Bryan D. Hayes, PharmD, FAACT, FASHP
Massachusetts General Hospital/Harvard Medical School
bryanhayes13@gmail.com
Twitter: @PharmERToxGuy

What's New in Antibiotics in the ED

Session Overview

Selection of the most appropriate antibiotic is critical to the management of our patients with infectious diseases; however, there are so many options and so many conditions that it can be a challenge to correctly choose. The presenter will discuss best practices for matching common infectious diseases and various antibiotics.

Objectives

1) Discuss the primary choices of antibiotics for common infections like skin and soft tissue infections and urinary tract infection
2) Discuss the primary choices of antibiotics for patients presenting with intra-abdominal infections and neutropenic fever
3) Discuss the options of antivirals for common viral infections in the ED

Virtual ACEP Questions

1. Which of the following agents does not provide coverage for atypical organisms?
    a. Levofloxacin
    b. Ceftriaxone
    c. Azithromycin
    d. Doxycycline
2. Which classification of diabetic foot infection generally requires broad-spectrum antibiotic coverage including anaerobes?
    a. Uninfected
    b. Mild
    c. Moderate
    d. Severe
3. Which antibiotic provides adequate anaerobic coverage for intrabdominal infections?
    a. Cefepime
    b. Metronidazole
    c. Levofloxacin
    d. Cefoxetan
4. Which antibiotic contributes more than 1 gm/day of sodium?
    a. Piperacillin/tazobactam
    b. Ceftriaxone
    c. Clindamycin
    d. Vancomycin

PNEUMONIA

The Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) published a 2019 update to the Adult Community-Acquired Pneumonia (CAP) guidelines.

Empiric Treatment in Outpatients

1. No comorbidities or risk factors for antibiotic-resistant pathogens: Amoxicillin 1 gm TID **OR** Doxycycline 100 mg BID [Azithromycin is listed, but resistance is too high in all of the continental U.S. to use it as monotherapy]
2. Comorbidities (chronic heart/lung/liver/renal disease; diabetes; malignancy; asplenia)
    1. Combination: Amoxicillin/Clavulanate 875/125 mg BID **OR** Cefpodoxime 200 mg BID **OR** Cefuroxime 500 mg BID **PLUS** azithromycin 500 mg X 1, then 250 mg QDAY **OR** Doxycycline 100 mg BID
    2. Monotherapy: Levofloxacin 750 mg QDAY **OR** Moxifloxacin 400 mg QDAY [FQs have several boxed warnings, other serious adverse reactions, and drug interactions – use combination therapy above unless patient absolutely can't tolerate]

Empiric Treatment in Inpatients

1. Non-severe without MRSA or *P. aeruginosa* risk factors: Ceftriaxone 1-2 gm QDAY **PLUS** Azithromycin 500 mg QDAY [FQs are listed for monotherapy, but should be avoided whenever possible] [Doxycycline can be substituted for macrolides]
2. Severe without MRSA or *P. aeruginosa* risk factors: Same as non-severe. If using a FQ, add beta-lactam as well. [Avoid FQs whenever possible]
3. With MRSA or *P. aeruginosa* risk factors: As was alluded to in the 2016 Hospital-Acquired and Ventilator-Associated Guidelines, there is no more HCAP. The new guidelines recommend only covering empirically for MRSA or *P. aeruginosa* "if locally validated risk factors for either pathogen are present." Vancomycin or Linezolid for MRSA, when indicated. Cefepime or Piperacillin/Tazobactam for *P. aeruginosa*, when indicated. Consider adding atypical coverage as well (Eljaaly 2017, Maruyama 2013).

Aspiration in Inpatients - Do not routinely add anaerobic coverage unless lung abscess or empyema is suspected.

Corticosteroids - Do not routinely use steroids in CAP (non-severe or severe) or severe influenza pneumonia. Follow Surviving Sepsis Campaign recommendations in refractory septic shock.

Concomitant Influenza - Guidelines recommend anti-influenza treatment in CAP patients testing positive for influenza, in inpatients and outpatients, independent of duration of illness before diagnosis. [Data on antivirals is controversial, but IDSA and CDC both support their use]

Duration of Treatment - ≥ 5 days with discontinuation guided by a validated measure of clinical stability

What About HCAP?

- No more health-care-associated pneumonia (Kalil 2016, Metlay 2019)
    - Risk of multidrug-resistant organisms (MDR) is low
    - Most patients who previously would have been designated as HCAP can be treated similarly to the community-acquired pneumonia (CAP) pathway (Ewig 2019)

- Empiric treatment in the ED for MDR organisms should be individualized
  - Biggest risk factor = IV antibiotics within the last 90 days
  - Other risk factors include comorbidities, functional status, and severity of illness (Shorr 2012, Webb 2016); in the critically ill: acid suppression therapy within the previous 90 days, mechanical ventilation, and history of MDRO infection (Lat 2018)

What is so bad about fluoroquinolones? **See handout from my ACEP 2022 talk 'Black Box Drugs We Use: What's the Risk?'**

SKIN AND SOFT TISSUE INFECTIONS

The IDSA guideline is still the gold standard for managing Skin and Soft Tissue Infections in the ED (Stevens 2014). Generally, non-purulent infections should be managed with coverage against Strep species (eg, cephalosporins) and purulent infections should include coverage for Staph species including MRSA (eg, doxycycline, TMP-SMX, vancomycin).

Despite the increased incidence of community-acquired MRSA, cephalexin is still as effective as cephalexin + TMP-SMX for uncomplicated SSTI. (Pallin 2013, Moran 2017)

Most ED patients with SSTI can be managed with oral antibiotics.

What about vancomycin? Don't give vancomycin as a first-line or as a one-time dose. If IV antibiotics are truly indicated, choose the IV form of the antibiotics you plan to continue at home.

IV vs. PO

Most ED patients with SSTI can be managed with oral antibiotics (Stevens 2014). Many of the antibiotics we use in the ED have good oral bioavailability (MacGregor 1997). In fact, even one dose of IV antibiotics in the ED can lead to an increased risk of antibiotic-associated diarrhea, *C. diff*, and other deleterious outcomes (Haran 2014, Belforti 2016). There are clinical risk factors associated with oral antibiotic failure in SSTI which may be taken into account when developing a plan (Volz 2013, Peterson 2014, Yadav 2019).

Some EDs are implementing pathways with long-acting antibiotics (eg, dalbavancin) to decrease hospitalizations (Talan 2021).

DIABETIC FOOT INFECTIONS

IDSA guideline published in 2012 (Lipsky 2012), IWGDF guideline published in 2023 (Senneville 2023)

- Severities: uninfected, mild, moderate, severe
- Microbiology

    - Target aerobic gram-positive pathogens only (beta-hemolytic streptococci and Staphylococcus aureus including methicillin-resistant strains if indicated) for mild diabetes-related foot infection, who have not recently received antibiotic therapy, and who reside in a temperate climate area.
    - Do not empirically target antibiotic therapy against *Pseudomonas aeruginosa* in cases of diabetes-related foot infection in temperate climates, but use empirical treatment of *P. aeruginosa* if it has been isolated from cultures of the affected site within the previous few weeks in a person with moderate or severe infection who resides in tropical/subtropical climates.
- Risk factors for resistant bugs
    - MRSA: previous MRSA infections or known colonization, prior antibiotic use, previous hospitalization, and residence in a long-term care facility
    - *P. aeruginosa*: warm climates, macerated ulcers, foot soaking, and other exposure to water or moist environments
    - Resistant enteric gram-negative rods (ESBL): prolonged hospital stays, prolonged catheterization, prior antibiotic use, or residence in a long-term care facility
- Treatment
    - Mild and some moderate: target the same bugs as we do for non-diabetic SSTI
    - More serious moderate and severe cases: broad-spectrum antibiotics including vancomycin, gram-negative, and anaerobic coverage
- Duration
    - Treat for 1-2 weeks; consider 3-4 weeks if the infection is improving but is extensive

URINARY TRACT INFECTIONS

The IDSA guideline for Uncomplicated Cystitis and Pyelonephritis is a decade old (Gupta 2011) with an update in progress.

Acute Simple Cystitis in women: Nitrofurantoin first-line. (Huttner 2018 w/ PharmERToxGuy summary) TMP-SMX and fosfomycin are other first-line options if resistance is less than 20% (Gupta 2011). Cephalosporins such as cefuroxime or cefpodoxime can be used as alternatives.

E. Coli resistance in otherwise healthy female patients may be less than what the institutional or ED antibiogram reports (Hines 2015).

What about pyelonephritis?

- Outpatient
    - Fluoroquinolones if *E. Coli* resistance rate < 10%, OR
    - Ceftriaxone (or aminoglycoside) followed by FQ (for 5-7 days) or TMP-SMX, cephalosporin, or amoxicillin-clavulanate (for 7-10 days)
- Inpatient
    - Standard: ceftriaxone or piperacillin-tazobactam or FQ
    - MDR: Cefepime or pip-tazo or carbapenem

What about male patients?

Acute simple cystitis (otherwise healthy without neurogenic bladder with mild symptoms): treat similarly to women; nitrofurantoin ok for 7 days or FQs for 5 days (Drekonja 2021)

- Nitrofurantoin/fosfomycin/beta-lactams do not reach adequate levels in prostate

INTRAABDOMINAL INFECTIONS

Similar to UTI, these guidelines are old and being revised (Solomkin 2010).

Bacteria: gram-negatives (*Escherichia coli*, *Klebsiella* spp, *Proteus* spp, and *Enterobacter* spp) streptococci, enterococci, and anaerobes

Outpatient regimens (eg, diverticulitis): Amoxicillin-clavulanate, trimethoprim-sulfamethoxazole + metronidazole, ciprofloxacin or levofloxacin + metronidazole, or moxifloxacin

Low-risk community-acquired: piperacillin/tazobactam, cephalosporin + metronidazole, or levofloxacin/ciprofloxacin + metronidazole

High-risk community-acquired: piperacillin/tazobactam, meropenem, cefepime or ceftazidime + metronidazole

NEUTROPENIC FEVER

These guidelines are also being revised (Freifeld 2011, Zimmer 2019).

Bacteria: gram-negative AND gram-positive (in cancer patients, 40:60)

Fungal: rare in low-risk patients

Low risk (stable): piperacillin/tazobactam, cefepime, or meropenem

High-risk (unstable): double cover with gram-negative AND add gram-positive coverage with vancomycin or linezolid

SURVIVING SEPSIS 2021 (Evans 2021)

Timing

- Possible septic shock or high likelihood for sepsis, recommend administering antimicrobials immediately, ideally within 1 hr of recognition
- Possible sepsis without shock, suggest a time-limited course of rapid investigation and if concern for infection persists, administer antibiotics within 3 hr of recognition

Coverage

- Sepsis or septic shock at high risk of MRSA - recommend MRSA coverage
- Sepsis or septic shock and high risk for multidrug-resistant (MDR) organisms - suggest using two antimicrobials with gram-negative coverage for empiric treatment

WHAT DOES BRYAN HAVE AGAINST ZOSYN?

Really nothing; I just want to reserve it for the right patients and have it available in the future.

1. Susceptibility patterns for target gram-negative organisms (Pseudomonas, Klebsiella, E. Coli) in many hospitals are slightly inferior to cefepime
2. Do we really need anaerobic coverage in all situations where broad-spectrum antibiotics are given in the ED?
3. There is a signal of increased AKI risk when combined with vancomycin compared to cefepime or meropenem (Contejean 2021, Downes 2017, Luther 2018, Chen 2018). This holds true in adult and pediatric patients and appears to inform us that penicillins (not cephalosporins) enhance the nephrotoxicity of vancomycin (Tong 2020). Further reading: Is piperacillin-tazobactam nephrotoxic? from PulmCrit blog. Therapies like magnesium are being studied as a preventive measure (Khalili 2021). Courses less than 72 hours also seem to lower the risk (Schreier 2019).
4. Particularly in critically ill patients with lung infections or obesity, standard dosing may not reach sufficient concentrations in the target organs (Zander 2016, Felton 2014, Jung 2017, Damen 2019, Allen 2023). Pediatric patients are often underdosed (Sosnin 2019).
5. Each 4.5 gm dose of piperacillin/tazobactam contains 250 mg of sodium. Use caution in heart failure patients receiving q6 hour dosing. It will add a gram of sodium per day.
6. The need for q6-hour dosing with piperacillin/tazobactam can be problematic in the ED. With long boarding times, subsequent doses get missed. The opposite problem also occurs when admitted patients receive two doses within an hour or two of each other (Leisman 2017, Kemmler 2021, Lykins 2021)
    a. Importance of Second Antibiotic Doses in ED Sepsis Patients from PharmERToxGuy blog
    b. We implemented an electronic alert to improve timeliness (Lee 2023)

ANTIVIRALS

Influenza

CDC/IDSA recommends oseltamivir if a patient (Uyeki 2019):

- Is hospitalized
- Has severe, complicated, or progressive illness
- Is at higher risk for complications

Multiple studies demonstrate no benefit with increased adverse effects (REBEL EM summary 2020)

COVID

Remdesivir

Hospitalized patients (generally used with dexamethasone) - 200 mg as a single dose on day 1, followed by 100 mg once daily. Duration is generally 5 days or until hospital discharge.

Nonhospitalized patients with high risk of progression to severe illness - 200 mg as a single dose on day 1, followed by 100 mg once daily on days 2 and 3. Initiate within 7 days of symptom onset.

Nirmatrelvir-ritonavir (Paxlovid)

General indications in mild-to-moderate infection with symptoms:

- Adults ≥ 65 years old
- Immunocompromised
- Risk factors for progression to severe disease
- Adults ≥ 50 years old, not vaccinated

Dose adjusted for renal function

Multiple drug interactions - can use the University of Liverpool tool

Miscellaneous

Acyclovir

- One of the most common antivirals in the ED
- Based on ideal or adjusted weight (important to have accurate weight)
- Adjusted based on renal function