Disclosure

- I do have a vested interest in or affiliation with the following companies or organizations:
  - Received a research grant from Cubist Pharmaceuticals
  - Served on advisory boards for:
    - Cubist Pharmaceuticals, Inc.
    - Theravance, Inc.
    - Melinta Therapeutics, Inc.

Objectives

**Pharmacist Objectives:**
- Describe the newest antimicrobial agents approved by the FDA
- Discuss the role of the new agents in the current treatment paradigm

**Technician Objectives:**
- Identify key considerations regarding preparation, administration, and cost of the new antimicrobials

Bad Bugs, No Drugs 10 x ‘20

- Few drugs in the pipeline for resistant pathogens
- "ESKAPE" pathogens:
  - Enterococcus faecium
  - Staphylococcus aureus
  - Klebsiella pneumoniae
  - Acinetobacter baumannii
  - Pseudomonas aeruginosa
  - Enterobacter species
- Goal is to create 10 new, safe, and effective antibiotics by 2020
- Key global leaders are needed to solve this crisis

Generating Antibiotics Incentives Now (GAIN) Act

- Passed by Congress in July 2012
- Designed to incentivize companies to develop antibiotics for "qualified infectious diseases"
  - Allows for expedited review by FDA
  - 5 extra years of market exclusivity
- Does not include any stewardship mandate to manage the usage of new antimicrobials
- No guidance or control on appropriate trial design
- Qualifying pathogen: has the potential to pose a serious threat to public health

Updated R&D Chart

- Number of new antimicrobial agents from 1983 to 2015

- Dalbavancin (Dalvance) – Approved May 2014
- Tedizolid (Sivextro) – Approved June 2014
- Oritavancin (Orbactiv) – Approved August 2014
- Ceftolozane/tazobactam (Zerbaxa) – Approved December 2014
- Ceftazidime/Avibactam (Avycaz) – Approved Feb 2015
- Isavuconazonium (Cresemba) – Approved Mar 2015

Gram-Positive Agents

- Dalbavancin
- Oritavancin
- Tedizolid

Dalbavancin (Dalvance)

- Originally developed by Vicuron, later sold to Pfizer, Durata, and now owned by Activas Therapeutics
- Lipoglycopeptide (analogue of teicoplanin)
- Concentration-dependent, bactericidal
- AUC/MIC correlates best with activity
- FDA approved indications:
  - Acute Bacterial Skin & Skin Structure Infections (ABSSSI)

What's Unique about it?

- Dual mechanism of action:
  - Inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan
  - Binds to the bacterial membrane and disrupts membrane barrier function
- Long half-life: 204 hours
- No drug interactions

Dosing

- ABSSSI recommended dose:
  - 1000 mg IV Day 1, followed by 500 mg IV Day 8
  - Severe renal impairment (CrCl < 30 ml/min)
  - 750 mg IV day 1, followed by 375 mg IV Day 8
- Hemodialysis
  - No dose adjustment necessary (< 6% removed by dialysis)
  - No adjustment for mild liver dysfunction
  - Infused over 30 minutes
  - Comes in 500mg vials: Cost ~ $4,500 for 2 dose regimen

Dalbavancin Pros and Cons

Pros:

- Once weekly dosing
- Conc-dependent, bactericidal
- Active against MDR Gram-positive pathogens
  - Minimal coverage for VRE
- No need for TDM
- No drug interactions
- No need for extended IV access (e.g., PICC)

Cons:

- High cost compared to standard therapy
- Requires a 2nd dose
- Phase 3 study underway for single dose regimen
- Limited data for other indications
- Hypersensitivity reaction? Long half-life
Oritavancin (Orbactiv)

- Originally discovered by Eli Lilly, acquired by InterMune, followed by Targanta, and later sold to The Medicines Company
- Lipoglycopeptide (analog of vancomycin)
- Concentration-dependent, bactericidal
- AUC/MIC correlates best with activity
- FDA approved indications:
  - Acute Bacterial Skin & Skin Structure Infections (ABSSSI)

What’s Unique about it?

- Three different mechanisms of action:
  - Inhibition of the transglycosylation (polymerization) step of cell wall biosynthesis
  - Inhibition of the transpeptidation (crosslinking) step of cell wall biosynthesis
  - Disruption of bacterial membrane integrity, leading to depolarization, permeabilization, and cell death
- Long half-life: 245 hours
- Contraindicated with Heparin
- Drug interaction with warfarin, also inhibits CYP1A2, 2B6, 2C9, 2C19, weak inducer of CYP3A4, 2D6

Dosing and Cost

- ABSSSI recommended dose:
  - 1200 mg IV ONCE
  - No adjustment for renal impairment
  - No data available in dialysis patients
  - No adjustment for mild or moderate hepatic impairment
  - Infused over 3 hours
  - Only compatible with D5W (1000 mL of volume)
  - Available in 400mg vials
  - Cost ~ $2,900 per dose

Oritavancin Pros and Cons

Pros:

- One dose only
- Conc-dependent, bactericidal
- Active against MDR gram-positive pathogens
- No need for TDM
- No need for extended IV access (e.g., PICC)

Cons:

- High cost compared to standard therapy
- Large volume (1 Liter)
- 3 hour infusion
- Several Drug/lab interactions
- Limited data for other indications
- Hypersensitivity reaction? Long half-life, not dialyzable

By the Numbers...

- MS DRG 602: Cellulitis w/ major complication or comorbidity
  - National average length of stay: 6.3 days
  - SMH average Medicare payment (n=25): $7,580.40
- MS DRG 603: Cellulitis w/o major complication or comorbidity
  - National average length of stay: 4.2 days
  - SMH average Medicare payment (n=112): $3,789.79
- Oritavancin and Dalbavancin Cost ~ $3,000 for one dose
- Inpatient reimbursement for drug = $0
- Not an inpatient drug!
  - May have a role in ED, observation, or outpatient infusion centers

Role in Therapy

- Try to choose only one if possible
  - Limit confusion for MDs, nurses, RPhs, and case managers
- We added to formulary for use in the outpatient infusion center ONLY with the following restrictions:
  - Infectious Disease Physicians approval
  - Patients who are not ideal candidates for oral antibiotics (e.g., doxycycline, linezolid, tedizolid) or once a day IV antibiotics
  - Key patient groups: homeless, lack of transportation, live too far away, indigent, IV drug users
- Drug assistance programs available for indigent patients
Tedizolid (Sivextro)

- Originally developed by Trius, acquired by Cubist
- Member of oxazolidinone class (similar to linezolid)
- Given as a prodrug (tedizolid phosphate), which is converted quickly by phosphatases in vivo to active form
- Free AUC/MIC correlates best with activity
- FDA approved indications:
  - Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

What’s Unique About It?

- Mechanism of action: (similar to linezolid)
  - Inhibits protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit, preventing the formation of 70S complex
  - Cross resistance with other drug classes is unlikely
  - More potent activity against MDR gram-positive pathogens allows for lower amounts of drug to be given
  - Less risk for adverse effects (limited data)
    - MAO inhibition, bone marrow effects

Dosing and Cost

- ABSSSI recommended dose:
  - 200 mg IV/PO daily for 6 days
  - No adjustment for renal dysfunction including dialysis
  - No adjustment for liver dysfunction
  - IV form is infused over 60 minutes
  - PO form can be taken with or without food
  - Available in 200 mg vials and tablets ~ $282/dose

Tedizolid Pros and Cons

**Pros**

- Once daily dosing
- Available in IV and oral formulations
- Active against MDR gram-positive pathogens
- No contraindication with serotonergic agents
- Limited Data

**Cons**

- Higher cost
- No data for other indications
- Phase 3 for HABP/VABP
- No safety data beyond 6 days
- Poorer response in the setting of neutropenia

Tedizolid Role in Therapy

We added to formulary with the following restrictions:

- Infectious disease physicians or ID pharmacist approval
- 2nd line treatment of ABSSSI when other options are not feasible
- May be beneficial in patients who would otherwise be given PO linezolid but are restricted due to drug interactions
  - e.g., Serotonergic agents
- Drug assistance program is available for outpatient therapy
  - Copay assistance and indigent care program

Gram-Negative Agents

- Ceftolazane/Tazobactam
- Ceftazidime/Avibactam
Ceftolazane/Tazobactam (Zerbaxa)
- Cubist Pharmaceuticals, a subsidiary of Merck
- Cephalosporin/Beta-Lactamase Inhibitor
- Binds to penicillin-binding proteins, resulting in an inhibition of bacterial cell wall biosynthesis
- FDA approved indications:
  - Complicated Urinary Tract Infections (cUTI), including Pyelonephritis for 7 to 14 days
  - Complicated Intra-Abdominal Infections (cIAI), in combination with metronidazole for 5 to 14 days

What's Unique About It?

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<th>% Susc</th>
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<th>% Susc</th>
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<th>% Susc</th>
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Dosing and Cost
- Standard Dosing: 1.5 (1/0.5) grams IV every 8 hours infused over 1 hour
- Renal impairment adjustments (CrCl <50 mL/min):
  - 30-50 mL/min: 750 mg IV q8h
  - 15-29 mL/min: 375 mg IV q8h
  - ESRD on HD: single loading dose of 750 mg followed by 150 mg maintenance dose q8h
- Nosocomial Pneumonia Trial: 3 grams IV q8h for 8-14d
- Available in 1.5 gram vials ~ $83/vial

TOL/TAZ Pros and Cons
**PROS**
- In vitro activity against most *P. aeruginosa*, including many carbapenem-resistant strains and some ESBL producing organisms
- Efficacy and safety data for cUTI and cIAI

**CONS**
- No clinical data for other infections (e.g., pneumonia, bacteremia)
- High cost compared to standard therapy
- Must send isolate out for susceptibility testing (E-test strips are for research use only at this time)
- Frequent dosing - three times daily dosing
- Limited anaerobic activity

Ceftazidime/Avibactam (Avycaz)
- Cerexa, Inc., a subsidiary of Actavis
- Cephalosporin/Beta-Lactamase Inhibitor
- FDA approved indications:
  - Complicated Urinary Tract Infections (cUTI), including Pyelonephritis for 7 to 14 days
  - Complicated Intra-Abdominal Infections (cIAI), in combination with metronidazole for 5 to 14 days
  - For patients who have limited or no alternative treatment options

Dosing and Cost
- Standard dose: 2.5 grams (2 g/0.5 g) IV every 8 hours infused over 2 hours
- Available in 2.5 gram vials ~ $268/vial = $804/day
What's Unique About It?

Avibactam is a beta-lactamase inhibitor active against Class A, C, and some D Beta-lactamases.

<table>
<thead>
<tr>
<th>Organism</th>
<th>N MIC50</th>
<th>MIC90</th>
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<td>Meropenem - NS</td>
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<td>S. cerevisiae</td>
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<td>Ceftazidime - NS</td>
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<tr>
<td>Meropenem - NS</td>
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<td>4</td>
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<tr>
<td>Acinetobacter spp.</td>
<td>321</td>
<td>16</td>
<td>&gt;32</td>
</tr>
</tbody>
</table>


CAZ-AVI Pros and Cons

**PROS**

- In vitro activity against most MDR Gram-negatives, including most ESBL producing and carbapenem-resistant strains.
- Efficacy and safety data for cUTI and cIAI.

**CONS**

- No clinical data for other infections (e.g., pneumonia, bacteremia).
- Higher cost compared to standard therapy.
- Must send isolate out for susceptibility testing (E-test strips are for research use only at this time).
- Frequent dosing - three times daily dosing.
- Limited anaerobic activity.

Role in Therapy

We added both to formulary with the following restrictions:

- Infectious disease physicians or ID pharmacist approval.
- 2nd line treatment of MDR Pseudomonas or Enterobacteriaceae that are:
  - Resistant to all standard β-lactams (piperacillin/tazobactam, ceftazidime, and Meropenem) and Fluoroquinolones.
  - Susceptible to CAZ-AVI or TOL/TAZ.
  - Confirmation of organism susceptibility will be via send out test until FDA approved testing is available.
- See biggest role of CAZ-AVI in CRE cases and TOL/TAZ for MDR Pseudomonas when limited options are available.

Conclusion

- New incentives from the FDA have led to a resurgence of interest in the development of antimicrobial agents.
- More studies are needed to see if they have a role in other disease states where treatment options are limited.
- Hospitals and antimicrobial stewardship programs will need to identify the optimal patient population for these new agents in order to maximize their benefit while keeping costs and resistance in check.

References

- Dalvance (Dalbavancin) prescribing information. Chicago, IL, USA: Durata Therapeutics, 2014.
- Zerbaxa (ceftolozane/tazobactam) prescribing information. Lexington, MA: Cubist Pharmaceuticals; December 2014.
The Changing Landscape of Antibiotics

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