



# New Antibiotics

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## Disclosures

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

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## Objectives

- Summarize the scope of our antibiotic resistance problem
- List some new antibiotics to treat MRSA, VRE, ceftriaxone-resistant Pneucoccus, 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

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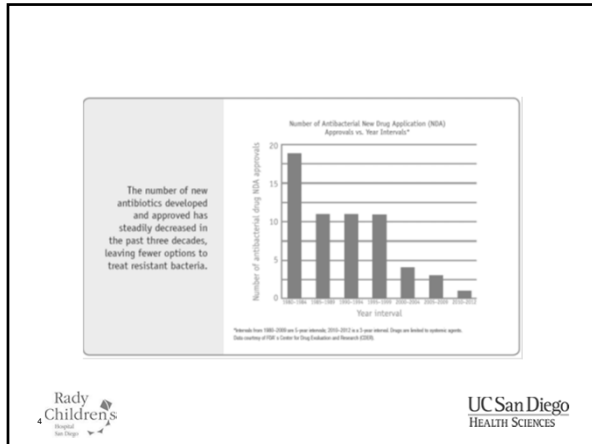
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- ### The Acronyms
- VISA-Vancomycin Intermediate Staph aureus (MIC 4-8 mcg/ml)
  - VRSA-Vancomycin Resistant Staph aureus (MIC<sub>≥</sub>16 mcg/ml)
  - VRE-Vancomycin Resistant Enterococcus
  - ESBL-Extended Spectrum Betalactamase (inactivates ceftriaxone, ceftazidime, cefepime)
  - CRE-Carbapenem Resistant Enterobacteriaceae (resistant to meropenem)
  - MDR-Multidrug resistant Mycobacteria
  - XDR-Extensively drug resistant Mycobacteria
- Rady Children's  
UC San Diego HEALTH SCIENCES

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

At least **2,049,442** illnesses,  
**23,000** deaths

\*bacteria and fungus included in this report

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least **250,000** illnesses,  
**14,000** deaths

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**HAZARD LEVEL URGENT**  
 ○○○○○○  
 These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.  
*Clostridium difficile* (*C. difficile*), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

**HAZARD LEVEL SERIOUS**  
 ○○○○○○  
 These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.  
 Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum  $\beta$ -lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumoniae*, Drug-resistant tuberculosis (MDR and XDR)

**HAZARD LEVEL CONCERNING**  
 ○○○○○○  
 These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.  
 Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

7 Antibiotic Resistance Threats in the United States, 2013 CDC  
<http://www.odc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf>

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**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*

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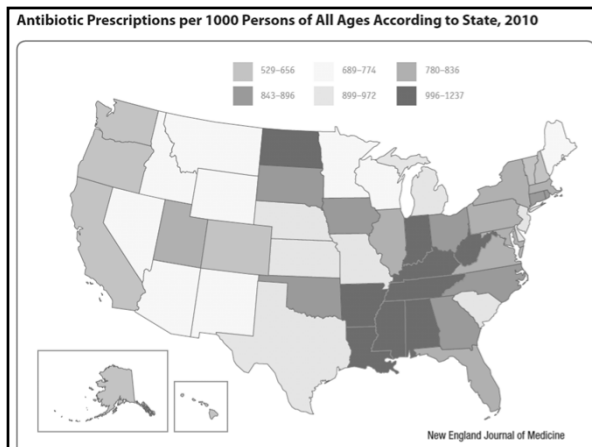
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18 month old with left leg cellulitis following a scrape. Mom has a history of MRSA. Prescription written for clindamycin liquid. Mom calls the next day saying he won't take the clindamycin because it tastes so bad.

What are your options?

- Do a culture!
- TMP-SMX
- Clindamycin capsules
- Linezolid



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### 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



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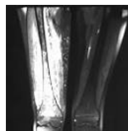
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12 yo admitted to the hospital with osteomyelitis of the femur and septic arthritis of the hip. Blood culture positive for MRSA. Treated for 4 days with Vancomycin but she continues to have fever, leg pain, and the CRP remains significantly elevated.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

What are your treatment options?

- Daptomycin
- Ceftaroline
- Tigecycline
- Linezolid
- Levofloxacin/moxifloxacin



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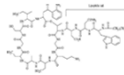
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### Daptomycin/Cubicin (2003)



- Daptomycin = Vancomycin without the renal toxicity
- K-Ca channel disruption=rapidly bacteriocidal
- Effective for MRSA, VRE, Coag-negative Staph, penicillin-reisitant 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



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### 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



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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



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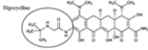
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### Tigecycline/Tygalil (2005)



- 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



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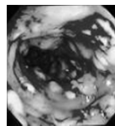
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4 yo who develops C. difficile colitis after receiving amoxicillin for otitis media. Responded to a course of oral metronidazole but 5 days after stopping had a test-confirmed relapse with diarrhea, fever, bloody stool. Treated with oral vancomycin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

What are your treatment options?

- More vancomycin
- More metronidazole
- Fidaxomicin



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### Fidaxomicin/Dificid (2011)

- Fidaxomicin=?Better Vancomycin
- Narrow spectrum of activity (Clostridia spp)/minimal absorption
- More active invitro 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!**



Scott L, Drugs 2013;73:1733-47



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## 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: fidaxomicin, nitazoxandide, IVIG, Cholestyramine, rifampin
- Stool transplant is highly effective. Protocols on line.
- FDA using enforcement discretion



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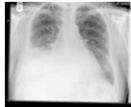
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12yo with moderate right sided pneumonia with effusion. Low grade fever, slight tachypnea. Allergic to penicillins and erythromycin. Trial of oral clindamycin not helping.

What are your options?

- > Doxycycline
- > IV antibiotics
- > A quinolone
- > Which one?



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## 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



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## Use of Quinolones in Pediatrics

TABLE 4. Most Common Infections for Which Fluoroquinolones Are Effective Therapy (See Text)

Infection	Primary Pathogen(s) <sup>a</sup>	Fluoroquinolone
Systemic antibiotic requirement <sup>b</sup>		
UTI	<i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i> <i>Enterobacter</i> species <i>Citrobacter</i> species <i>Serratia</i> species	Ciprofloxacin <sup>c</sup>
Acute otitis media, sinusitis	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>	Levofloxacin <sup>c</sup>
Pneumonia	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> (macrolides preferred for <i>Mycoplasma</i> infections)	Levofloxacin
Gastrointestinal infections	<i>Shigella</i> species <i>Stigella</i> species	Ciprofloxacin <sup>c</sup>
Topical antibiotic requirement <sup>d</sup>		
Conjunctivitis	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>	Bevofloxacin Levofloxacin Gatifloxacin Ciprofloxacin Moxifloxacin
Acute otitis externa, tympanostomy tube-associated otitis	<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> Mixed Gram-positive/Gram-negative organisms	Ofloxacin Ciprofloxacin <sup>c</sup> Ofloxacin

## 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 faecium*
  - *E. faecium* 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
- Erythromycin
  - Pyloric stenosis-use azithromycin in newborns
- ....and of course C. difficile colitis




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## Nafcillin to treat MRSA?!?

Table 1. Clinical Summary of Cases Where NM or OLA Were Added to High-Dose DAP to Clear Persistent or Relapsing MRSA Bacteremia

Age/sex	Underlying condition	Diagnostic findings	Primary source	1st-line therapy	2nd-line therapy	3rd-line therapy	4th-line therapy	Comments
1. 2yM	MCA	Neutropenia T <sub>H</sub> 2/CD4 T <sub>H</sub> 1/CD8 normal	TS	Van 10 mg/kg bid relax 10	DAP 10 10 mg/kg bid	DAP 10 + OLA 10 mg/kg bid	N/A	TRC 453 10 mg/kg 10 mg/kg or 10 mg/kg
2. 4yM	DM	DM anemia neutropenia CD4 low	Unknown	Van 10 mg/kg bid	DAP 10 + 10 mg/kg bid	DAP 10 + nap 10 mg/kg bid	Linezolid 10 mg/kg bid	Alteplase 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg
3. 6yM	DM, HTN, COPD, on steroids	TRC 453 10 mg/kg bid	Unknown	Van 10 mg/kg bid MIC 48 MIC 1 MIC 1 MIC 18 MIC 18	DAP 8 10 mg/kg bid	DAP 8 + OLA 10 mg/kg bid VAN MIC 4 DAP MIC 18	DAP 10 + nap 10 mg/kg bid 10 mg/kg	Serial CRP 10 mg/kg
4. 6yM	DM, HTN, COPD, rheumatoid	TRC 453 10 mg/kg bid	Unknown	Van 10 mg/kg bid MIC 18 MIC 18 MIC 18	DAP 8 10 mg/kg bid	DAP 8 + OLA 10 mg/kg bid VAN MIC 2 DAP MIC 18	DAP 10 + nap 10 mg/kg bid 10 mg/kg	Linezolid 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg
5. 8yM	DM, HTN, PNEUMONIA, ASTHMA, with steroids	TRC 453 10 mg/kg bid	Unknown	Van 10 mg/kg bid MIC 18 MIC 18	DAP 8 10 mg/kg bid	DAP 8 + OLA 10 mg/kg bid VAN MIC 2 DAP MIC 18	DAP 10 + nap 10 mg/kg bid 10 mg/kg	DAP 10 + nap 10 mg/kg bid 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg
6. 4yM	DM, renal failure	TRC 453 10 mg/kg bid	Unknown	Van 10 mg/kg bid	DAP 10 + 10 mg/kg bid	DAP 10 + nap 10 mg/kg bid	N/A	DAP 10 + nap 10 mg/kg bid
7. 6yM	DM, renal failure	TRC 453 10 mg/kg bid	Unknown	Van 10 mg/kg bid	DAP 8 10 mg/kg bid	DAP 8 + nap 10 mg/kg bid	N/A	Linezolid 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg 10 mg/kg

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## 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




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### 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) -???



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### 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



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