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Top 10 Antibiotic Mistakes in the ED

Session Overview

On a daily basis, we prescribe a multitude of medications with various mechanisms of action to treat a broad range of diseases, but are we doing our patients a disservice? Who better than an ED pharmacist to help us recognize potential pitfalls when prescribing antibiotics? Do all patients really need the broad-spectrum gram-positive, gram-negative, and anaerobic coverage the vancomycin/piperacillin-tazobactam combination provides?

Objectives

1) Review interactions between common daily medications & antibiotics in an effort to decrease dangerous side effects
2) Design an appropriate antimicrobial regimen that includes atypical coverage for your patient with healthcare-associated pneumonia
3) Highlight deleterious side effects of medications that might be hurting your patient more than helping
4) Discuss antibiotic stewardship strategies in the ED

Virtual ACEP Questions

1. Which cephalosporin should be avoided in a patient with an amoxicillin allergy?
    a. Cefpodoxime
    b. Cefuroxime
    c. Cephalexin
    d. Ceftriaxone
2. What is the evidence-based loading dose of vancomycin for a critically ill 100 kg patient with suspected sepsis?
    a. 1 gm (10 mg/kg)
    b. 1.5 gm (15 mg/kg)
    c. 3 gm (30 mg/kg)
    d. 2 gm (30 mg/kg, but capped at a max dose of 2 gm)
3. Which antibiotic or antibiotic class has the most clinically significant adverse effects and drug interactions?
    a. Cephalosporins
    b. Fluoroquinolones
    c. Macrolides
    d. Aminoglycosides
4. In a patient on methadone with a baseline QTc interval of 510 msec, which antibiotic choice to cover atypical bacteria has the lowest likelihood of further prolonging the QTc interval?
    a. Doxycycline
    b. Ciprofloxacin
    c. Azithromycin
    d. Levofloxacin

Mistake 1: Not prescribing the recommended antibiotic due to allergy cross-reactivity concerns

We're up against a difficult challenge when navigating patient allergy histories. We're still taught incorrect information regarding true rates of cross-reactivity in school, package inserts still list outdated statistics, and electronic medical record alerts will not be disabled due to perceived liability. So, education has to be the primary solution. (Shenoy 2019)

Penicillin 'Allergy' in the Patient Chart

Simply having a penicillin allergy listed in a patient's chart (whether true hypersensitivity or not) leads to worse outcomes. They spend significantly more time in the hospital, are exposed to significantly more antibiotics previously associated with C difficile and VRE, and are associated with increased hospital use and increased C difficile, MRSA, and VRE prevalence. (Macy 2014, MacFadden 2016, Blumenthal 2020)

Anaphylaxis Risk

The actual anaphylaxis risk is low for both penicillins (0.004-0.015%) and cephalosporins (0.0001-0.1%). (Idsoe 1968, Kelkar 2001) In fact, there are more reported cases of anaphylaxis to cephalosporins in patients without a known penicillin allergy compared with those with known penicillin allergy. (Pichichero 2005, Anne 1995)

Busting Common Myths

1) The true incidence of penicillin allergy in patients who report that they are allergic is less than 10%. (Pichichero 2014)
2) Penicillin-cephalosporin cross-reactivity is largely unrelated to the beta-lactam ring.

Where did the 10% cross-reactivity between penicillins and cephalosporins originate?

The high cross-reactivity found in the early studies probably was caused, at least in part, by contamination of the study drugs with penicillin during the manufacturing process. Before the 1980s, pharmaceutical companies used Acremonium (formally called Cephalosporium) to create both penicillins and cephalosporins. (Campagna 2012)

Furthermore, the authors of the early studies loosely defined ''allergy'' and did not account for the fact that penicillin-allergic patients have an increased risk of adverse reactions to any medication.

Where does the true cross-reactivity come from?

The cross-reactivity seems to come mostly from similar side chains. (Campagna 2012, Pichichero 2014) **If a patient is allergic specifically to amoxicillin or ampicillin, avoid these cephalosporins: cephalexin, cefaclor, cefadroxil, cefprozil.**

Does the risk of cross-reactivity decrease with later-generation cephalosporins?

Technically, yes. But, the real reason is that the side-chain issue only exists with first and second-generation cephalosporins. Third, fourth, and fifth-generation cephalosporins don't have a similar side chain to any penicillin.

Solutions

1) Detailed patient history to determine the extent of 'allergy'
2) Possible test doses in the ED (Blumenthal 2017)
3) Possible skin testing (Bland 2019)

What about using carbapenems in penicillin-allergic patients?

Cross-reactivity with Carbapenems is also very low. In patients who were skin-test positive to penicillins, the incidence of allergic reaction to carbapenems is less than 1% (Atanaskovic-Markovic 2009, Atanaskovic-Markovic 2008, Romano 2007, Romano 2006, Wall 2014, Kula 2014, Frumin 2009).

Mistake 2: Using the IV route instead of PO

Bioavailability - Proportion of drug that enters the circulation

- Many of the antibiotics we use in the ED have good oral bioavailability (MacGregor 1997)

Guideline Recommendations

- Many guidelines for empiric treatment of common infections (SSTI, UTI, PNA) recommend oral antibiotics for mild and some moderate severity cases (Stevens 2014, Gupta 2011, Metlay 2019)

Comparing IV vs PO

- RCTs in cellulitis patients found no difference in outcomes between IV and PO regimens (Aboltins 2015, Bernard 2002, Bernard 1992, Jorup-Ronstrom 1984, Dalen 2018)
- Cochrane review of severe UTIs: no evidence oral less effective than parenteral (Pohl 2007)
- RCTs in pediatric PNA (Addo-Yobo 2004, Atkinson 2007, Hazir 2008, Agweyu 2015) and adult PNA (Oosterheert 2006, Belforti 2016) found no difference in outcomes
- No difference in outcomes for complex bone and joint infections (Li 2019)

Harms of IV

- Even one dose of IV antibiotics in the ED can lead to an increased risk of antibiotic-associated diarrhea and *C. diff* (Haran 2014)
- Expense, prolonged length of stay, phlebitis, extravasation injury, thrombosis, local or systemic infection (Kwong 2015)

When IV is Needed

Severe infection, critically ill, oral dose can't be tolerated or patient can't swallow, anticipated altered absorption (Lehmann 2017)

Mistake 3: One-time doses of vancomycin before discharge

Don't give vancomycin as a first-line or as a one-time dose. Even a 30 mg/kg dose will only achieve therapeutic levels 34% of the time (Rosini 2015). If IV antibiotics are truly indicated, choose the IV form of the antibiotics you plan to continue at home (Mueller 2015).

Mistake 4: Underdosing vancomycin

A new vancomycin guideline was published in 2020 (Rybak 2020). The changes to dosing were summarized even prior to its release (Heil 2018). In the ED, load with 15-20 mg/kg (actual body weight, max 2 gm) and consider 25-30 mg/kg in critically-ill patients. There is a strategy for loading if the patient requires more than 2 gm. (Denetclaw 2015)

Even loading with 30 mg/kg in the ED only achieves therapeutic levels 34% of the time (Rosini 2015)

Doses > 20 mg/kg in the ED do not increase the risk of nephrotoxicity, even in the setting of preexisting kidney disease (Rosini 2016, Marvin 2019)

When is vancomycin 1 gm ok? Patients < 50 kg or on dialysis (though HD pts can still get weight-based loading)

We dose correctly in only about 20% of cases (Rosini 2013, Fuller 2013), though incorporating weight-based dosing in electronic medical records helps (Hall 2015, Frankel 2013)

Mistake 5: 'Double covering' for gram-negative infections

Double coverage (ie, using two antimicrobial agents with differing mechanisms of action) targeting suspected gram-negative bacteria is generally not indicated (Tamma 2012, Johnson 2011, Paul 2014). However, the Surviving Sepsis guidelines suggest using two gram-negative agents empirically for patients with sepsis or septic shock and high risk for multidrug-resistant (MDR) organisms (Evans 2021).

Mistake 6: Underdosing in the critically ill

Critically ill patients, obese patients, and patients receiving renal replacement therapy pose a challenge for proper antibiotic dosing (Hoff 2020, Jung 2017, Zander 2016, Meng 2017, Roberts 2014, Erstad 2004, Medico 2010, Damen 2019). Pediatric patients are often underdosed (Sosnin 2019). In general, in the ED, we should be using loading doses or the high-end of the dosing range for one-time doses.

Bonus pearl: Second doses of antibiotics in the ED pose a different, yet equally important challenge. With long boarding times, subsequent doses get missed or delayed (Leisman 2017). An in-depth discussion of this issue: Importance of Second Antibiotic Doses in ED Sepsis Patients from PharmERToxGuy blog.

Mistake 7: Not investigating previous cultures

One advantage to electronic health records and hospital systems is that we now have instant access to detailed patient histories, including microbiology results. Before ordering antibiotics, be sure to peruse the susceptibility patterns from previous cultures, at least in the past 6-9 months. We know antibiotic

choice matters with respect to mortality (Garnacho-Montero 2003, Zilberberg 2014, Garnacho-Montero 2015). So, it is important to avoid empiric antibiotics for which there is recent documented resistance.

Mistake 8: Not considering important antibiotic drug interactions

1. Warfarin - major interaction [moxifloxacin, metronidazole, TMP-SMX] and moderate interaction [azithromycin, ciprofloxacin, doxycycline, levofloxacin] (Seamans 2018)
2. Sulfonylureas - TMP-SMX inhibits metabolism = hypoglycemia. Levofloxacin and ciprofloxacin can also have this issue (Schelleman 2010)
3. Methadone - QT prolongation with fluoroquinolones
4. ACE-I, ARB, potassium-sparing diuretics - Increased hyperkalemia risk with TMP-SMX (Antoniou 2010, Fralick 2014)
5. Ethanol - The interaction with metronidazole may be less clinically significant than we think (EMPharmD blog 2014)

Bonus Myth Buster: Antibiotics, other than rifampin, generally do not interact with hormonal contraception (Simmons 2018)

Mistake 9: Not considering important adverse effects

Fluoroquinolones are the worst. Two great summaries of the FQ adverse effects from EMPharmD blog and ALiEM blog. The risk rarely outweighs the benefit even in critically ill patients, as summarized on the EMCrit blog. Unless contraindications exist to first-line therapies, FQs should generally be reserved for second-line (FDA safety alert 2018). **Also, see handout from my ACEP 2020 talk 'Black Box Drugs We Use: What's the Risk?'**

Risk of C. diff in order by antibiotic class: clindamycin, fluoroquinolones, cephalosporins, penicillins, macrolides, TMP-SMX (Brown 2013, Deshpande 2013)

Mistake 10: Not practicing antimicrobial stewardship

ED pharmacists are key clinicians that help optimize antibiotics and decrease time to antibiotic administration in sepsis patients (Flynn 2014, DeFratus 2013).

"Antimicrobial stewardship efforts in the ED should target high-impact areas: antibiotic prescribing for nonindicated respiratory tract conditions, such as bronchitis and sinusitis; overtreatment of asymptomatic bacteriuria; and using two antibiotics (double coverage) for uncomplicated cases of cellulitis or abscess." (Pulia 2018)