Antibiotic Update

Ashley Gustafson, Pharm.D., BCPS
PGY-2 Critical Care Pharmacy Resident
Baptist Hospital of Miami

Disclosure

• I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Pharmacist Objectives

• Review antimicrobial resistance patterns
• Assess new antimicrobial agents and their appropriate indications
• Discuss what is new in the antimicrobial pipeline
• Explain why antimicrobial stewardship is important

Technician Objectives

• Recognize new antimicrobial agents and their appropriate use in infectious disease
• Discuss what is new in the antimicrobial pipeline
• Explain why antimicrobial stewardship is important

Antibiotic Resistance Threats

“The microbes are educated to resist penicillin …… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”

- Sir Alexander Fleming 1945

Antibiotic Resistance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Microbes</th>
<th>Humans</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. on earth</td>
<td>$5 \times 10^{11}$</td>
<td>$6 \times 10^{9}$</td>
<td>$\sim 10^{22}$</td>
</tr>
<tr>
<td>Mass, metric ton</td>
<td>$5 \times 10^{16}$</td>
<td>$3 \times 10^{9}$</td>
<td>$\sim 10^{6}$</td>
</tr>
<tr>
<td>Generation time</td>
<td>30 min</td>
<td>30 years</td>
<td>$\sim 5 \times 10^{5}$</td>
</tr>
<tr>
<td>Time on earth, years</td>
<td>$3.5 \times 10^{8}$</td>
<td>$4 \times 10^{6}$</td>
<td>$\sim 10^{5}$</td>
</tr>
</tbody>
</table>
Antibiotic Resistance

- Existed before antibiotics
- Caused by 4 general mechanisms
  - Inactivation/modification of antibiotic
  - Alteration of the target site
  - Modification of metabolic pathways to evade antibiotic effect
  - Reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing efflux
- Intrinsic in some species, acquired in others
- So common that some organisms survive on antibiotics as their carbon source
- Selected for by antibiotic pressure

Types of Resistance

<table>
<thead>
<tr>
<th>MOA</th>
<th>ESBL</th>
<th>AmpC</th>
<th>Carbapenemases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydrolyze penicillins, cephalosporins, aztreonam</td>
<td>Hydrolize narrow, broad and expanded spectrum cephalosporins and cephamycins</td>
<td>Vary in the ability to hydrolyze carbapenems and other β-lactams</td>
</tr>
<tr>
<td>Common enzymes</td>
<td>C/TX-M</td>
<td>SHV</td>
<td>TEM</td>
</tr>
<tr>
<td>Common bacteria</td>
<td>E. coli</td>
<td>K. pneumoniae</td>
<td>P. aeruginosa</td>
</tr>
<tr>
<td>Antibiotic Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Antibiotic Pressure

- How Antibiotic Resistance Happens

Antibiotic Approvals

- Antibiotic approvals chart
Government Takes Action

• FDA Safety and Innovation Act
  – GAIN Act Generating Antibiotic Incentives Now
    • Extends by 5 years the exclusivity period during certain antibiotics can be sold without generic competition
  – Qualified Infectious Disease Product (QIDP)
    • Provides incentives for the development of new antibiotics, including priority review and eligibility for the FDA’s fast track program, and a 5 year extension of exclusivity under the Hatch-Waxman Act

• Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria
  – Section 5. Improved Antibiotic Stewardship

New Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>FDA Approval</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>2010</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>2011</td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>Tedizolid</td>
<td>June 2014</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>August 2014</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>May 2014</td>
<td>Gram positive</td>
</tr>
<tr>
<td>Ceftolozane + Tazobactam</td>
<td>December 2014</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Ceftazidime + Avibactam</td>
<td>February 2015</td>
<td>Gram negative</td>
</tr>
<tr>
<td>Delafloxacin</td>
<td>Phase 3 Trials</td>
<td>Gram negative and gram positive</td>
</tr>
</tbody>
</table>

Ceftaroline (Teflaro®) 2010

<table>
<thead>
<tr>
<th>Class/MOA</th>
<th>Broad-spectrum cephalosporin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum</td>
<td>Gram positive (MRSA) and gram negative associated with skin and skin structure infections and community acquired pneumonia</td>
</tr>
<tr>
<td>Does not cover</td>
<td>Pseudomonas, Enterococcus, Acinetobacter or gram negative anaerobes</td>
</tr>
<tr>
<td>Dose</td>
<td>600mg q12h or 400mg q24h</td>
</tr>
<tr>
<td>Safety</td>
<td>In clinical trials, no adverse reactions in &gt;5% of patients</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Seroconversion from a negative to a positive direct Coombs’ test has been reported</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>No clinical drug-drug interaction studies have been conducted</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Pregnancy category B</td>
</tr>
</tbody>
</table>

Ceftaroline Publications

• Persistent Staphylococcal Bacteremia
  – After vancomycin failure, MRSA guidelines recommend combination therapy for bacteremia
  – Ceftaroline has synergistic activity with daptomycin and may be a treatment option for resistant MRSA infections
    • Induces daptomycin binding to MSSA and MRSA to a comparable degree as studies with nafcillin |
    • Sensitization to innate host defense peptide cathelicidin LL37, which could attenuate virulence of the pathogen

Fidaxomicin (Dificid®) 2011

<table>
<thead>
<tr>
<th>Class/ MOA</th>
<th>Macrolide, protein synthesis inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectrum</td>
<td>Clostridium spp. Including all types of C. difficile</td>
</tr>
<tr>
<td>Does not cover</td>
<td>Gram negative organisms, bacteroides spp., staph aureus, coagulase-negative staph, enterococcus</td>
</tr>
<tr>
<td>Dose</td>
<td>200mg tablet POBid for 10 days, with or without food</td>
</tr>
<tr>
<td>Safety</td>
<td>Most common adverse reactions: nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Acute sensitivity reactions have been reported</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Several tested, none noted</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Not approved in patients &lt;18 years of age</td>
</tr>
</tbody>
</table>

Fidaxomicin Publications

• Fidaxomicin Preserves the Intestinal Microbiome During and After Treatment of C. diff
  – Preservation of the major microbiome components with fidaxomicin versus vancomycin |
  – Reappearance of toxin in fecal filtrates observed in 28% vanco treated patients vs 14% fidaxomicin |
  – 23% vanco patients C. diff reoccurrence vs 11% fidaxocmicin reoccurrence |

• Fidaxomicin Inhibits Spore Production in C. Diff
  – Possible mechanism of reducing recurrence |
  – Compared to vanco, metronidazole, rifaximin |
  – Fidaxomicin inhibited sporulation when added to early stationary phase cells in C. diff strains, the comparator drugs did not
### Tedizolid Phosphate (SIVEXTRO™) 2014

**Class/Mode of Action (MOA):** Oxazolidinone, protein synthesis inhibitor

**Spectrum:** MSSA, MRSA, Streptococcus spp, Enterococcus faecalis

**Does not cover:** Gram negatives

**Dose:**
- 200mg once daily for 6 days (IV and PO formulations)

**Safety:**
- Peripheral and optic neuropathy, dizziness, nausea

**Drug Interactions:** None, several tested, does NOT have the labeling warning for MAOI or Serotonin toxicity

**Pharmacokinetics:**
- Oral bioavailability 91%
- t½: 12h
- 70-90% protein binding

### Tedizolid vs Linezolid

<table>
<thead>
<tr>
<th>Studies</th>
<th>Tedizolid</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing</td>
<td>200mg q24h IV or PO 5-6 days</td>
<td>600mg q12h IV or PO 5-10 days</td>
</tr>
<tr>
<td>Dose Adjustments</td>
<td>No renal/hepatic adjustments</td>
<td>No renal/hepatic adjustments</td>
</tr>
<tr>
<td>Kinetics</td>
<td>T½ = 12h</td>
<td>T½ = 6h</td>
</tr>
<tr>
<td>ESTABLISH-1 EndPoint</td>
<td>Early clinical improvement in 264/332 (79.5%)</td>
<td>Early clinical improvement in 266/335 (79.4%)</td>
</tr>
<tr>
<td>ESTABLISH-2 EndPoint</td>
<td>Early clinical improvement in 283/332 (85%)</td>
<td>Early clinical improvement in 276/334 (83%)</td>
</tr>
<tr>
<td>Serotonin Toxicity</td>
<td>0% mouse head twitch</td>
<td>4.5 x mouse head twitch at human equivalent dose, same with fluoxetine</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Phase 1 study: Day 21 possible dose and duration effect (seen at 400mg)</td>
<td>Observed with underlying hemato logical abnormalities and renal insufficiency</td>
</tr>
<tr>
<td>Platelets &lt;112k</td>
<td>2.3% patients</td>
<td>Observed with underlying hematologic abnormalities and renal insufficiency</td>
</tr>
<tr>
<td>Peripheral/optic neuropathy</td>
<td>Not tested in patients over 6 days</td>
<td>Seen in patients after 28 days of therapy</td>
</tr>
</tbody>
</table>

### Oritavancin (Orbactiv™) 2014

**Class/Mode of Action (MOA):** Lipoglycopeptide antibacterial

**Spectrum:** MSSA, MRSA, Streptococcus spp, Enterococcus faecalis

**Does not cover:** Gram negative

**Dose:**
- 1200mg single dose IV infusion over 3 hours

**Safety:**
- Headache, nausea, vomiting, diarrhea, limb and subcutaneous abscess in ~3% of patients

**Drug Interactions:**
- Nonspecific weak inducer of CYP3A4 and 2D6

**Pharmacokinetics:**
- T½: 200 hours
- 85% protein binding

### Oritavancin Study

- **Primary endpoints**
  - Early clinical improvement (FDA)
  - Both cessation of spread of erythema associated with the infection and a temperature of 37.6°C or lower
  - Post-therapy cure (EMA)

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Oritavancin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary efficacy</td>
<td>391/475 (82.3%)</td>
<td>378/479 (79.9%)</td>
</tr>
<tr>
<td>Post-therapy</td>
<td>378/457 (79.9%)</td>
<td>383/479 (80%)</td>
</tr>
<tr>
<td>Lesion reduction</td>
<td>413/475 (86.9%)</td>
<td>397/479 (82.9%)</td>
</tr>
<tr>
<td>MRSA success</td>
<td>84/104 (80.8%)</td>
<td>80/100 (80%)</td>
</tr>
</tbody>
</table>

### Dalbavancin (Dalvance™) 2014

**Class/Mode of Action (MOA):** Lipoglycopeptide antibacterial

**Spectrum:** MSSA, MRSA, Streptococcus spp including Strep. pyogenes, Strep. agalactiae and Strep. Anginosus

**Does not cover:** Gram negative

**Dose:**
- Two dose regimen:
  - 1000mg followed one week later by 500mg
  - CrCl<30mL/min dose 750mg followed by 375mg
  - Patients receiving regular hemodialysis receive full dose (administered without regard to HD time)

**Adverse Reaction:** Nausea, headache, diarrhea

**Pharmacokinetics:**
- T½: 200 hours
- 86% protein binding

### Dalbavancin Studies

- **Primary end point: Early clinical improvement**

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Dalbavancin</th>
<th>Vancomycin/Vence/linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCOVER 1</td>
<td>240/288 (83.3%)</td>
<td>233/285 (81.8%)</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>285/371 (76.8%)</td>
<td>288/368 (78.3%)</td>
</tr>
<tr>
<td>Pooled Analysis</td>
<td>352/659 (79.7%)</td>
<td>352/653 (79.8%)</td>
</tr>
<tr>
<td>MRSA Success</td>
<td>72/74 (97.3%)</td>
<td>49/50 (98%)</td>
</tr>
</tbody>
</table>
Oritavancin vs Dalbavancin

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Oritavancin</th>
<th>Dalbavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200mg one time dose</td>
<td>1000mg then one week later 500mg</td>
<td></td>
</tr>
</tbody>
</table>

Dose Adjustment
- Oritavancin: No renal/hepatic adjustments
- Dalbavancin: Renal adjustment required

Pharmacokinetic
- Oritavancin: T½ = 10.2 days, Protein binding 85%
- Dalbavancin: T½ = 8.5 days, Protein binding 93-99%

Safety
- Oritavancin: Headache, nausea, vomiting, limb and subcutaneous abscesses and diarrhea
- Dalbavancin: Nausea, headache, diarrhea

Drug Interaction
- Oritavancin: Unfractionated heparin, drugs predominaently metabolized by CYP450
- Dalbavancin: None noted

Ceftolozane/tazobactam (Zerbaxa™) 2014

Class/MOA
- Novel cephalosporin/established Beta-lactamase inhibitor combination

Spectrum
- Activity against multidrug-resistant gram negative bacilli
- Potent anti-psudomonal activity
- Tazobactam protects ceftolozane from many ESBLs and cephalosporinases

Dose / Adjustment
- Oritavancin: No renal/hepatic adjustments
- Dalbavancin: Renal adjustment required

Protein binding 85%
5% of drug recovered in urine after 7 days

T½ = 8.5 days
Protein binding 93-99%
Renal excretion 33%

Safety
- Oritavancin: Headache, nausea, constipation, hypertension, diarrhea, fever, insomnia and vomiting
- Dalbavancin: None noted

Ceftolozane/tazobactam

- Double-blind, active control study of ceftolozane/tazobactam 1000/500mg IV q8h vs levafuqin 750mg IV q24h for complicated UTI
- Non-inferiority with 10% margin
- Primary endpoint: composite of microbiological eradication and clinical cure rate at 5-9 days after end of therapy (test of cure)

Population Ceftolozane/ tazobactam Levofoxacin Difference
Microbiological modified intent to treat patients 306/398 (76.9%) 275/388 (68.4%) 8.5%
Microbiologically evaluable patient 284/341 (83.3%) 266/353 (75.4%) 8.0%
E. Coli eradication rates 90.5% 79.6% 10.9%
K. Pneumonia eradication rate 84% 61% 23.1%
P. Aeruginosa eradication rate 86% 58% 28%

Ceftolozane/tazobactam + MTZ

- Modified intention-to-treat 323/389 (83.0%) 364/417 (87.3%) -4.2%
- Clinically evaluable 259/275 (94.2%) 304/321 (94.7%) -1.0%
- E. Coli n=426 96% 95%
- K. Pneumonia n=53 100% 88%
- P. Aeruginosa n=53 100% 100%

Avibactam (NXL104)

- Novel beta-lactamase inhibitor
- Not based on beta-lactam structure
- Active against KPC-type carbapenemases
- Being studied with ceftazidime, ceftaroline (Phase II) and aztreonam (phase I)

Avibactam

Avibactam

Ceftazidime/Avibactam (Avycaz™) February 2015

Class/MOA
- Established ceftazidime Novel beta-lactamase inhibitor

Spectrum
- Gram negative infections including pseudomonas
- ESBLs and KPCs

Dose
- 2000mg/500mg IV q8h given over 2 hours

Safety / Monitoring
- Expected typical cephalosporin safety profile
Ceftazidime/Avibactam

- Intra-abdominal Infection
  - Phase II clinical trial, n= 203
  - Ceftazidime/avibactam 2gm/500mg IV q8h given with metronidazole 500mg IV q8h vs meropenem 1g IV q8h

- Complicated urinary tract infection, pyelonephritis
  - Phase II clinical trial, n= 135
  - Ceftazidime/avibactam 500mg/125mg IV q8h vs imipenem 500mg IV q6h

Population

<table>
<thead>
<tr>
<th></th>
<th>Ceftazidime/avibactam + Metronidazole</th>
<th>Meropenem</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiologically evaluable patients</td>
<td>82/86 (94.1%)</td>
<td>75/76 (93.4%)</td>
<td>-0.7%</td>
</tr>
<tr>
<td>mMITT</td>
<td>70/75 (82.5%)</td>
<td>79/89 (88.8%)</td>
<td>-6.4%</td>
</tr>
</tbody>
</table>

Population

<table>
<thead>
<tr>
<th></th>
<th>Ceftazidime/avibactam</th>
<th>Imipenem-clavulanate</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiologically evaluable patients</td>
<td>19/27 (70.4%)</td>
<td>25/35 (71.4%)</td>
<td>-1.1%</td>
</tr>
<tr>
<td>Clinically evaluable patients</td>
<td>24/28 (85.7%)</td>
<td>21/26 (80.6%)</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Delafloxacin – Phase 3

Class/MOA
Fluoroquinolone

Spectrum
Gram positive including MRSA, N. gonorrhoeae, some GNR activity

Uses/Pending Approvals
- Skin and skin structure infections vs vancomycin and linezolid
- Uncomplicated gonorrhea vs ceftriaxone

Dose
- ABSSI: Delafloxacin 300mg IV q12h vs Vanco 15mg/kg IV q12h and linezolid 600mg IV q12h
- Gonorrhea: Delafloxacin 900mg PO x1 dose vs ceftriaxone 250mg IM x1 dose

Safety
Nausea (22%), diarrhea (15%), and vomiting (13%)

Delafloxacin

In a Phase 2 trial for skin and skin structure infections, the primary endpoint of Investigators’ Global Assessment of Cure, delafloxacin was comparable to vancomycin (95% Confidence Interval -30.3%, -2.3%; p=0.031)

Pipeline Antimicrobials

<table>
<thead>
<tr>
<th>Agent</th>
<th>Coverage</th>
<th>Trial Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaroline/Avibactam</td>
<td>+ Gram + (MRSA) + Enterobacteriaceae (ESBL and KPC) + NOT pseudomona or Acinetobacter</td>
<td>Phase II</td>
</tr>
<tr>
<td>Aztreonam/Avibactam</td>
<td>+ Gram – coverage</td>
<td>Phase I</td>
</tr>
<tr>
<td>Imipenem/Clavulanate/Relbeactam</td>
<td>+ Gram + similar to imipenem + Enterobacteriaceae (ESBL and KPC) + Anaerobes</td>
<td>Phase II, Phase II planned for 2015</td>
</tr>
<tr>
<td>Meropenem/MPX7009</td>
<td>+ ESBL and KPC</td>
<td>Phase III</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>+ Semisynthetic aminoglycoside + KPC and metallo-beta lactamases + Moderate Pseudomonas activity</td>
<td>Phase II UTI Phase III superiority study for CRE</td>
</tr>
<tr>
<td>Betalacine</td>
<td>+ Novel antibiotic + Gram + (MRSA, Enterococcus faecium) + Gram – (CRE)</td>
<td>Phase II</td>
</tr>
<tr>
<td>Sulithromycin</td>
<td>+ Fluoroquinolide antibiotic + Gram + (MRSA, S. pneumoniae) + Atypicals and gonorrhea</td>
<td>Phase III</td>
</tr>
<tr>
<td>Eravacycline</td>
<td>+ Tetracycline, similar to tigecycline + MRSA, VRE, CRE, Anaerobes</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Antimicrobial Stewardship

- Pharmacist Role
  - Ensure all orders have a
    - Dose
    - Duration
    - Indication
  - Obtain cultures before starting antibiotics
  - Take an “antibiotic timeout” reassessing antibiotics after 48-72 hours

Fighting Back Against Antibiotic Resistance

- Preventing infections, preventing spread
- Tracking resistance patterns
- Improving use of antibiotics
- Developing new antibiotics and diagnostic tests
True/False Questions

• Ceftaroline covers the same bacteria as ceftriaxone but adds on coverage for MRSA

• Linezolid and tedizolid are both in the oxazolidinone class and have contraindications for MAOI and serotonin toxicity

• Delafloxacin is a new fluoroquinolone that has better gram negative coverage than ciprofloxacin

References