New Antibiotics

Mark H. Sawyer, MD
UCSD School of Medicine
Rady Children’s Hospital San Diego

Disclosures

- I have no financial relationships to disclose or Conflicts of Interest to resolve.
- I will discuss the off label use antibiotics in children

Objectives

- Summarize the scope of our antibiotic resistance problem
- List some new antibiotics to treat MRSA, VRE, ceftriaxone-resistant Pneuococcus, resistant GNR
- Explain the options for treating recurrent C. difficile colitis
- Respond to cues from the microbiology lab
- List common class-specific antibiotic side effects
The Acronyms

- VISA - Vancomycin Intermediate Staph aureus (MIC 4-8 mcg/ml)
- VRSA - Vancomycin Resistant Staph aureus (MIC>16 mcg/ml)
- VRE - Vancomycin Resistant Enterococcus
- ESBL - Extended Spectrum Betalactamase (inactivates ceftriaxone, cefazadime, cefepime)
- CRE - Carbapenem Resistant Enterobacteriaceae (resistant to meropenem)
- MDR - Multidrug resistant Mycobacteria
- XDR - Extensively drug resistant Mycobacteria

Estimated minimum number of illnesses and deaths caused by antibiotic resistance:

- At least 2,049,442 illnesses, 23,000 deaths
- At least 250,000 illnesses, 14,000 deaths

*Data sourced from CDC and WHO reports.*
Antibiotic Resistance Threats in the United States, 2013 CDC

Problem organisms

- Carbapenem-resistant Enterobacteriaceae (Enterobacter)
- Drug-resistant Neisseria gonorrhoeae
- Multidrug-resistant Acinetobacter
- Fluconazole-resistant Candida
- Extended–spectrum Beta-lactamase producing Enterobacteriaceae (ESBL’s)
- Vancomycin-resistant Enterococcus (VRE)
- Drug-resistant Salmonella
- MRSA
- Ceftriaxone-resistant Strep pneumoniae

Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010
18 month old with left leg cellulitis following a scrape. Mom has a history of MRSA. Prescription written for clindamycin liquid. Mom calls the next day saying he won’t take the clindamycin because it tastes so bad.

What are your options?
- Do a culture!
- TMP-SMX
- Clindamycin capsules
- Linezolid

Linezolid/Zyvox (2000)
- Linezolid=vancomycin but orally available
- Unique class-oxazolidinones/protein synthesis inhibitor/bacteriostatic
- Good for MRSA, Coag-neg Staph, VRE, PCN-resistant
  Pneumococcus. Has activity against anaerobes, Chlamydia, Mycoplasma, Mycobacteria
- Good for skin/bone infection, pneumonia
- Dose: 10 mg/kg/dose every 8h for <11yo; 600 mg q12h for older
- Comes as a suspension; $56 per tablet; $280 for 150ml (generic in 2015)
- Adverse events: neutropenia, thrombocytopenia

12 yo admitted to the hospital with osteomyelitis of the femur and septic arthritis of the hip. Blood culture positive for MRSA. Treated for 4 days with Vancomycin but she continues to have fever, leg pain, and the CRP remains significantly elevated. Organism is resistant to clindamycin.

What are your treatment options?
- Daptomycin
- Ceftaroline
- Tigecycline
- Linezolid
- Levofloxacin/moxifloxacin
Daptomycin/Cubicin (2003)
- Daptomycin = Vancomycin without the renal toxicity
- K-Ca channel disruption=rapidly bacteriocidal
- Effective for MRSA, VRE, Coag-negative Staph, penicillin-resistant
  Pneumococcus
- Good for skin/bone infections, bacteremia, abscesses, probably OK
  for meningitis
- NOT GOOD FOR PNEUMONIA-inhibited by surfactant
- Once daily dosing; no peds dosing established but use 4-6 mg/kg/d
- Adverse events: Myopathy manifested as weakness and elevated
  CPK

Ceftaroline/Teflaro (2010)
- Ceftaroline = ceftriaxone + vancomycin
- Covers MRSA, Coag-negative Staph, ceftriaxone-resistant
  Pneumococcus, Group A/B Strep, “simple GNR” (H. flu, Moraxella, E.
  coli, Klebsiella)
- Bonus coverage-some oral anaerobes
- Not good for ESBL GNR, CPE, AmpC B-lactamases
- Good for skin and soft tissue infection, pneumonia
- Could be used for UTI
- No oral form
- No unique side effects

16yo patient with cystic fibrosis now has a ruptured appendix. Intra-
abdominal cultures are now growing a ESBL Enterobacter and
meropenem-resistant Pseudomonas. The patient has fevers to 39
degrees, a WBC of 22,000 and markedly elevated CRP

What are you treatment options?
- A quinolone (Cipro/Moxifloxacin)
- Colistin
- Tigecycline
Tigecycline/Tygecil (2005)

- Tigecycline=meropenem +
- A derivative of minocycline—it is a protein synthesis inhibitor
- Good for MRSA, Coag-negative Staph, VRE, PCN-resistant Pneumococcus, ESBL GNR, anaerobes
- Good for skin/bone, intra-abdominal infections, hospital acquired infections
- Dose: no pediatric dose. Adult dose 50mg IV q12h
- Metabolized by the liver so good for patients with renal issues
- Adverse events: all cause mortality higher when this drug used alone

4 yo who develops C. difficile colitis after receiving amoxicillin for otitis media. Responded to a course of oral metronidazole but 5 days after stopping had a test-confirmed relapse with diarrhea, fever, bloody stool. Treated with oral vancomycin for 14 days but again relapsed 7 days after stopping antibiotics.

What are your treatment options?
- More vancomycin
- More metronidazole
- Fidaxomycin

Fidaxomcin/Dificid (2011)

- Fidaxomcin=?Better Vancomycin
- Narrow spectrum of activity (Clostridia spp)/minimal absorption
- More active in vitro than Vanco or metronidazole
- Less intestinal flora disruption than vancomycin
- Protein synthesis inhibitor thus reduces toxin production
- Fewer recurrences in clinical trials (8.4% vs 25.3%, p<0.001
- Dose: no specific peds dose; 200mg BID x 10 days
- Adverse events: none unique
- Cost: >$2000 per course!
Recurrent C. difficile colitis

- 15-30% of patients recur within 30 days
- No clear antibiotic drug resistance
- Repeated treatments or stool transplant are the recommended therapies
- Metronidazole/Flagyl not recommended after the first recurrence due to potential toxicity and no better efficacy
- Avoid other antibiotics when possible
- Probiotic-/Saccharomyces boulardii
- Alternative drugs: fidaxomycin, nitazoxamide, IVIG, Cholestyramine, rifampin
- Stool transplant is highly effective. Protocols on line.
- FDA using enforcement discretion

12yo with moderate right sided pneumonia with effusion. Low grade fever, slight tachypnea. Allergic to penicillins and erythromycin. Trial of oral clindamycin not helping.

What are your options?
- Doxycycline
- IV antibiotics
- A quinolone
- Which one?

Moxifloxacin/Avelox

- Quinolones have generally been tolerated in children
- Ciprofloxacin still a good drug for Gram negative infections (UTI, Salmonella)
- Moxifloxacin has better Gram positive coverage. Good for Staph aureus, Pneumococcus. Retains reasonable Gram negative coverage.
- Also good for Mycoplasma, Chlamydia, and tuberculosis
- Dose: No pediatric dose; 400mg IV or PO daily
- Adverse events: tendinopathy (very rare), ?arthropathy

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Use of Quinolones in Pediatrics

Boceprevir/Telaprevir (2011)
• Millions infected with hepatitis C; 15-30% will develop cirrhosis; 1-4% annual risk of hepatocellular carcinoma
• Most asymptomatic
• Ribavirin plus peg-interferon has 40-80% cure rates
• Boceprevir/telaprevir inhibit viral protease
• Combination of boceprevir or telaprevir plus ribavirin plus peg-interferon generally have 1.5 fold higher cure rates
• Very expensive!
• Other drugs: simeprevir, sofosbuvir approved in 2013

The micro lab called and said…..
• The urine culture is growing Serratia with an inducible beta-lactamase
  ➢ Inducible beta-lactamase (IB) simply means the organism has the potential to become resistant while on therapy.
  ➢ Uncomplicated infections (UTI, cellulitis) can still be treated with IB antibiotics
• The sputum is growing a non-fermenting GNR
  ➢ Think Pseudomonas
• The wound culture is growing Staph aureus that is PBP2 positive
  ➢ Rapid assay for penicillin binding protein 2 associated with MRSA
• The urine is growing Enterococcus faeceum
  ➢ E. faeceum usually resistant to ampicillin and more likely to be VRE.
Common and not so common antibiotic side effects

- Beta lactams
  - Neutropenia
  - Interstitial nephritis
- Trimethoprim-sulfamethoxazole
  - Neutropenia
  - Rash (watch for Stevens Johnson)
- Ciprofloxacin
  - Tendinopathy, arthropathy
- Vancomycin
  - Neutropenia, deafness
  - Esophagitis
- Erythromycin
  - Pyloric stenosis-use azithromycin in newborns
- ...and of course C. difficile colitis

Nafcillin to treat MRSA?!?


New directions in antibiotic therapy

- Testing and screening drugs in liquid media in the lab may not really predict how they work in people
- Some drugs that you would think would never work actually do
- Some drugs (e.g. azithromycin) augment the innate host immune response and work for infections you would never predict they would work for
Possible Future antibiotics

- Ceftolozane/tazobactam-ESBL GNR, Pseudomonas
- Ceftazidime-avibactam-ESBL GNR, Pseudomonas
- Ceftaroline-avibactam-MRSA
- Imipenem/MK-7655- ESBL GNR, Pseudomonas
- Plaxomicin (aminoglycoside)- ESBL GNR
- Brilacidin (peptide cell defense protein)-???

Summary

- Antibiotic resistance becoming a BIG problem
- Several new drugs available for resistant Gram positive organisms
- A few options for resistant Gram negative organisms
- Recurrent C. difficile is very challenging without any ideal treatment options
- Lots of new antivirals being developed