Role of New Antimicrobials From a Stewardship Perspective: Focus on Ceftaroline, Telavancin, and Fidaxomicin
Christopher M. Bland, Pharm.D., BCPS
Critical Care Pharmacist/ID Specialist
Dwight D. Eisenhower Army Medical Center
Augusta, GA
Adjunct Assistant Professor
University of Georgia College of Pharmacy

Objectives
- Highlight the available data on the new antimicrobials ceftaroline, telavancin and fidaxomicin.
- Explain advantages and disadvantages of ceftaroline, telavancin and fidaxomicin.
- Formulate a perspective on the utility of ceftaroline, telavancin and fidaxomicin in current clinical practice.
- Identify the areas of research needed to expand the evidence based use of ceftaroline, telavancin and fidaxomicin.

What is Antimicrobial Stewardship?
"Antimicrobial stewardship includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost."


Sobering Reality
- Industry is withdrawing from anti-infective research due to lack of financial return
- MRSA, ESBL, and KPC organisms are increasing worldwide
- 70 years after introduction of Penicillin, facing bacteria that have no active antimicrobials

2008 Hospital Drug Expenses

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>2008 Expenditures ($ Thousands)</th>
<th>% Change from 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplastics</td>
<td>3,344,742</td>
<td>5.0</td>
</tr>
<tr>
<td>Hemostatic modifiers</td>
<td>3,459,980</td>
<td>6.6</td>
</tr>
<tr>
<td>Antiinfectives, systemic</td>
<td>3,188,596</td>
<td>7.3</td>
</tr>
<tr>
<td>Blood growth factors</td>
<td>2,196,040</td>
<td>–9.6</td>
</tr>
<tr>
<td>Hospital solutions</td>
<td>1,697,024</td>
<td>17.5</td>
</tr>
</tbody>
</table>

**Antibacterial Approvals by FDA**

Approved by the US Food and Drug Administration (FDA), 1983-2007

**Antibiotic Development 10 X "20 Initiative**

Telavancin

- "Hybrid" of Vancomycin/Daptomycin (Lipoglycopeptide)
- Binds to both cell wall and cell membrane
- Gram-positive only agent
- In-vitro activity vs. VISA, Linezolid-resistant *S. aureus,* and daptomycin-nonsusceptible *S. aureus*
- Bactericidal versus *S. aureus* and Enterococcal species
- In-vitro synergy with rifampin/gentamicin

**Telavancin–PK/PD**

- Only given IV over at least 60 minutes to limit infusion–related reactions
- Distributes well into ELF and macrophages
- Linear up to 12.5mg/kg QD healthy volunteers
- Postantibiotic effect of 1–4h for *S. aureus*
- T1/2 = 8–12 hours
- 76% renal excretion (adjust for Clcr ≤ 50ml/min)
- Normal dose: 10mg/kg IV once daily

Telavancin—Monitoring Pearls
- Acute kidney injury more than comparators
- Infusion-related reactions
- Coagulation testing interference (PT/INR/aPTT)
- Pregnancy Category C (test required prior to giving)
- QTc monitoring due to potential for prolongation

Telavancin—cSSTI Demographics
- Mean age of 49 yo
- All adults 18 yo or older
- 60% male; 78% caucasian
- 38% BMI > 30
- Mean duration of therapy: 9d vs 10d
- 3% concurrent bacteremia
- 25% DM
- Primarily abscesses, cellulitis, and wound infection
- Abscesses were drained; More than 2 failure
- 53% of S. aureus isolates were MRSA

Telavancin—Clinical Trials—cSSTI
- Two parallel randomized, double blind Phase III noninferiority trials (ATLAS)
- 1897 patients randomized with 1489 available for primary endpoint
- Patients received telavancin 1gq IV QD or vancomycin 1g IV q12h (dose adjustment permitted)
- Primary endpoint= Clinical response at test of cure (7–14d post end of therapy)
- Adverse effects monitored and reported

Telavancin—Clinical Trials—cSSTI
- Non-inferior to vancomycin for MRSA cSSIs and nosocomial pneumonia
- Role in significantly ill patients unknown
- Bacteremia/Endocarditis role? (Phase II–2006?)
- C-III recommendation for vancomycin/daptomycin resistant/nonsusceptible S. aureus complicated bacteremia

Telavancin—Efficacy

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Proportion of patients (%)</th>
<th>Difference in cure rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>25/27 (94.4)</td>
<td>22/29 (79.3)               1.1 (1.1 to 2.1)**</td>
</tr>
<tr>
<td>MSSA</td>
<td>15/17 (88.2)</td>
<td>21/25 (84.0)               0.1 (0.1 to 1.1)</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>15/17 (88.2)</td>
<td>21/25 (84.0)               0.1 (0.1 to 1.1)</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>12/13 (92.3)</td>
<td>17/18 (94.7)               0.1 (0.0 to 0.2)</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>11/11 (100.0)</td>
<td>18/18 (100.0)              0.0 (0.0 to 0.0)</td>
</tr>
</tbody>
</table>

NOTE: All percentages were calculated relative to the number of patients with known outcomes.
** For the difference in the proportion of patients who were cured between the telavancin treatment arm and the vancomycin treatment arm for the proportion of patients with known outcomes.

Telavancin—Efficacy by Pathogen

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Proportion of patients (%)</th>
<th>Difference in cure rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>25/27 (94.4)</td>
<td>22/29 (79.3)               1.1 (1.1 to 2.1)**</td>
</tr>
<tr>
<td>MSSA</td>
<td>15/17 (88.2)</td>
<td>21/25 (84.0)               0.1 (0.1 to 1.1)</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>15/17 (88.2)</td>
<td>21/25 (84.0)               0.1 (0.1 to 1.1)</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>12/13 (92.3)</td>
<td>17/18 (94.7)               0.1 (0.0 to 0.2)</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>11/11 (100.0)</td>
<td>18/18 (100.0)              0.0 (0.0 to 0.0)</td>
</tr>
</tbody>
</table>

NOTE: All percentages were calculated relative to the number of patients with known outcomes.
** For the difference in the proportion of patients who were cured between the telavancin treatment arm and the vancomycin treatment arm for the proportion of patients with known outcomes.

Liu C et al. CID 2011; 1-38.
Clinicaltrials.gov
Telavancin-cSSTI—Adverse Effects

- 8% (Tela) vs. 6% (Vanc) discontinued therapy for an adverse event
- Similar adverse effects except mild nausea, vomiting, taste disturbances, and foamy urine more common in telavancin group
- Renal dysfunction more common in Telavancin group (3% vs. 1%)
- Most AKI resolved or "was resolving" at the end of follow-up

Telavancin—Hospital—Acquired Pneumonia

- Randomized, double-blind, multicenter international noninferiority trial (ATTAIN 1 & 2)
- Telavancin 10mg/kg IV QD compared to vancomycin 1g IV q12h for 7–21 days
- 1503 treated patients with 654 available for clinical evaluation
- Primary efficacy endpoint—clinical response at follow-up (test of cure) in the all-treated and clinically evaluable populations
- Piperacillin/Tazobactam or Aztreonam could be added for gram-negative coverage
- Adverse effects also monitored

Telavancin—Efficacy Results

| Study | Telavancin group % | Vancomycin group % | Treatment difference % of patients | Clavulanate | Piperacillin/Tazobactam or Aztreonam | Clavulanate
|-------|--------------------|---------------------|------------------------------------|-------------|--------------------------------------|-------------
| AF    | 13.0 (74/572)      | 12.3 (74/596)       | -0.7 (-74/572)                     | 9/74        | 12/74                                | 9/74        |
| OR    | 14.8 (21/137)      | 13.9 (21/151)       | -0.9 (-21/137)                     | 2/21        | 1/21                                 | 2/21        |
| MUL   | 14.3 (53/371)      | 13.9 (53/383)       | -0.4 (-53/371)                     | 1/53        | 1/53                                 | 1/53        |

Telavancin—Hospital—Acquired Pneumonia: Demographics

- Mean age=62
- Approximately 65% Male
- 70% Caucasian
- 25% COPD
- 34% CrCl ≤ 50ml/min
- Mean APACHE score=15
- 6% concurrent bacteremia
- 63% multilobar pneumonia
- 60% of S. aureus isolates MRSA

Telavancin—HAP: Results continued

- Many not clinically evaluable due to isolation of just a GNR, response indeterminate or missing, or received potentially effective MRSA therapy
- Number of patients not switched to semisynthetic PCN not specified
- How patients with Cr <50 ml/min adjusted not specified...
- Most patients vancomycin troughs were in 5–15 mcg/mL range (Many MICs of 1.0)
- Mortality higher in telavancin group (21.5% vs. 16.6%) p=NS

Telavancin—HAP—Adverse Effects

- Overall comparable in both groups
- Most common AE leading to discontinuation was AKI (telavancin) and septic shock (vancomycin) in about 1% of patients
- AKI occurred in 16% of telavancin patients and 10% of vancomycin patients
- Hypokalemia, anemia, and LAE abnormalities common in both groups
- No differences in QTc prolongation (2% both groups)


Telavancin—HAP—Conclusion

- Telavancin noninferior to vancomycin for tx of HAP due to S. aureus
- Higher cure rates achieved in S. aureus isolates with vancomycin MICs ≥1 mcg/mL (p=0.03 NS)
- Higher mortality overall for telavancin but not statistically significant
- Acute kidney injury major toxicity of concern
- Stewardship opportunity...Approx 100 patients in study had inadequate GNR therapy
- FDA has asked for more information about this data so no indication for HAP has been granted

Telavancin—Osteomyelitis

- Case series of four patients with vancomycin treatment failures for MRSA osteomyelitis
- Telavancin was given as salvage osteomyelitis for those patients with appropriate incision, drainage, and debridement
- All four patients responded but one patient had to stop therapy due to AKI (SCr=2.5 with eosinophiluria)

Twila JD et al. JAC 2011; Aug (online).

Telavancin—Advantages

- Dual mechanism of action (potential for less induction of resistance)
- Once daily dosing makes OPAT an option
- In vitro activity versus MDR gram positives such as hVISA, VISA, linezolid-resistant MRSA and dapt resistant MRSA
- No oral dosage form

Telavancin—Disadvantages

- Decreased efficacy versus vancomycin for cSSTIs in renal insufficient patients
- Increased incidence of AKI vs. vancomycin in both cSSTI and HAP trials
- Interference with coagulation tests
- Not dependable activity vs. VRE
- No indication for HAP
**Telavancin—Future Research**

- MRSA bacteremia
- Synergy studies
- Obesity dosing
- Pediatric Data
- Long-term outcomes in patients with AKI
- More data in bone/joint infections
- Pharmacoeconomic Studies regarding length of stay
- Dosing in Hemodialysis patients

**Telavancin—Formulary Positioning**

- Not a first-line agent over vancomycin for cSSTI
- Potential use for MRSA pneumonia in patient’s with higher vancomycin MICs (where is the linezolid data?!)  
- Long-term safety data including AKI will limit broad use in sicker populations
- Likely restricted to infectious diseases for allergy/intolerances/resistance to standard therapies

---

**Ceftaroline**

- Only available beta-lactam with MRSA activity
- Binds to PBP 2a in MRSA
- Gram positive and some gram negative activity
- Bactericidal activity vs. strep and staph species
- Post antibiotic effect 1–7 hours for MRSA
- In-vitro activity vs. the following:
  - hVISA
  - VISA
  - VRSA
  - Highly–resistant *S. pneumoniae* (including cepharaxone–resistant strains)

**Ceftaroline—Pharmacokinetics/Dynamics**

- In vitro has time-dependent killing (T>MIC)
- Administered over one hour as a prodrug (ceftaroline fosamil)
- In-vitro models offer no advantage of q8h vs. q12h dosing
- T1/2: 2.6 hours
- Normal dosing: 600mg IV q12h
- Decreased dosing for Clcr ≤50ml/min
- No oral dosage form available

---

**Ceftaroline: Complicated skin/skin structure infections**

- Randomized, multicenter, double-blind noninferior studies (CANVAS 1 & 2)
- 1378 patients combined received either ceftarline 600mg IV q12h or vancomycin plus aztreonam
- Primary Endpoint: Clinical cure rate in both clinically evaluable and microbiologically evaluable populations
- Adverse effects also monitored and reported

---

**Ceftaroline—cSSTI**

- No differences in baseline characteristics
- 64% male; 74% caucasian
- 33% BMI > 30
- Average duration of therapy 8 days
- 4% concurrent bacteremia (only 9 MRSA)
- 1.7% DM
- Primarily cellulitis, major abscesses, and infected wounds
- No diabetic foot infections
- All abscesses received appropriate I & D
- 39.8% *S. aureus* isolates were MRSA

---

### Ceftaroline–Efficacy Results

#### Table 4. Clinical Core Rates by Analysis Population at the Test-of-Cure Visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Case rate, no. of patients enrolled</th>
<th>No. of patients evaluable</th>
<th>Clinical cure at 8–15 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftaroline</td>
<td>641-50</td>
<td>605</td>
<td>96.9%</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>641-50</td>
<td>600</td>
<td>89.4%</td>
</tr>
</tbody>
</table>

#### Core Data


- Pruritis more common in vancomycin arm (8.2% vs. 3.5%)
- Two cases of *C. difficile* in ceftaroline versus one case in vancomycin/aztreonam group

### Ceftaroline–cSSTI–Tolerability

- Allergic reaction most common reason for discontinuation in both groups
- Diarrhea more common ceftaroline (4.9% vs. 3.8%)
- Pruritis more common in vancomycin arm (8.2% vs. 3.5%)
- Two cases of *C. difficile* in ceftaroline versus one case in vancomycin/aztreonam group

### Ceftaroline–Community–Acquired Pneumonia (CAP)

- Two randomized, double-blinded, multicenter trials in PORT III/IV CAP hospitalized patients (FOCUS 1 & 2)
- Ceftaroline 1gm IV QD for 5–7 days or ceftaroline 600mg IV q12h
- North American pts received clarithromycin 500mg BID for 24 hours
- OPAT or step-down therapy not permitted
- Primary endpoint: Clinical cure at test of cure (day 8–15)

### Ceftaroline–Efficacy by Pathogen

#### Table 5. Clinical Core Rates for Selected Baseline Isolates at the Test-of-Cure Visit

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftaroline</th>
<th>Vancomycin</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>20/20 (%)</td>
<td>10/10 (%)</td>
<td>10/10 (%)</td>
</tr>
<tr>
<td><em>MRSA</em></td>
<td>19/19 (%)</td>
<td>9/9 (%)</td>
<td>10/10 (%)</td>
</tr>
<tr>
<td><em>N. gonorrhoeae</em></td>
<td>1/1 (%)</td>
<td>1/1 (%)</td>
<td>0/0 (%)</td>
</tr>
<tr>
<td><em>B. fragilis</em></td>
<td>1/1 (%)</td>
<td>1/1 (%)</td>
<td>0/0 (%)</td>
</tr>
</tbody>
</table>

### Ceftaroline–CAP

- 18 yo or older
- 93% Caucasian; 63% male
- 25% with structural lung disease
- 4% bacteremic
- Notable exclusions
  - *MRSA*
  - *Clcr* ≤ 30 ml/min
  - HIV
  - Positive Legionella urinary antigen
  - Empyema
  - Admission to ICU at baseline (PORT V)

### Ceftaroline–Efficacy Results


- Notable exclusions
  - MRSA
  - Clcr ≤ 30 ml/min
  - HIV
  - Positive Legionella urinary antigen
  - Empyema
  - Admission to ICU at baseline (PORT V)
Ceftaroline—Efficacy by Pathogen

Similar between two groups
Overall well tolerated
Ceftaroline: Diarrhea, Headache, Insomnia
Ceftriaxone: Diarrhea, Hypertension, Hypokalemia
Five total patients d/c therapy due to AE
Ceftaroline: Sudden death (1); Vomiting/Fatigue (1)
Ceftriaxone: Hepatic Failure (2); Increased liver enzymes (1)

Ceftaroline—Advantages
- Beta-lactam with MRSA coverage
- Good efficacy vs. *Streptococcus pneumoniae*, including MDRSP
- Activity vs. many MDR gram positive organisms including ceftriaxone resistant Strep species as well as dapti-resistant *S. aureus*
- Cephalosporin class associated with excellent safety

Ceftaroline—Disadvantages
- No clinical data for MRSA infections outside of cSSTI
- BID dosing not ideal for OPAT
- Bacteremia data lacking
- Gram negative coverage
- Severe PCN hypersensitivity not candidates
- Potential collateral damage similar to 3rd generation cephalosporins including *C. difficile*

Ceftaroline—Future Research
- MRSA pneumonia
- MRSA bacteremia including salvage
- Comparison versus FQ for pneumonia
- Pediatric efficacy
- Long-term safety data
- Efficacy/Safety in severe renal insufficiency
- Bone and Joint Infections
- Dosing in Obesity
- Synergy studies

Ceftaroline—Formulary Positioning
- Not a first-line therapy for CAP or cSSTI at most institutions
- May be useful in institutions with high FQ/ceftriaxone S. pneumo resistance
- In institutions with high usage of daptomycin, linezolid, telavancin or tigecycline for cSSTIs, may be reasonable alternative due to lower acquisition cost ($80/day)
- Most institutions likely a niche’ medication with restrictions to infectious diseases
Fidaxomicin—Pharmacology

- 18-membered macrocyclic antibiotic
- Binds to RNA polymerase to inhibit protein synthesis
- Gram positive activity only
- Bactericidal versus *Clostridium difficile*
- Postantibiotic effect of 6–10 hours
- No cross-resistance with other classes


Fidaxomicin—Pharmacokinetics

- Absorption: Extremely low
- Metabolism: Active metabolite (OP–1118) via intestinal enzymes/gastric hydrolysis
- Excretion: Primarily feces with mean concentrations of 1433 mcg/g at 400mg/d dosing
- No significant renal excretion


Fidaxomicin—Phase III Trials

- Two randomized, DB, multicentered noninferior trials (n=1105 ITT population)
- Vancomycin 125mg PO Q6h vs. Fidaxomicin 200mg PO BID for confirmed *C. difficile* infection
- Primary endpoint: Clinical Cure at day 10 of *C. difficile* therapy
- Secondary endpoint: Sustained clinical response at 28 days post end of therapy


Fidaxomicin—Patient population by the numbers in Phase III trials

- Median age=64
- 90% Caucasian
- 58% female
- 63% inpatients
- 6 BMs daily
- 84% First CDI
- 37% severe disease
- 35% B1/NAP 1 strains (that were identified)
- Toxic megacolon, hypotensive patients excluded

Table 2. Summary of Phase III Trial Results

<table>
<thead>
<tr>
<th>Efficacy with continued antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. difficile</em> cure rates compared in patients continuing antibiotic therapy</td>
</tr>
<tr>
<td>Both vancomycin and fidaxomicin had decreased cure rates compared to stopping antimicrobials</td>
</tr>
<tr>
<td>Overall cure rates were 90% and 79% for fidax and vanc groups respectively</td>
</tr>
<tr>
<td>Recurrence rates were 17% vs. 29% for fidax and vanc groups</td>
</tr>
</tbody>
</table>

**Fidaxomicin—Advantages**

- Excellent safety profile
- Low systemic exposure
- Lack of cross-resistance to other agents
- Similar efficacy compared to vancomycin
- Decreased recurrence compared to vancomycin for first episodes of *C. difficile*
- BID dosing compared to QID dosing

**Fidaxomicin—Disadvantages**

- Cost: $2800/10–day course
- Cost comparisons are needed on per patient basis (vancomycin suspension/pulvules/etc.)
- Lacks data in severe disease complicated by toxic megacolon, sepsis, etc.
- Confirmation of Insurance Coverage Crucial (Infection Control Issue)
- Dosage form for pseudoobstruction/obstruction

**Fidaxomicin—Future research**

- Efficacy data versus vancomycin plus metronidazole for severe disease
- Sustained responses in patients with multiple recurrences??
- Efficacy in fulminant disease
- Combination with vancomycin?
- Partial/Complete Obstruction
- Macrolide allergies??
- Pharmacoeconomic Analyses
- Pediatric Data

**Fidaxomicin—Formulary Positioning**

- Noninferior to vancomycin for clinical cure of first episodes of *C. difficile* infection including severe disease
- Superior to vancomycin for recurrence in patients with no previous *C. difficile* infection with overall NNT=10 to prevent one recurrence
- No more effective than vancomycin for B1/NAP 1 strains
- Cost will limit use as first–line agent

**Conclusion**

- Pharmacists involved in antimicrobial stewardship must stay current in the literature involving new antimicrobials
- Stewardship involves using the overall most effective therapy that will consume the lowest overall healthcare cost
- Pharmacoeconomic analyses are becoming more crucial in helping determine overall benefit of antimicrobial therapies