The Confusing World of Antibiotics

Alexandru Petre David MD
Infectious Diseases

February 9, 2014
THE BIG PICTURE

NEXT EXIT
Background


- 2000 – 2013 – 5 new classes:
  1. Linezolid – systemic – 2000
  2. Daptomycin – systemic 2003
  4. Fidaxomicin – 2010

Problem: antibiotic classes limited to Gram-positive infections
Background

- Pre-antibiotic era:
  - Superbugs
  - The dearth of new classes of antibiotics
  - Disengagement of pharmaceutical companies from research
Background

• **Research stimulation:**

• **US Generating Antibiotic Incentives Act** — automatic priority review and an additional 5-7 years of market exclusivity for qualified infectious disease products

• **Innovative Medicines Initiative New Drugs for Bad Bugs (IMI ND4BB)** — $280 million fund to support the clinical development of new antibiotics and conduct basic research into how antibiotics penetrate Gram-negative bacteria

• **2010 IDSA – the 10 x 20 Initiative** — to develop 10 new safe antibiotics by 2020

• **May 2013** - $200 million public-private partnership between US government Biomedical Advanced Research and Development Authority (**BARDA**) and GSK to study new drugs
Background

- 1990 – 18 large pharmaceutical companies engaged in antibiotic research

- 2013 – 4!!!

AstraZeneca – London, UK
Novartis – Basel, Switzerland
GSK – London, UK
Sanofi-Aventis – Paris, France

Pfizer – Groton, CT, USA – closed its R&D center in Connecticut in 2011
Compounds Undergoing Clinical Evaluation
Phase – III trials and NDA/MAA applications

NP and NP – derived compounds in phase – III trials:

1. **Dalbavancin/Oritavancin** – lipoglycopeptide analogs of the vancomycin / teicoplanin class designed for Gram-positive infections (DISCOVER 1 and 2 trials / SOLO I and SOLO II trials)

2. **Omadacycline** – tetracycline derivative – treatment of ABSSSi, CABP, UTIs

3. **Eravacycline** – tetracycline derivative – treatment of cIAI – broad-spectrum activity that includes bacteria with tetracycline-specific efflux and ribosomal protection

4. **Solithromycin** – semi-synthetic 2 fluoroketolide – treatment of CABP and phase-II trial for uncomplicated urogenital gonorrhea

5. **Surotomycin** – semi-synthetic daptomycin derivative evaluated by Cubist for the treatment of *C.difficile*-associated diarrhea (NAP1 strain; minor impact on *Bacteroides* spp.)
Compounds Undergoing Clinical Evaluation

Phase – III trials and NDA/MAA applications

*Synthetic compounds in phase-III trials:*

6. **Tedizolid phosphate** – oxazolidinone for the treatment of Gram-positive ABSSSi including linezolid resistant strains

7. **Delamanid** – derived from bicyclic nitroimidazole – for the treatment of MDR TB

8. **Perchlozone** – perchlorate salt – TB treatment

9. **SQ109** – ethambutol analogue – for the treatment of MDR TB

10. **Finafloxacin** – fluoroquinolone – for the treatment of inner and outer ear infections and it is in a phase-II trial for complicated UTI; improved activity at slightly acidic pH
Compounds Undergoing Clinical Evaluation

Phase – III trials and NDA/MAA applications

*Synthetic compounds in phase-III trials:*

11. *Delafloxacin* – for the treatment of ABSSSi


13. *Zabofloxacin* – treatment of acute bacterial exacerbation COPD

Compounds Undergoing Clinical Evaluation

Phase – III trials and NDA/MAA applications

*Beta-Lactam/Beta-lactamase inhibitor combinations in phase-III trials:*

15. **Ceftolozane/tazobactam** – for the treatment of cUTI; activity against MDR *Pseudomonas aeruginosa*

16. **Ceftazidime/avibactam** – for the treatment of cUTI

N.B. Avibactam is also being evaluated in phase-II and phase-I trials in combination with ceftaroline and aztreonam
Preserving Antibiotics, Rationally - NEJM

Value for human life = immeasurable

?Rough estimate – 2 to 10 years increase in life expectancy attributable to antibiotics

Worth of the current stock of antibiotics of $60 trillion to $300 trillion in US alone

*Gradual depletion:*
- Genetic mutations
- Selective pressure – antibiotics released into the environment

51 TONS of antibiotics are consumed daily in US alone

*80% agriculture and aquaculture:*
- Farms
- Food pellets fish
- Sprayed on fruit trees
- Embedded in marine paint

Non-pharmaceutical-grade antibiotics - $25 /kg – little regulation
Estimated Annual Antibiotic Use in the United States

- **Livestock**: 13,540,000 kg
- **Humans**: 3,290,000 kg
- **Aquaculture**: 150,000 kg
- **Crops**: 70,000 kg
- **Pets**: 150,000 kg
Preserving Antibiotics, Rationally - NEJM

FDA:

2005 – fluoroquinolones banned for use in poultry
2012 – issued nonbinding guidance to farmers – recommended not to use as animal-growth promoters
2013 – encouraged pharmaceutical suppliers to voluntarily remove “production” uses from labeling within 3 years

Problems:
- Growth promotion vs therapeutic purposes vs prophylaxis
- Number of veterinarians to oversight
- Food prices – estimated increase of production costs in US: from 1.2 billion to 2.5 billion/year

?Impose a user fee on the nonhuman use of antibiotics?

**Perfect fee** = calibrated to the extent of antibiotic resistance caused by each use

**Practical fee** = based on the volume of antibiotics used
Preserving Antibiotics, Rationally - NEJM

User fee:

- Better than a ban – easy to administer (manufacturing/importing stage)
- Deter low-value uses
- Revenues – reward research/education/antibiotic stewardship
- International replicability

More numbers:

A 1% reduction in the usefulness of existing antibiotics could impose costs of $600 billion to $3 trillion in lost human health
Overview
I think I need antibiotics for my col...

IT'S A VIRUS!
Mechanism of action

Cell Wall Synthesis
- Beta Lactams: Penicillins, Cephalosporins, Carbapenems, Monobactams
- Vancomycin
- Bacitracin

Folate synthesis
- Sulfonamides
- Trimethoprim

Nucleic Acid Synthesis
- DNA Gyrase: Quinolones
- RNA Polymerase: Rifampin

30S subunit
- Tetracyclines
- Aminoglycosides

50S subunit
- Macrolides
- Clindamycin
- Linezolid
- Chloramphenicol
- Streptogramins

Protein Synthesis

Cell Membrane
- Polymyxins

©2011 TheMedSchool.com
Ceftaroline

FDA indications:
- Complicated skin and skin structure infections (including cases caused by MRSA)
- Community acquired pneumonia (including cases caused by PCN-resistant *S. pneumoniae*)

“5th generation” cephalosporin

It does not have activity against Pseudomonas spp. or Acinetobacter spp. Or Gram negative anaerobes.

Active in vitro vs. hVISA, VISA and VRSA

Inactivated by Amp C and ESBL beta-lactamases

Usual dose: 600mg IV q12 hrs

Clinical data are needed to better define the role in treatment of osteomyelitis, bacteremia and infective endocarditis.
**Linezolid**

**FDA indications:**

- HCAP caused by MRSA, MSSA and *S.pneumoniae*
- CAP caused by *S.pneumoniae* and MSSA
- Infections due to vancomycin-resistant E.faecium, with or without concurrent bacteremia
- Complicated and uncomplicated skin and skin structure infection

Acceptable use: high suspicion of CA-MRSA necrotizing pneumonia

Usual dosing 600 mg twice daily

**Toxicity:**

Be aware of bone marrow suppression – usually after 2 weeks of treatment

Serootonin syndrome reported with SSRI co-administration

Optic neuritis and irreversible sensory motor polyneuropathy (usually >28 days of use)
Daptomycin

FDA indications:

Treatment of complicated skin and skin structure infections (Gram-positive microorganisms including MSSA and MRSA)
*S. Aureus* bacteremia, including those with right-sided endocarditis, caused by MSSA and MRSA

Usual dosing:
Soft tissue infection: 4mg/kg IV q24hrs
Bacteremia and endocarditis: 6mg/kg IV q24hrs
Experts recommend higher doses (up to 8-10 mg/kg q24h/d) for severe infections

Unacceptable uses:
NOT be used for pneumonia due to its inactivation by pulmonary surfactant
VRE colonization of the urine, respiratory tract, wounds, or drains

Toxicity:
Myopathy (CK ≥ 10 times ULN without symptoms or ≥ 5 times ULN with symptoms)
Eosinophilic pneumonia
Phosphomycin

FDA indications:

Treatment of uncomplicated UTIs due to *E.coli* and *E.faecalis*

Non-FDA approved uses: treatment of complicated UTI w/o bacteremia

It is a synthetic bactericidal antibiotic (wall synthesis)

Broad-spectrum including MRSA, *E.coli, Klebsiella spp, Proteus spp, Pseudomonas spp, Citrobacter spp, Enterobacter, Serratia marcescens* and VRE

Only oral formulation in US
Uncomplicated UTI: 3g PO once
Complicated UTI: 3g PO every 3 days (up to 21 days of treatment)

Antacids and foods decrease absorption

DO NOT use for severe pyelonephritis and urosepsis
Fidaxomicin

FDA indications:
C. difficile – associated infection (CDI)
Macrolide antibacterial
Dose: 200 mg twice-daily with or without food x 10 days

Adverse effects: nausea, vomiting and abdominal pain.
Rare: anemia and neutropenia (unclear association).

Clinical studies:
Rates of clinical cure were noninferior to those after treatment with vancomycin
Significantly lower rate of recurrence of C. difficile infection associated with non-North American Pulsed Field type 1 strains. (NAP-1)

Cost ~ $2600/course
# Adverse effects

## Table 185-2 Major Adverse Effects and Partial List of Drug-Drug Interactions of Antibiotics

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Major Adverse Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>Allergic and hypersensitivity reactions, including fever, rash, anaphylaxis; high intravenous doses may be associated with sodium load and edema, as well as central nervous system toxicity in patients with renal insufficiency; hepatitis (especially oxacillin)</td>
<td>Nafcillin decreases the effect of warfarin and cyclosporine; the combination of ampicillin and allopurinol is associated with a higher risk of rash; oral absorption of beta-blockers is diminished in patients taking amoxicillin or ampicillin; risk of anaphylaxis may be increased in patients taking beta-blockers</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>C difficile colitis; less often associated with allergy than penicillins; cefepime associated with mental status change in elderly patients with renal insufficiency</td>
<td>Minimal</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Seizures, especially when doses not properly adjusted for renal function; seizure risk is highest with imipenem, and lowest with meropenem; C difficile colitis</td>
<td>Decreased levels of valproic acid</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Nephrotoxicity, ototoxicity, neuromuscular blockade in critically ill patients</td>
<td>Increased risk of nephrotoxicity with use of other nephrotoxic agents, such as cyclosporine, cisplatin, NSAIDs, and vancomycin; increased ototoxicity when administered with diuretics</td>
</tr>
<tr>
<td>Sulfa drugs</td>
<td>Rash, fever, hyperkalemia, cytopenias, crystalluria (at high doses or with impaired renal function)</td>
<td>Increased anticoagulation with warfarin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Gastrointestinal upset, hepatitis, cholestatic jaundice, pancreatitis, QT interval prolongation</td>
<td>Increases the levels of many drugs by inhibiting hepatic cytochrome P450 metabolism, including cyclosporine, tacrolimus, theophylline, ergot alkaloids, carbamazepine, antihistamines, cisapride, warfarin, statins, class I antiarrhythmics, and some benzodiazepines and neuroleptics</td>
</tr>
<tr>
<td>Lincosamides (e.g., clindamycin)</td>
<td>Diarrhea, including C difficile colitis; rash</td>
<td>May potentiate the effect of warfarin</td>
</tr>
</tbody>
</table>
## Adverse effects

<table>
<thead>
<tr>
<th>Class</th>
<th>Adverse effects</th>
<th>Prevention and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td><em>C. difficile</em> colitis; tendinopathy; mental status changes; rash</td>
<td>Oral absorption inhibited by antacids, <em>ferrous sulfate</em>, <em>cimetidine</em></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Diarrhea, photosensitivity, hepatitis, pill esophagitis</td>
<td>Oral absorption inhibited by antacids, <em>ferrous sulfate</em>, calcium supplements, tube feedings</td>
</tr>
<tr>
<td>Glycopeptides (eg, vancomycin)</td>
<td>Infusion-related flushing (red person syndrome), nephrotoxicity, ototoxicity</td>
<td>Use with caution when patient taking other potentially nephrotoxic agents, such as aminoglycosides, <em>cisplatin</em>, or <em>colistin</em></td>
</tr>
<tr>
<td>Oxazolidinones (eg, linezolid)</td>
<td>Nausea, diarrhea, cytopenias, neuropathy</td>
<td>Serotonin syndrome in patients also taking selective serotonin reuptake inhibitors (SSRIs)</td>
</tr>
<tr>
<td>Lipopeptides (eg, daptomycin)</td>
<td>Gastrointestinal upset, creatine kinase elevations</td>
<td>Rhabdomyolysis in patients also taking <em>statin</em> therapy</td>
</tr>
<tr>
<td>Polymixins (eg, colistin)</td>
<td>Nephrotoxicity (20%), neuropathy (7%)</td>
<td>May potentiate neuromuscular blockade associated with aminoglycosides and curariform muscle relaxants</td>
</tr>
<tr>
<td>Polyene antifungals (amphotericin B)</td>
<td>Febrile infusion reaction (nearly universal side effect); renal tubular injury with severe potassium and magnesium wasting, metabolic acidosis, and nephrogenic diabetes insipidus; electrolyte imbalances and possibly direct cardiotoxicity may lead to life-threatening arrhythmias; cytopenias</td>
<td>Renal toxicity more common and severe with concomitant use of other nephrotoxins, such as <em>cisplatin</em> and diuretics</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>QT prolongation and hepatotoxicity possible with all azoles</td>
<td>Azoles inhibit the cytochrome P450 system, leading to extensive drug interactions, including <em>cyclosporine</em>, oral hypoglycemic agents, antiretroviral therapy, <em>phenytoin</em>, <em>rifabutin</em>, <em>rifampin</em>, theophylline, and warfarin; dose adjustment of other medications may be necessary</td>
</tr>
<tr>
<td></td>
<td>Voriconazole: transient blurring of vision (unknown mechanism)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluconazole: generally well tolerated; less hepatotoxic than other azoles because of major renal route of excretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posaconazole: gastrointestinal upset</td>
<td></td>
</tr>
</tbody>
</table>
Antimicrobial Stewardship

**Definition:**
Series of interventions to monitor and direct antimicrobial use at a health care institution providing a standard, evidence-based approach to judicious antimicrobial use.

**Goals:**
- Reduction of emergence of antimicrobial resistance
- Optimizing antimicrobial selection, dose, route, duration to maximize clinical cure
- Reduce health care costs without compromising the quality of care

**N.B.**
- Antimicrobials account for up to 20% of hospital pharmacy budgets
- It is estimated that up to 50% of antimicrobial use is inappropriate
- According to the Office of Technology Assessment antibiotics are the 2nd most commonly prescribed class of drugs in the US
Antimicrobial Stewardship

**Participants:**

Infectious diseases Physician

Clinical Pharmacist

Microbiology Laboratory

Information Technology

Hospital Administration

Pharmacy and Therapeutics Committee

Infection Control and Hospital Epidemiology Staff
Antimicrobial Stewardship

**Strategies:**

*Development of Clinical Guidelines and Education Approaches*

**Preprescription Approval**

**Postprescription Review**
- Streamlining
- Discontinuation of empiric therapy
- Dose optimization
- Parenteral to oral antimicrobial conversion
- Organism and antimicrobial mismatch
- Drug-drug interactions
- Therapeutic monitoring

**Antibiotic cycling**
“The darkest places in hell are reserved for those who maintain their neutrality in times of moral crisis”

*Dante Alighieri, The Divine Comedy*