severity
  - Practice is not consistent between hospitals
- Other factors often influence decision regarding patient placement in the hospital

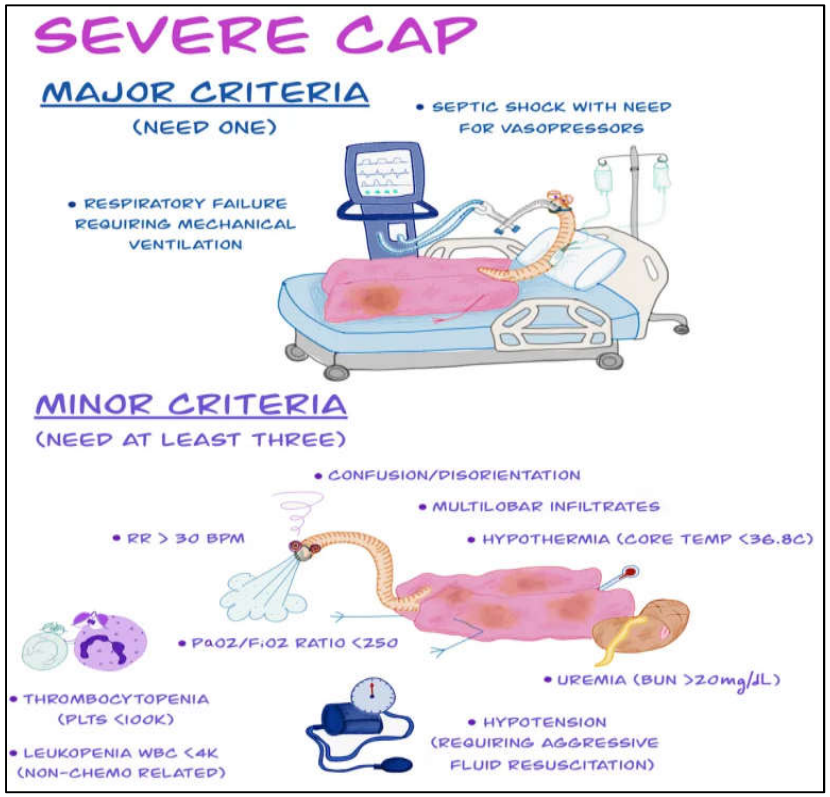

Image adapted from pulmccm.org.
Am J Respir Crit Care Med. 2019; 200(7):e45.

Culture Recommendations

	Outpatient Recommendation	Inpatient Recommendation
Respiratory Cultures	Do no obtain sputum Gram stain and culture	Obtain cultures in following situations: 1. Severe CAP (For respiratory cultures: esp. if intubated) 2. Empirically treated for MRSA/P. aeruginosa 3. Previous infection with MRSA/P. aeruginosa 4. Hospitalized and received IV antibiotics in last 90 days
Blood Cultures	Do not obtain blood cultures	

Am J Respir Crit Care Med. 2019; 200(7):e45.

Pathogen specific testing

Pneumococcal antigen

- Do not routinely test except:
  - Adults with severe CAP

Legionella antigen

- Do not routinely test except:
  - In cases where indicated by epidemiological factors or recent travel
  - Adults with severe CAP

Influenza Virus

- Test adult patients with CAP when influenza virus is circulating in community
  - Recommendation for rapid influenza molecular assay over rapid influenza diagnostic test

Am J Respir Crit Care Med. 2019; 200(7):e45.

CAP with Positive Influenza Test

- In CAP patients with a positive influenza test, treatment with oseltamivir should be initiated
  - Included both inpatient and outpatient settings
  - Regardless of duration of illness prior to diagnosis
    - Even though the strongest benefit is when oseltamivir is initiated within 48 hours of symptom onset
    - Literature supports reduced mortality with antiinfluenza agents
- In patients with radiographic evidence of CAP and positive influenza test, antibiotics should be initiated
  - Included both inpatient and outpatient settings
  - Discontinue antibiotics if no evidence of bacterial CAP after 48-72 hours
    - Given that patient is clinically stable, including a low procalcitonin level

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Biomarkers

- Procalcitonin (PCT)
  - Recommend empiric antibiotic therapy initiated regardless of initial serum PCT level
  - Recent meta-analysis concluded use of PCT is unlikely to guide evidence to provide/exclude patients from antibiotic treatment
    - Sensitivity 0.55 (95% CI, 0.37-0.71)
    - Specificity 0.76 (95% CI, 0.62-0.86)
- C-Reactive Protein (CRP)
  - No recommendation included in guidelines
  - Literature does support use to confirm CAP
  - Accuracy is not able to distinguish bacterial CAP from viral CAP

Clin Infect Dis. 2020; 70(3):538-542.
Critical Care. 2015; 19:366.
Am J Respir Crit Care Med. 2019; 200(7):e45.

Common Bacterial Pathogens

CAP

- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Haemophilus influenza*
- *Moraxella catarrhalis*
- *Staphylococcus aureus*
- *Legionella* Species

HAP

- Gram-negative bacilli
  - *Acinetobacter*
  - *Pseudomonas*
  - *Strenotrophomonas*
  - *Klebsiella*
  - *Serratia*
- *Staph Aureus*
  - MRSA

VAP

- Gram-negative bacilli
  - *Acinetobacter*
  - *Pseudomonas*
  - *Strenotrophomonas*
  - *Klebsiella*
  - *Serratia*
- *Staph Aureus*
  - MRSA

Clin Infec Dis. 2016; 63:1-51.
Clin Infec Dis. 2007; 44:S27-72.
Am J Respir Crit Care Med. 2019; 200(7):e45.

CAP Outpatient Treatment

- Previously healthy patient with no risk factors for antibiotic resistant pathogen infection
  - Amoxicillin 1g TID
  - Doxycycline 100 mg BID
  - Macrolide (Only in areas with pneumococcal resistance < 25%)
    - Azithromycin 500 mg day 1, then 250 mg daily OR Clarithromycin 500 mg BID
- Presence of comorbidities
  - Combination Therapy (β-lactam **plus** a macrolide)
    - β-lactam
      - Amoxicillin/clavulanate 875 mg/125 mg BID

        OR
      - Cephalosporin: cefuroxime 500 mg BID OR cefpodoxime 200 mg BID **(NF)**
    - Macrolide
  - Monotherapy
    - Respiratory fluroquinolone
      - Levofloxacin 750 mg daily or moxifloxacin 400 mg daily **(NF)**

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CAP Inpatient Treatment
Patients without risk factors for MRSA/P. *aeruginosa*

Non-severe CAP

- β-lactam **plus** a macrolide
  - Ceftriaxone 1-2g **daily**
  - Ampicillin/Sulbactam 1.3-3g q6h
    - Currently on shortage/backorder
  - Cefotaxime 1-2g q8h **(R)**
- Monotherapy respiratory fluoroquinolone
- β-lactam **plus** doxycycline
  - Doxycycline 100 mg BID

Severe CAP

- β-lactam **plus** a macrolide
- β-lactam **plus** a respiratory fluoroquinolone

- Regimens that are not well studied and are **not recommended**
  - Fluroquinolone monotherapy
  - β-lactam **plus** doxycycline

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CAP Inpatient Treatment
Patients with risk factors for MRSA/P. *aeruginosa**

- MRSA coverage
  - Vancomycin pharmacy to dose (adjusted based on levels)

    OR
  - Linezolid 600 mg Q12h
- P. *aeruginosa*
  - Piperacillin-tazobactam 4.5g q6h
  - Cefepime 2g q8h
  - Ceftazidime 2g q8h **(R)**
  - Aztreonam 2g q8h (usually for PCN allergic patients)
  - Carbapenem
    - Meropenem 1g q8h
- Continue empiric treatment for these pathogens while obtaining cultures to justify/refute continued treatment

*Risk Factors: MRSA or P. *aeruginosa* respiratory infection in past year OR hospitalization with IV antibiotics in last 90 days

Am J Respir Crit Care Med. 2019; 200(7):e45.

Aspiration Pneumonia

- Do not routinely add anaerobic coverage to inpatients with CAP and suspected aspiration pneumonia
  - Unless lung abscess or empyema is suspected
- Recent studies show that anaerobic organisms are uncommon pathogens in aspiration pneumonia
- Patients who aspirate gastric contents often have aspiration pneumonitis
  - Symptoms resolve usually within 24-48 hours
  - Requires supportive treatment without antibiotics
  - Judicious use of antibiotics is recommended given increasing rates of C. difficile (often associated with clindamycin)

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Healthcare-associated Pneumonia (HCAP)

- Removed from the 2016 HAP/VAP guidelines
  - Patients with HCAP found to not be at risk for MDR pathogens
  - HAP/VAP guidelines suggested that this designation will be included in updated CAP guidelines
- Recommend abandoning HCAP categorization
  - Utilize local epidemiology and validated risk factors for MRSA or P. *aeruginosa* antibiotic coverage
  - Will decrease over usage of anti-MRSA and antipseudomonal broad spectrum antimicrobial therapy

Am J Respir Crit Care Med. 2019; 200(7):e45.
CID. 2016; 63(5):e61-111.

Corticosteroid usage

- Routine corticosteroids are not recommended in adults with non-severe or severe CAP
- Corticosteroids are not recommended in patients with influenza pneumonia
- Follow Surviving Sepsis Campaign recommendations for use of corticosteroids
  - Use IV hydrocortisone 50 mg q6h in patients if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability
    - In practice this is usually added with the addition of a 2nd pressor

Am J Respir Crit Care Med. 2019; 200(7):e45.
Critical Care Medicine. 2017: 45(3):1.

Duration of therapy

- Patients with CAP should be treated for minimum of 5 days
  - Most patients will become clinically stable in 48-72 hours
  - Decision should be guided by clinical stability
    - Vital signs
    - Ability to eat
    - Normal mentation
- Either parenteral or oral antibiotics may be used
- Repeat chest imaging is not recommended
- In cases with suspected or confirmed MRSA or P. *aeruginosa*, duration of treatment should be 7 days

Am J Respir Crit Care Med. 2019. 2019:200(7):e45.

Final Takeaways

- Utilize clinical judgement with PSI and 2007 IDSA/ATS CAP severity criteria for clinical prediction and placement
- Consider illness severity and MRSA/P. *aeruginosa* risk factors to direct treatment decisions
- Macrolide monotherapy is not recommended in Upstate SC
- Duration of therapy: 5 days (Unless MRSA or P. *aeruginosa* are isolated*)*

NOVEL THERAPEUTIC OPTIONS FOR MULTIDRUG-RESISTANT PATHOGENS

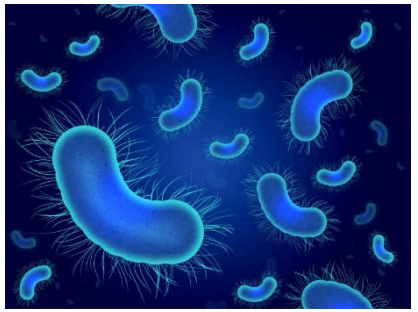
How did we get here?

Bacteria are everywhere

Antibiotic-resistant bacteria multiply

Antibiotics kill bacteria that cause infections

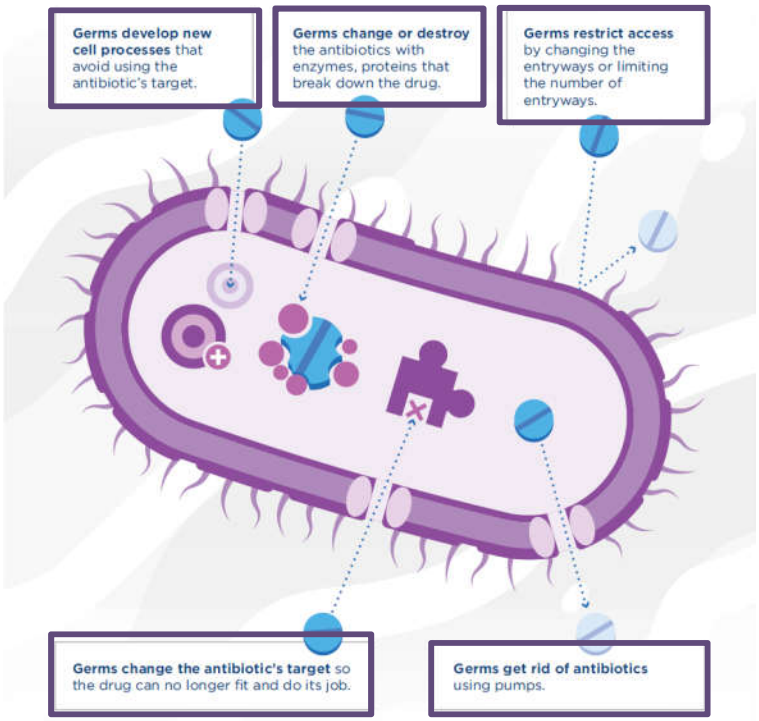
Antibiotics kill normal flora that protect us



Antibiotic resistance can spread

CDC. Antibiotic Resistance Threats in the United States, 2019.

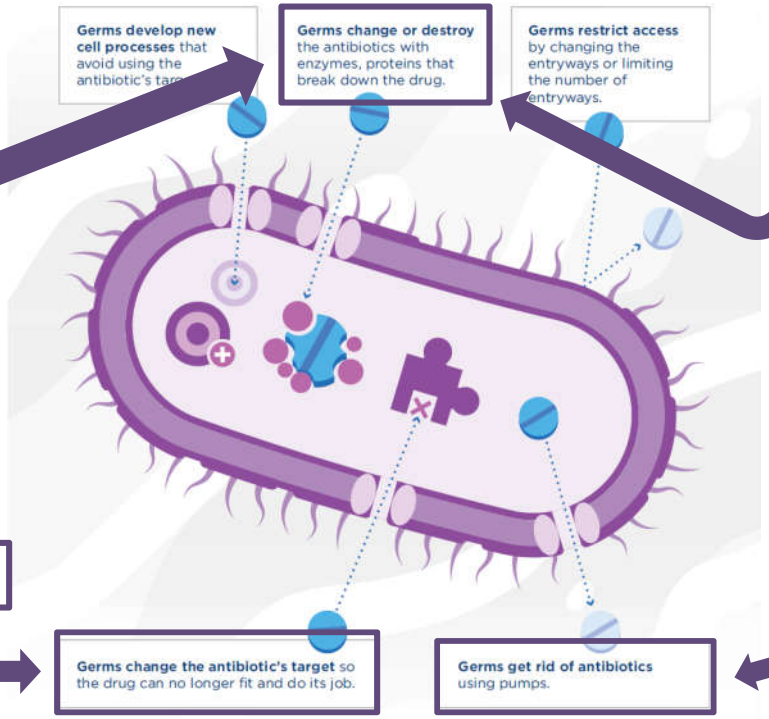
Bacteria Use 1 of 5 Mechanisms to Become Resistant to Antibiotics



CDC. Antibiotic Resistance Threats in the United States, 2019.

Bacteria Use 1 of 5 Mechanisms to Become Resistant to Antibiotics

- Beta-lactamase enzymes: bacterial resistance to penicillins, cephalosporins, and/or carbapenems
- Beta-lactamase inhibitors act as target for enzymes



Aminoglycoside resistance

Fluoroquinolone resistance

Tetracycline resistance

First, Some Abbreviations and Definitions

- MRSA: methicillin resistant *Staphylococcus aureus*
- PRSP: penicillin resistant *Streptococcus pneumonia*
- Atypicals: bacteria that cause community-acquired pneumonia and do not have a cell wall. *Legionella, Chlamydia, Mycoplasma*
- Enterobacterales: formerly Enterobacteriaceae – Gram negative enteric bacteria like *E. coli, Klebsiella, Proteus, Enterobacter*
- ESBL: extended-spectrum beta-lactamase enzyme, resistance to broad-spectrum penicillins and cephalosporins
- CRO: carbapenem-resistant organism

Lefamulin (XENLETA)

- Pleuromotilin
- Dosing
  - IV: 150 mg every 12 hours
  - Oral: 600 mg every 12 hours
- Indications
  - Community acquired pneumonia: 5 days
- Clinical Pearls
  - Active against MRSA, PRSP, *H. influenza, M. cattarhalis,* atypicals
  - Take on empty stomach
  - More GI upset seen compared to alternatives

Delafloxacin (BAXDELA)

- Fluoroquinolone
- Equally potent preference for target sites
- Dosing
  - IV: 300 mg every 12 hours
  - Oral: 450 mg every 12 hours
- Indications
  - Community acquired pneumonia: 5 days
  - Skin and skin structure infection: 5 days

- Clinical Pearls
  - Active against **MRSA**, *Streptococcal* species, Enterobacterales, ***P. aeruginosa***, *M. catarrhalis, H. influenza,* atypicals, anaerobic organisms, mycobacterium
  - Take with or without food
  - Separate by 2 hours before or 6 hours after antacids, vitamins containing zinc or iron
  - Fluoroquinolone adverse effects
- Place in therapy: polymicrobial infections, future directions
  - Diabetic foot infections

Omadacycline (NUZYRA)

- Semisynthetic tetracycline = chemically stable against some tetracycline-resistant organisms
- Dosing – needs a loading dose
  - IV: 200mg on day 1 then 100 mg once daily
  - Oral: 450mg once daily on day 1+2 then 300 mg once daily
- Indications
  - Community acquired pneumonia: 7-14 days
  - Skin and skin structure infection: 7-14 days

- Clinical Pearls/Utility
  - Active against **MRSA**, *Streptococcal* species, some Enterobacterales **(including some ESBL and CRO),** *M. catarrhalis, H. influenza,* atypicals, mycobacterium
  - Take without food: 4 hours before OR 2 hours after food
  - Separate antacids, vitamins containing zinc or iron, calcium or dairy by 4 hours after administration
  - Specialty pharmacy product

Eravacycline (XERAVA)

- Semisynthetic tetracycline = chemically stable against some tetracycline-resistant organisms
- Dosing
  - IV: 1 mg/kg every 12 hours
- Indications
  - Complicated intra-abdominal infection
- Clinical Pearls/Utility
  - Active against MRSA, some *Strep, Enterococcus,* some Enterobacterales **(including some ESBL and CRO)**, anaerobes
  - IV only
  - Like tigecycline, less adverse effects esp. nausea & vomiting
  - Distributes into tissues = does not stay in bloodstream = cannot be used for bloodstream infections

Plazomicin (ZEMDRI)

- Aminoglycoside
- More stable against enzymes that inactivate aminoglycosides
  - Little benefit against *Pseudomonas* or *Acinetobacter* ← resistant to aminoglycosides by other mechanisms
- Dosing
  - IV: 15 mg/kg once daily
- Indications
  - Complicated urinary tract infection
- Clinical Pearls/Utility
  - Active against Enterobacterales
  - IV only – infusion center
  - Serum trough monitoring before second dose

Ceftolozane/Tazobactam (ZERBAXA)

- Cephalosporin + Beta-lactamase inhibitor
- Dosing – IV only
  - cUTI, cIAI: 1.5 g every 8 hours
  - HAP/VAP: 3 g every 8 hours
- Indications
  - Serious infections due to multidrug resistant organisms (off-label)
  - Complicated urinary tract infection
  - Complicated intra-abdominal infection
  - Hospital-acquired pneumonia and ventilator-associated pneumonia
- Clinical Pearls/Utility
  - Active against: ***Pseudomonas,*** Enterobacterales (including some ESBL), some *Strep* species
  - Combine with metronidazole for cIAI
  - Can be given via continuous infusion

Ceftazidime/Avibactam (AVYCAZ)

- Cephalosporin + Beta-lactamase inhibitor
- Dosing – IV only
  - 2.5 g every 8 hours
- Indications
  - Serious infections due to multidrug resistant organisms
  - Complicated urinary tract infection
  - Complicated intra-abdominal infection
  - Hospital-acquired pneumonia and ventilator-associated pneumonia
- Clinical Pearls/Utility
  - Combine with metronidazole for cIAI
  - Infusion 2 hours long

Meropenem/Vaborbactam (VABOMERE)

- Carbapenem + Beta-lactamase inhibitor
- Dosing – IV only
  - 4g every 8 hours
- Indications
  - Complicated urinary tract infection
  - Infections due to carbapenem-resistant Enterobacterales (off-label)
- Clinical Pearls/Utility
  - Active against **ESBL and some CRO**, carbapenem sensitive *Pseudomonas,* anaerobes
  - Serious infection due to multi-drug resistant organisms
  - Infusion over 3 hours

Imipenem/Cilastatin/Relebactam (RECARBRIO)

- Carbapenem + Beta-lactamase inhibitor
- Dosing – IV only
  - 1.25 g every 6 hours
- Indications
  - Complicated urinary tract infection
  - Complicated intra-abdominal infection
  - Hospital-acquired and ventilator-associated pneumonia (off label)
- Clinical Pearls/Utility
  - Active against **most CRO** including some *Pseudomonas*, **ESBL** Enterobacterales, anaerobes
  - Serious infections due to multi-drug resistant organisms

Cefiderocol (FETROJA)

- Cephalosporin
- Unique way of entering bacterial cell: binds to free iron and is actively transported across cell membrane by bacteria's own iron transport system
- Dosing – IV only
  - 2 g every 8 hours
- Indications
  - Complicated urinary tract infection
  - Serious infections due to CRO (off-label)
- Clinical Pearls/Utility
  - Active against Enterobacterales **including CRO**, *Pseudomonas, H. influenza, M. catharralis*
  - Very weak against Gram positives
  - May require higher doses if excellent renal function (CrCl > 120 mL/min)
  - Infusion over 3 hours
  - Serious infections due to multidrug resistant organisms

Final Takeaways

- New agents add to armamentarium against antibiotic-resistant bacteria
- Most new antibiotics seek FDA approval for common infectious disease syndromes in community
- Off-label use against serious, multidrug resistant organisms
- Clinically evaluate patients in your practice with common ID syndromes
- Consider cost & availability of new agents
- Use antibiotics for shortest effective duration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