Antimicrobials Update

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Disclosures:
Dr. Amini has no significant financial interest in any of the products or manufacturers mentioned.
Objectives

- Current state of antibiotics pipeline
- Initiatives and polices
- Neoglycosides
- Oxazolidinones
- β-lactams
- Glycopeptides
Where we are today

* Antibiotics have revolutionized human development
* Play a major role in advances in medicine and surgery
* Yet we are facing serious threats by drug-resistant bacteria today.
* WHO has identified antimicrobial resistance as 1 of 3 greatest threats to human health.
* Sir Alexander Fleming in 1943 notices that microbes can learn to resist penicillin
Era of Stunted Growth

14 classes of antibiotics were introduced for human use between 1935 and 1968; since then, 5 have been introduced.
Era of Stunted Growth

- The nature of antibiotic use
- Suboptimal approach to resistance
- Unbalanced development of new agents
- Over-regulation
- Uncertain future
10 X 20 Initiative

* IDSA sponsored initiative in 2010
* Development of 10 new systemic antibacterial drug through discovery of new drug classes as well as from existing classes of antibiotics.
* Concurrent need to advance development of improved diagnostic tests
Key Stakeholders

* Global political leaders
* Pharmaceutical and diagnostics industries
* Healthcare providers
* Policy and legal communities
* Medical and public health philanthropic organizations
* Patient advocacy groups
The Generating Antibiotic Incentives Now (GAIN) Act was signed into law by President Obama on July 9, 2012 as part of FDA Safety and Innovation ACT (FDASIA).

- Qualified Infectious Disease Product (QIDP) designation
- Incentivizes research and development of antibiotics
- Extends the length of time an approved drug is free from competition
- Clarifies regulatory pathway for new antibiotics
New generation of aminoglycosides

Plazomicin is a new agent in this class that is resistant to enzymatic inhibition

Exhibits dose-dependent bactericidal activity

Covers gram negative and gram positive bacteria

Synergistic with daptomycin and ceftobiprole against MRSA

Synergistic with cefepime, doripenem, and pip/tazo against Pseudomonas
In healthy volunteers, has shown no evidence of ototoxicity or nephrotoxicity.

Achaogen, Inc. announced on May 15, 2012 that phase II randomized trial of this agent was completed. Plazomicin was compared to levofloxacin for treatment of complicated UTI and acute pyelonephritis in adults. Results will be available later this year.
**Oxazolidinones**

- **Linezolid**– Inhibit protein synthesis (50S ribosomal subunit), bacteriostatic
- Q 12 hr or BID dosing; IV and PO
- Some resistance in MRSA and VRE
- Mild MAO inhibitor – Potential for DDI
- Adverse events
  - Thrombocytopenia – after 14 days, reversible
  - Serotonin syndrome – **do not** use with SSRIs
  - Peripheral/Optic neuropathy (long-term therapy)
Two new agents, tedizolid & radezolid, may offer advantage over linezolid.

MICs are lower for staphylococci, streptococci, and enterococci compared with linezolid.

Tedizolid is a pro-drug and binds to 23S ribosome

Active against linezolid resistant strains (MRSA strains carrying cfr gene)

Available in both oral and IV form

Phase II dose-ranging study showed 200 mg daily for 5-7 days was the lowest effective dose (compared to linezolid 600 mg BID x 10-14 days)
Tedizolid vs. Linezolid

- ESTABLISH-1 was a phase 3, randomized, double-blind, non-inferiority trial in 2010
- 6-day treatment with oral tedizolid was statistically non-inferior to a 10-day course of oral linezolid for the treatment of ABSSTI.  

  * JAMA, Feb 13, 2013;309(6):559-569

- Adverse event rates were similar for both groups with lower GI events for tedizolid. Low PLT were less than half as frequent in the tedizolid group.
- Preliminary pharmacology studies suggest the unique mode of action of tedizolid, improved PK/PD, lower doses, and lack of MAOI may translate to improved safety.
* Trius Therapeutics, Inc. announced on May 13, 2013 that it has received a Notice of Allowance from US Patent and Trademark Office.

* Combination of tedizolid with daptomycin prevents development of daptomycin non-susceptible bacterial strains. Tedizolid at concentrations much lower than its current therapeutic dose, prevents the formation of daptomycin resistant staph aureus.
* Broad-spectrum activity, proven PK/PD parameters, and established efficacy and safety of cephalosporins make this class an important part of antimicrobial armamentarium.

* However, the spread of ESBLs, KPCs, and MBLs as well as presence of chromosomal AmpC β-lactamases in gram negative bacilli has reduced the utility of this class.
New broad-spectrum cephalosporin with activity against MDR staph aureus including MRSA, VISA, and VRSA as well as gram negative respiratory pathogens

- Approved in October 2010 for CAP and SSSI
- Higher affinity for PBP2a, makes it bactericidal
- Dose: 600 mg IV Q 12 hours
- Renally eliminated and will require dosage adjustment
- Common adverse events: nausea, diarrhea, insomnia
**Ceftaroline**

**TABLE 1: CEFTAROLINE IN VITRO ACTIVITY**

<table>
<thead>
<tr>
<th>Gram-Positive Organisms</th>
<th>Gram-Negative Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Hemolytic group A and group B streptococci</td>
<td>Citrobacter koseri</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>Citrobacter freundii</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td><em>Enterobacter aerogenes</em></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td><em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td>MRSA, MSSA, VISA, VRSA</td>
<td>ESBL-negative <em>Escherichia coli</em></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td><em>Heamophilus influenza</em></td>
</tr>
<tr>
<td><em>Streptococcus dysgalactiae</em></td>
<td><em>Klebsiella oxytoca</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td><em>Klebsiella pneumonia</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td><em>Morganella morganii</em></td>
</tr>
<tr>
<td>Viridans group streptococci</td>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
</tr>
</tbody>
</table>

Adapted from reference 1.
Ceftaroline

- FOCUS 1 and 2 trials: Phase III trial comparing it to ceftriaxone for treatment of CAP
- CANVAS trials: Two Phase III, double-blind, randomized, non-inferiority trials comparing ceftaroline (600 mg every 12 hrs for 5–14 days) vs. aztreonam + vancomycin for treatment of complicated SSSI.  
  Clin Infect Dis 2010 ; 51:641-650
- Success rates similar among patients with MRSA infections (93.4 vs. 94.3%).
Avibactam

- Synthetic non-\(\beta\)-lactam, \(\beta\)-lactamase inhibitor
- Broad activity including against KPC
- Being developed in combination with ceftazidime and ceftaroline with the aim of broadening the spectra of these agents
- Ceftazidime-Avibactam is currently in phase III trial for treatment of complicated UTI and intra-abdominal infections
The addition of avibactam to ceftazidime greatly improves the activity of ceftazidime against enterobacteriacease and *pseudomonas* (by 4 fold).

It does not improve activity against *Acinetobacter* species or anaerobic bacteria.

It is renally eliminated.

Preliminary data show that the combo is as effective as standard carbapenem therapy and appears to be well tolerated.
Glycopeptide

* Telavancin
* Dalbavancin
* Oritavancin
Telavancin

- New lipoglycopeptide approved in 2009 for SSSI
- On June 21, 2013 FDA approved it for HAP/VAP when alternative treatments are not suitable
- Dual MOA: cell wall synthesis inhibition + depolarization of bacterial membranes
- Concentration dependent bactericidal activity
- Active against MRSA, VISA, and VRSA
- Dose once-daily 10 mg/kg IV
Telavancin

* Has a significant post-antibiotic effect (4-6 hours)
* Much more potent against MSSA compared to vancomycin (16 times) and oxacillin (40 times)
* Significant adverse events
  * N/V, taste disturbances,
  * Dizziness, insomnia, headaches
  * Infusion-site reactions
  * Congenital anomalies: Serum pregnancy test required
Telavancin

- Nephrotoxicity: more with underlying kidney dysfunction
- QT prolongation
- Patients with pre-existing renal impairment (CrCl < 50 ml/min) or diabetes who were treated with telavancin for HAP/VAP has increased mortality compared to vancomycin.
- Dosage adjustment for renal function (per package insert) versus discontinuing therapy should be assessed.
Dalbavancin

* Second generation, semi-synthetic lipoglycopeptide
* Active against MRSA, VISA, and VRSA

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**Comparative MIC90 (µg/ml) of selected agents and dalbavancin tested against Worldwide clinical isolates (2002)**

<table>
<thead>
<tr>
<th></th>
<th>S. aureus (1,815)</th>
<th>S. aureus (1,177)</th>
<th>β-hemolytic streptococci (234)</th>
<th>viridans group streptococci (30)</th>
<th>PCN-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbavancin</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>2</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Oxacillin</td>
<td>S</td>
<td>R</td>
<td>PCN = 0.06</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Streit, et al. DMID 2004, p137*
Dalbavancin PK Profile

Dalbavancin dosed with 1,000 mg IV on Day 1 and 500 mg IV on Day 8

- Broad tissue distribution
- Continuous cidalty
- Once weekly dosing
- Maintenance of high plasma concentration

Dorr, JAC 2005;55 Supp S2:i25; data on file
Dalbavancin

- In December 2007 FDA asked for more data
- Durata Therapeutics acquired it from Pfizer in 2009
- FDA designated it as a QIDP agent in November 2012
- Under two Phase III trials currently for the treatment of ABSSSI comparing it to vancomycin
- Preliminary data from DISCOVER I trial showed dalbavancin achieved non-inferiority at 48-72 hours after start of therapy compared to vancomycin.
- Adverse events were comparable for both groups with nausea, headache, and pruritis reported for dalbavancin most commonly.
Inhibits peptidoglycan carbohydrate chain formation by destroying the binding site (specific to oritavancin alone)

- Bactericidal, concentration-dependent PD profile
- High potency against all gram positive organisms
- Half-life = 200 hours
- Primarily metabolized by liver (renal clearance < 5 %)
- Adverse events: N/V, pruritis, ALT/AST elevation
**Oritavancin**

**Concentration-dependent killing**  
*In vitro* time-kill study with *S. aureus*

**Effect on NRS384 CA-MRSA (USA300)**
Oritavancin

High level potency against important G+ organisms

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
<th>Daptomycin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>0.06</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.06</td>
<td>1</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.06</td>
<td>1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>β streptococci</td>
<td>0.12</td>
<td>0.5</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>E. faecalis</td>
<td>0.06</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>E. faecium</td>
<td>0.06</td>
<td>&gt;16</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

US and European isolates collected between 2010-2012
SOLO I and II are two randomized controlled phase 3 trials comparing oritavancin to vancomycin for the treatment of ABSSSI due to gram positive organisms including MRSA.

- Oritavancin 1200 mg IV x one dose vs. vancomycin 1 g IV (or 15 mg/kg) Q 12 hours x 7 to 10 days
- Oritavancin was found to be non-inferior to vancomycin.
Oritavancin Phase III Clinical Studies
SOLO-I: primary efficacy (N = 954)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies
SOLO-II: primary efficacy (N = 1,005)

Non-inferiority margin of -10% was met
Oritavancin

Oritavancin Phase III Clinical Studies
Combined: primary efficacy (N = 1,959)

Non-inferiority margin of -10% was met
Oritavancin Phase III Clinical Studies
Combined MRSA: primary efficacy (N = 405)

Non-inferiority margin of -10% was met
Oritavancin

Oritavancin Phase III Clinical Studies
Adverse events including 60-day follow-up period

Favorable comparative results

<table>
<thead>
<tr>
<th></th>
<th>SOLO-I</th>
<th>SOLO-II</th>
<th>COMBINED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 954</td>
<td>N = 1,005</td>
<td>N = 1,959</td>
</tr>
<tr>
<td>ORIT VANC</td>
<td>ORIT VANC</td>
<td>ORIT VANC</td>
<td>ORIT VANC</td>
</tr>
<tr>
<td>Any AE</td>
<td>60% 64%</td>
<td>51% 50%</td>
<td>55% 57%</td>
</tr>
<tr>
<td>TEAEs</td>
<td>23% 31%</td>
<td>22% 26%</td>
<td>22% 28%</td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>4% 6%</td>
<td>4% 3%</td>
<td>4% 4%</td>
</tr>
</tbody>
</table>
Summary

Bacterial evolution is ancient and still active
We have not found an antibiotic yet to which resistance does not develop
We need a strategy that promotes research, efficient development of new agents, reduced unnecessary overuse of current antimicrobials, and limiting spread of resistant bacteria
You are the next class of drug-resistant bacteria. As human continue to abuse and overuse antibiotics, your ranks will swell. So, go out there and mutate! And remember: that which does not kill us makes us stronger!!!