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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 match them. The presenter will discuss the best matches between important 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) Describe how patient factors may influence antibiotic selection

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 (Question 8)

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 black box warnings, other serious adverse reactions, and drug interactions – use combination therapy above unless patient absolutely can't tolerate]

Empiric Treatment in Inpatients (Questions 9 and 11)

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 (Question 10)

Do not routinely add anaerobic coverage unless lung abscess or empyema is suspected. Standard inpatient CAP therapy above is sufficient.

Corticosteroids (Question 12)

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 (Questions 13 and 14)

1. 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]

2. Guidelines recommend antibacterial treatment be initially prescribed for adults with clinical and radiographic evidence of CAP who test positive for influenza in the inpatient and outpatient settings.

Duration of Treatment (Question 15): At least 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 similar 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); and 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 2020 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. In fact, even one dose of IV antibiotics in the ED can lead to an increased risk of antibiotic-associated diarrhea and *C. diff*. (Haran 2014)

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. (Mueller 2015, Belforti 2016)

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 and *C. diff* (Haran 2014, Belforti 2016). There are some clinical risk factors associated with oral antibiotic failure in SSTI which may be taken into account when developing a plan (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)

- Severities: uninfected, mild, moderate, severe
- Microbiology
    - Superficial: aerobic gram-positive cocci
    - Ulcers that are deep, chronically infected, and/or previously treated with antibiotics are more likely to be polymicrobial: above organisms in addition to enterococci, Enterobacteriaceae, Pseudomonas aeruginosa, and anaerobes
    - Wounds with extensive local inflammation, necrosis, malodorous drainage, or gangrene with signs of systemic toxicity should be presumed to have anaerobic organisms in addition to the above pathogens
- 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
    - Pseudomonas 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

URINARY TRACT INFECTIONS

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

Uncomplicated UTI in females: 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? Fluoroquinolones or TMP-SMX still first-line unless resistance rates > 20%. In that case, use cephalosporins (eg, cefuroxime, cefpodoxime) (Gupta 2011).

What about male patients? Treat similar to complicated UTI in women; generally no nitrofurantoin; longer treatment course (7-14 days)

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 2010).

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

New guidelines out in September (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). 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 where admitted patients receive two doses within an hour or two of each other (Leisman 2017)
    a. Importance of Second Antibiotic Doses in ED Sepsis Patients from PharmERToxGuy blog