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

Session Title: Becoming a Jedi Master of Antibiotics in the ED

Youngling: 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We're still taught incorrect information regarding true rates of cross-reactivity in school, package inserts still list outdated statistics, and electronic medical record alerts will not be disabled due to perceived liability.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, Olans 2022)

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, Sousa-Pinto 2021)

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).

Padawan: Using the appropriate route (IV vs. 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)
- There are some 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).

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, Belforti 2016)
- 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)

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

Jedi Knight: Vancomycin

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).

Proper vancomycin dosing

An updated 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)

Applying the Skin and Soft Tissue Infection Guidelines

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)

Jedi Master: 'Double covering' for serious 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).

Sepsis

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).

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 boxed 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.

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 prescribed for adults with clinical and radiographic evidence of CAP who test positive for influenza.

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 in last 90 days, mechanical ventilation, and history of MDRO infection (Lat 2018)

What about Severe Community Acquired Pneumonia? (2023 Guidelines)

Question 3: When using initial empirical therapy for sCAP, should a macrolide or FQ be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?

- We suggest the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalised patients with sCAP.
- The task force also considered the duration of treatment of macrolides being between 3 and 5 days. This would be a reasonable timing especially in the context of de-escalation therapy.

Question 5 (Oseltamivir)

- We suggest the use of oseltamivir for patients with sCAP due to influenza confirmed by PCR.
- When PCR is not available to confirm influenza, we suggest the use of empirical oseltamivir during the influenza season.

Question 6 (Steroids): We suggest the use of corticosteroids if shock is present.

Question 8 (Aspiration): We suggest standard CAP therapy regimen and not specific therapy targeting anaerobic bacteria.

Jedi Council: Proper dosing in the critically ill

Critically ill patients, obese patients, and patients receiving renal replacement therapy pose a challenge for proper antibiotic dosing (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.

Good references: Dialysis Dosing (Hoff 2020); Obesity Dosing (Meng 2023)

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. We implemented an electronic alert to improve timeliness (Lee 2023).

Grand Master: 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.