

Lisa G. Winston, MD
Professor, University of California, San Francisco
Vice Chief, Inpatient Medical Services and
Hospital Epidemiologist, San Francisco General Hospital

NEW DEVELOPMENTS AND CHALLENGING CASES IN HOSPITAL INFECTIOUS DISEASES


Case #1

- A 66 year woman with diabetes is sent by her primary care provider to the ED for admission. The patient had been seen for dysuria two days prior, a urine culture was obtained, and the patient was given ciprofloxacin. The urine culture shows > 100,000 col/mL *E. coli* resistant to ciprofloxacin and trimethoprim-sulfamethoxazole. The laboratory reports the organism is an extended-spectrum beta-lactamase (ESBL) producer. (Not all laboratories continue to report this.)



Case #1 continued

You evaluate the patient in the ED. She has continued dysuria but no systemic symptoms. She does not want to be admitted to the hospital.



Case #1: Options for Management

1. Admit for IV ertapenem. Place PICC with rapid transition to once daily outpatient parenteral therapy.
2. Prescribe trimethoprim-sulfamethoxazole. In vitro susceptibilities do not correlate well with efficacy.
3. Use IM once daily tobramycin.
4. Try fosfomycin.

What is fosfomycin?



- Phosphonic acid derivative that inhibits cell wall synthesis
- Activity against many gram positive and gram negative organisms
- In U.S., only oral salt available as a powder sachet dissolved in water
 - High concentration in the urine
- Usual dose 3g x 1 (single dose)
 - Can also consider 3g every other day x 3 doses or 3g q 72 hrs. x 14 days
 - 3g packet costs about \$50

Other oral options for cystitis due to resistant organisms

- Amoxicillin-clavulanate (susceptible ESBL-producing *E. coli*)
- Nitrofurantoin

Fosfomycin references:

- Falagas et al, Lancet Infect Dis 2010;10:43-50
- Neuner et al, Antmicro Agents Chemother 2012;56:5744-48

Avoid treatment asymptomatic bacteriuria

- Case #1 only required treatment due to symptoms
- One study that treating asymptomatic bacteriuria in young women with recurrent UTI INCREASES risk for symptomatic recurrence

Cai et al, *Clin Infect Dis* 2012;55:771-7

- No data for benefit except in pregnancy
- Guidelines recommend before invasive urologic procedures

Case #2

- You are admitting a 73 year-old man with zoster in the V₁ distribution (ophthalmic branch of the trigeminal nerve). A chest x-ray is negative. The ED is very full and you are being asked to expedite patient flow. The nurse manager wants to know what type of isolation bed the patient requires.

Case #2: Type of Isolation?

1. No special isolation needed. Use standard precautions.
2. Use droplet and contact precautions.
3. Use airborne and contact precautions.
4. Use droplet precautions only.
5. Use airborne precautions only.
6. Use contact precautions only.

Definition of disseminated zoster

- CDC: lesions outside the primary or adjacent dermatomes
- Commonly cited as 20 lesions outside the primary or adjacent dermatomes (? original source)
 - Also may see defined more than 3 dermatomes affected (i.e. more than primary and 2 adjacent dermatomes)

Isolation for Varicella-Zoster

- Primary varicella – airborne and contact
- Disseminated zoster – airborne and contact
- Localized zoster in immunocompetent host – standard
- Localized zoster in immunocompromised host – airborne and contact until disseminated disease ruled out; then standard
- Healthcare workers caring for patient should be immune – CDC says no comment regarding masks

Case #3

- A 57 year old woman presents with fever, right upper quadrant pain, and jaundice. Abdominal CT shows dilation of the common bile duct and cholangitis is suspected. The patient was told by her mother that she had a penicillin allergy as a child and does not know the reaction. You see that she has been treated 3 times in the last year with fluoroquinolones for UTI and most recently had ESBL-producing *E. coli* isolated. Her creatinine is acutely elevated at 2.9 mg/dL.

Case #3: What antibiotic regimen would you give?

1. Vancomycin , aztreonam, and metronidazole
2. Vancomycin and moxifloxacin
3. Vancomycin, gentamicin, and metronidazole
4. Ertapenem
5. Piperacillin-tazobactam

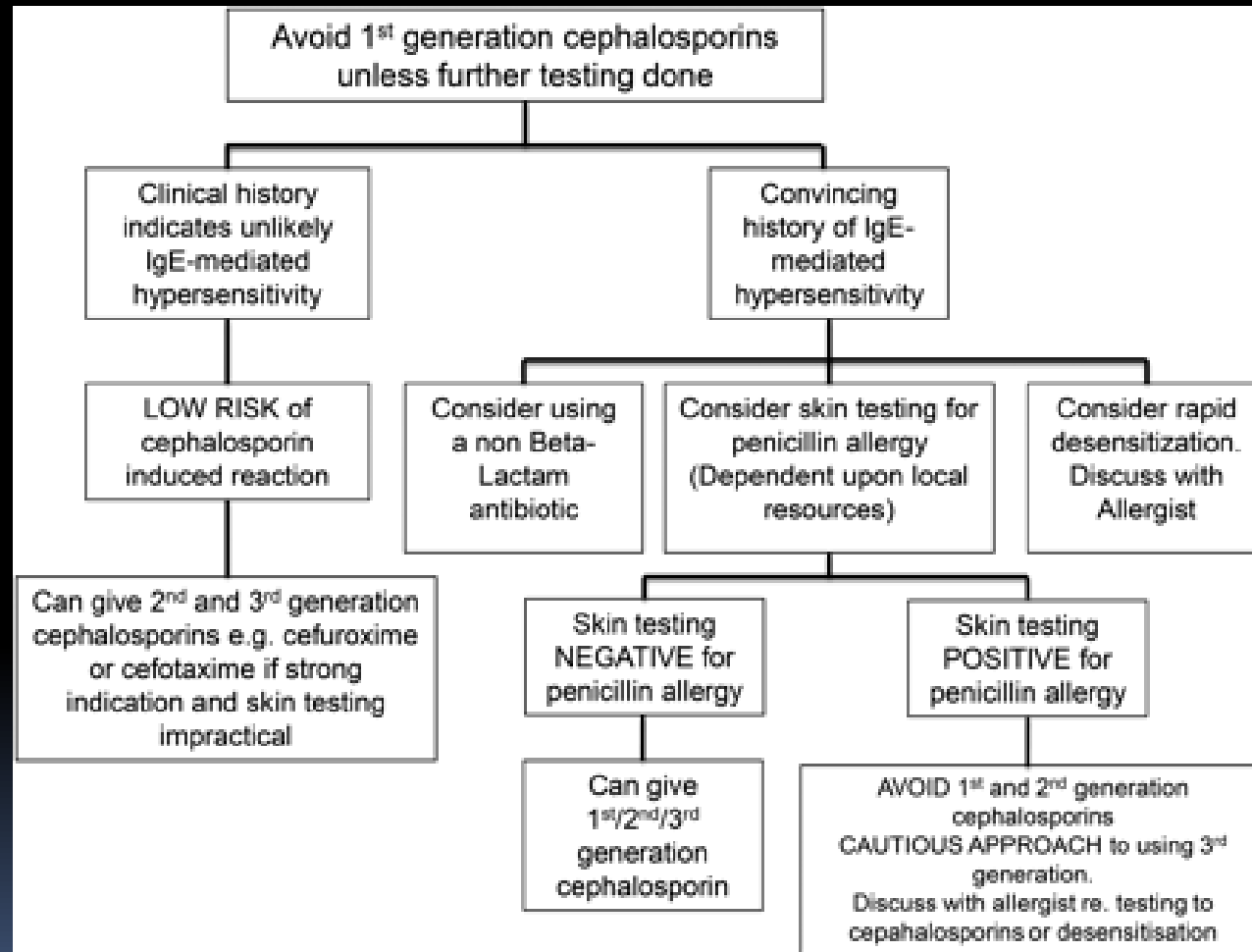
Antibiotic allergies in the hospital

- Skin testing for penicillin allergy and desensitization only useful for IgE mediated reactions
- Graded challenge can be considered for non-severe, non-IgE mediated reactions, e.g. maculopapular rash

Antibiotic allergies in the hospital

- Allergic cross reactivity is greatest for penicillins and first-generation cephalosporins
 - Risk with 3rd and 4th generation cephalosporins (e.g. ceftriaxone and cefepime) is low
- Risk with carbapenems appears similar to that of 3rd and 4th generation cephalosporins

Algorithm for the use of cephalosporins in patients with reported penicillin allergy



ORIGINAL ARTICLE

Absence of Cross-Reactivity between
Sulfonamide Antibiotics and Sulfonamide
Nonantibiotics

CONCLUSIONS

There is an association between hypersensitivity after the receipt of sulfonamide antibiotics and a subsequent allergic reaction after the receipt of a sulfonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions rather than to cross-reactivity with sulfonamide-based drugs.

Case #4

- A 37 year woman who uses injection drugs (heroin) is admitted with fever. Blood cultures grow MRSA (vancomycin MIC=1 mcg/mL), and an echocardiogram shows a 0.5 cm vegetation on the tricuspid valve. Blood cultures clear after 5 days, and the patient completes a 6 week course of vancomycin. Five days after discharge, the patient is readmitted with fever and IDU. Blood cultures are positive for MRSA with a vancomycin MIC=2 mcg/mL and a daptomycin MIC=0.5 mcg/mL.

Case #4: What antibiotic would you choose?

1. Re-treat with vancomycin
2. Vancomycin and gentamicin
3. Daptomycin
4. Tigecycline
5. Linezolid
6. Quinupristin/dalfopristin (Synercid)

Case #4 continued


- You start daptomycin, and blood cultures clear after 3 days. An echocardiogram is unchanged. Cardiothoracic Surgery is reluctant to do a valve replacement given active IDU, and the patient does not have heart failure. With encouragement, the patient completes 6 weeks of antibiotics. Four days after discharge, the patient is re-admitted with fever. Blood cultures grow MRSA with a vancomycin MIC=4 mcg/mL and a daptomycin MIC=8 mcg/mL . Isolate is fluoroquinolone resistant.

Case #4 continued: What would you do next?

1. Daptomycin 15 mg/kg daily
2. Ceftaroline fosamil
3. Vancomycin + rifampin
4. Daptomycin + rifampin
5. Ciprofloxacin + rifampin
6. Indefinite oral suppression with linezolid

Ceftaroline fosamil

- Prodrug is converted to active drug ceftaroline
- Approved for complicated skin and skin structure infections and community acquired pneumonia
- Broad-spectrum cephalosporin with enhanced activity against Gram positives including MRSA, penicillin resistant pneumococcus, and *Enterococcus faecalis* (including vancomycin resistant)
- Not active against ESBL-producing, AmpC producing, or non-fermenting Gram negative rods (e.g. *Pseudomonas*); also limited anaerobic activity



Ceftaroline for MRSA bacteremia

- 74% clinical success rate in case series of 31 patients, including 9 with endocarditis
 - Watch for eosinophilic pneumonia



Polenakovik and Pleiman, Int J Antimicrob Agents 2013 (epub)

Case #5

- An 88 year-old man is admitted from a skilled nursing facility to a New York City hospital. He was recently hospitalized with diverticulitis. The patient is hypotensive and febrile, and a GI source of infection is suspected. Blood cultures grow Gram negative rods, subsequently speciated as *Klebsiella pneumoniae*. The microbiology lab reports the organism as a carbapenemase producer. Of the antibiotics for which the lab reports susceptibilities, the isolate is only susceptible to gentamicin.

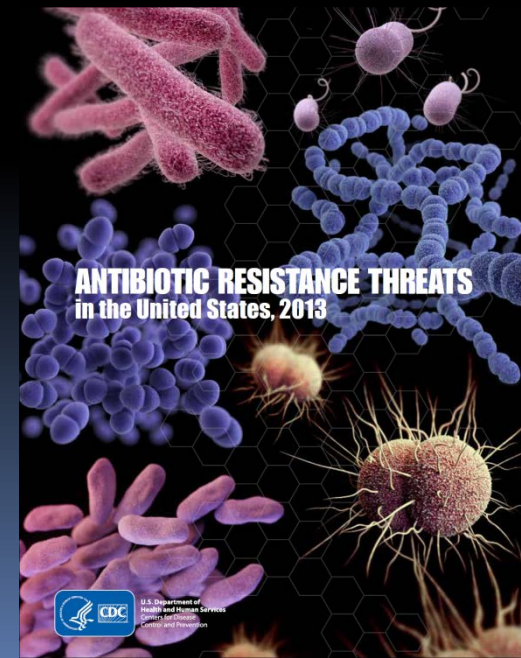
Case #5: What antibiotic regimen would you use?

1. Gentamicin
2. Colistin (polymyxin E)
3. Gentamicin plus colistin
4. Colistin plus tigecycline plus meropenem
5. Continuous infusion of doripenem

Top 3 threats based on antimicrobial resistance

- Carbapenem-resistant Enterobacteriaceae
- *Clostridium difficile*
- Drug resistant *Neisseria gonorrhoeae*

<http://www.cdc.gov/drugresistance/threat-report-2013/>





CARBAPENEM-RESISTANT ENTEROBACTERIACEAE



9,000 DRUG-RESISTANT INFECTIONS PER YEAR



600 DEATHS

CARBAPENEM-RESISTANT *KLEBSIELLA* SPP.

7,900



1,400

CARBAPENEM-RESISTANT *E. COLI*

THREAT LEVEL
URGENT



This bacteria is an immediate public health threat that requires urgent and aggressive action.



CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS



Carbapenem-resistant Enterobacteriaceae (CRE)

- CRE are difficult to treat and mortality rates may reach 40-50% with serious infections
- Production of carbapenemases is the most important mechanism of resistance
 - In the U.S., *Klebsiella pneumoniae* carbapenemase (KPC) is the most common – prevalence highest in the Northeast
 - Worldwide, metallo-beta-lactamases (VIM, NDM, IMP) are emerging and are also reported in the U.S.

Carbapenem-resistant Enterobacteriaceae (CRE)

- National Healthcare Safety Network data 2009-2010: of organisms reported from central-line associated bloodstream infections and catheter-associated urinary tract infections
 - 13% *Klebsiella* species not susceptible
 - 2% *E. coli* not susceptible
- Prevention – special measures
 - Screening – especially for contacts
 - Contact precautions, cohorting

Predictors of Mortality in Bloodstream
Infections Caused by *Klebsiella pneumoniae*
Carbapenemase–Producing *K. pneumoniae*:
Importance of Combination Therapy

- 3 large Italian teaching hospitals
- 125 patients with bloodstream infections due to KPC-producing *K. pneumoniae*
- Mortality with monotherapy compared with combination therapy 54% vs. 31%
- Lowest mortality in group treated with colistin, tigecycline, and meropenem 12.5% (low numbers)

Case #6

- After treatment for carbapenem-resistant *K. pneumoniae*, your patient in case #5 recovers and is discharged to a skilled nursing facility. Several days after discharge, he is readmitted with fever, WBC=18K, and loose stools. Stool testing for *Clostridium difficile* toxin is positive. Knowing the literature for selecting initial therapy for severe *C. difficile*, you elect to treat with oral vancomycin.

CLOSTRIDIUM DIFFICILE



250,000
INFECTIONS PER YEAR



14,000
DEATHS



\$1,000,000,000

IN EXCESS MEDICAL COSTS PER YEAR



THREAT LEVEL
URGENT



This bacteria is an immediate public health threat that requires urgent and aggressive action.

More Severe *C. difficile*

- Oral vancomycin probably preferred over metronidazole for severe disease (or long courses)
 - Contributing factors: age > 60, fever, low albumin, WBC > 15,000, pseudomembranous colitis, in ICU
 - Better clinical response but no difference in relapse
 - Zar et al, Clin Infect Dis 2007;45(3):302-7
- Fidaxomicin?

Fidaxomicin

- New macrocyclic antibiotic; inhibits RNA polymerase
- Narrow spectrum of activity – very specific for *C. difficile*
- Approved by the FDA in 2011
- NEJM study fidaxomicin vs. vancomycin: lower relapse rate (15% vs. 25%) but only in those without NAP₁/BI/027 strain

Louie et al, *N Engl Med* 2011;364:422-31

- Improved rates of clinical cure if taking concomitant antibiotics (90% vs. 79%) and lower rates of relapse (17% vs. 29%)

Mullane et al, *Clin Infect Dis* 2011; 53:440-47


Cost



- Vancomycin pulvules 125 mg cost ~ \$31 per pill: treatment cost \$124 per day (cost may be less in some settings)
- Fidaxomicin average wholesale price ~ \$135.00 per pill: treatment cost \$270 per day
- Metronidazole cost ~ \$.73 per pill: treatment cost \$2.19 per day

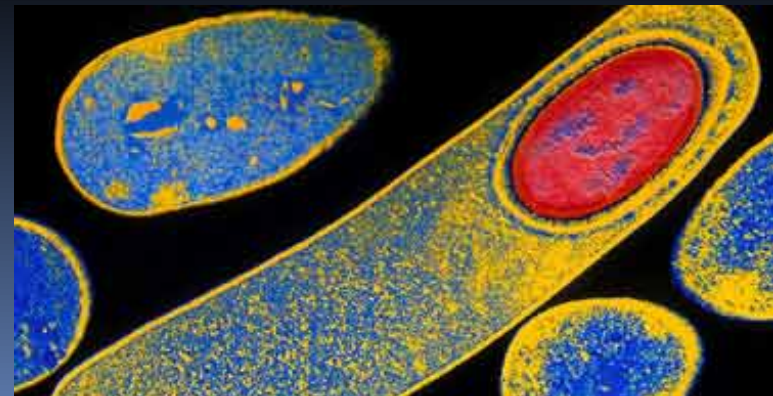


Case #6 continued

- Your patient responds well to treatment with oral vancomycin. Unfortunately, he has a relapse after therapy is complete and is re-treated with a 14-day course of vancomycin. He has a another more severe relapse after his second course of treatment and is readmitted.
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Case #6 continued: How would you treat the patient now?

1. Vancomycin – 14 day course
2. Fidaxomicin
3. Vancomycin – 14 day course at usual dose, then taper
4. Vancomycin – 14 day course, followed by rifaximin
5. Fecal bacteriotherapy



C. difficile Relapse

- Initial treatment success ~ 90% but relapse in 15-30% of cases
- After 2nd relapse, consider:
 - **Leffler and Lamont, Gastroenterol 2009;136:1899-1912**
 - Tapered / pulse dose vancomycin
 - Fidaxomicin
 - Prolonged course probiotics
 - Rifaximin, nitazoxanide, or cholestyramine chaser
 - IVIG
 - Chronic, low dose, suppressive vancomycin
 - Fecal bacteriotherapy
- Future – monoclonal antibodies against toxins A & B? **Lowy et al, New Engl J Med 2010;362:197-205**

Fidaxomicin again

- Multicenter, randomized, double blind study in Europe, Canada, and U.S.
- Fidaxomicin vs. vancomycin for 10 days
- Primary endpoint clinical cure: 87.7% vs. 86.8% in modified intention to treat population (509 patients total)
 - With severe infection, 76.2% vs. 70.5% clinical cure (NS)
- Recurrence 12.7% vs. 26.9% overall ($p < .001$)
 - 9.2% vs. 27.4% non-BI/o27 strain ($p < .001$)
 - 22.2% vs. 38% BI/o27 strain (NS)

“Stool Transplant”

- AKA intestinal microbiota transplantation (IMT)
- Results reported for more than 300 patients
- IMT given by enema, colonoscope, or nasojejunal (NJ) tube in most
- Majority received stool donation from a family member, spouse/partner
- Normal saline most commonly used to prepare suspension
 - About half given immediately
- Success rate > 90% - some received more than one infusion

Gough et al, Clin Infect Dis 2011;53:994-1002

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Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

- Study in Netherlands of patients with at least one relapse of *C. difficile* (median 3)
- Randomized (open label) to infusion of donor feces through a nasoduodenal tube after initial treatment vs. vancomycin vs. vancomycin with bowel lavage
- Stopped early – 13/16 (81%) patients in stool group had resolution; other 3 had resolution after 2nd infusion
- Resolution rate (combined) without stool infusion 27%