Infectious Disease in the Critically Ill Patient

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“New” Antibiotics: Telavancin

• Structure
  – Lipoglycopeptide
  – Synthetic derivative of vancomycin

• Mechanism
  – Inhibits cell wall synthesis
    • binds to D-Ala-D-Ala terminus of peptidoglycan in growing cell wall
    • interferes with polymerization and cross-linking
  – Disrupts bacterial membranes by depolarization
  – **Bactericidal** against MRSA, VISA, VRE and other Gram positives
  – Higher rate of **kidney failure** than vancomycin

• Parenteral, once daily dosing
  • FDA Indications
    – 2009 approved for CSSSI
    – 2013 approved for *Staph aureus* and *Streptococcus pneumonia* VAP, but only when alternative treatments are not suitable
“New” Antibiotics: Ceftaroline fosamil (Teflaro)

- Structure: Advanced generation cephalosporin
- Mechanism
  - Binds to PBPs including PBP2a and PBP2x (MRSA and MDR S. pneumoniae)
  - Bactericidal against MRSA and other Gram positive bacteria, as well as Gram negatives (limited activity against Pseudomonas spp.)
- Available only in IV formulation, q12h dosing
- FDA indications: Approved for CABP and acute bacterial skin infections (ABSSSI) 2010
- Potent in vitro activity against staph with reduced susceptibility to linezolid, vancomycin & daptomycin

New antibiotics: Tedizolid

- Structure: Oxazolidinone (like linezolid)
- Mechanism: Interacts with the bacterial 23S ribosome initiation complex to inhibit translation
- Bactericidal against Gram positive pathogens, including linezolid resistant *S aureus*
- Available as oral or iv, once daily dosing
- Phase III, double-blind non-inferiority trial
  - 200mg daily oral dose for 6 days vs 600mg BID oral linezolid for 10 days for adults with ABSSSIs
  - Key point is effectiveness of shorter treatment duration, emphasized in the GAIN act (new FDA approval process for antibiotics)

JAMA. 2013;309(6):559-569.
Table 3. Sensitivity Analyses for the Intent-to-Treat (ITT) and Clinically Evaluable at End of Treatment (CE-EOT) Analysis Sets

<table>
<thead>
<tr>
<th>Clinical Success Rate, No. (%) [95% CI]</th>
<th>Tedizolid Phosphate (n = 332)</th>
<th>Linezolid (n = 335)</th>
<th>Absolute Treatment Difference (95% CI), %</th>
</tr>
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<tbody>
<tr>
<td>Treatment response at the 48- to 72-h assessment (ITT analysis set)</td>
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<tr>
<td>≥20% Decrease in lesion area, no fever criteria</td>
<td>259 (78.0) [73.2 to 82.4]</td>
<td>255 (76.1) [71.1 to 80.6]</td>
<td>1.9 (−4.5 to 8.3)</td>
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<tr>
<td>No increase in lesion area, no fever criteria</td>
<td>289 (87.0) [83.0 to 90.5]</td>
<td>286 (85.4) [81.1 to 89.0]</td>
<td>1.6 (−3.5 to 7.0)</td>
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<tr>
<td>Sustained treatment response at the EOTa</td>
<td></td>
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<tr>
<td>ITT analysis set</td>
<td>268 (80.7) [76.1 to 84.8]</td>
<td>271 (80.9) [76.3 to 85.5]</td>
<td>−0.2 (−6.2 to 5.8)</td>
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<tr>
<td>CE-EOT analysis set</td>
<td>239 (87.5) [83.0 to 91.2] (n = 273)</td>
<td>249 (87.1) [82.6 to 90.7] (n = 288)</td>
<td>0.4 (−5.2 to 6.0)</td>
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<tr>
<td>No pain criteria (ITT analysis set)</td>
<td></td>
<td></td>
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<tr>
<td>289 (87.0) [83.0 to 90.5]</td>
<td>294 (87.8) [83.8 to 91.1]</td>
<td>−0.8 (−5.8 to 4.4)</td>
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</tr>
</tbody>
</table>

aIndeterminates and treatment failures at the 48- to 72-hour assessment were not carried forward.
Unlike linezolid
  Does not inhibit monoamine oxidase
  Preclinical data suggests no optic or peripheral neuropathy
Expected FDA approval in 2014
Other Abx in development

• Solithromycin (fluoroketolide, phase III trial recruiting)
• Dalbavancin (second-generation lipoglycopeptide, same class as vancomycin, once weekly dosing, phase III trial vs. vanc/linezolid for ABSSSI recently completed)
• Oritavancin (semi-synthetic next generation lipoglycopeptide, very long half-life, in phase III trials)

Rybak et al, Expert Opin. Pharmacother. (2013) 14(14)
Fewer antibiotics in the pipeline, increasing resistance

• IDSA “10 x ’20” initiative
  – ESKAPE pathogens
    • Enterococcus faecium
    • Staph aureus
    • Klebsiella Penumonia
    • Enterobacter spp.
  – Focus on MDR GNR
    • Important mechanisms of resistance are B-lactamases and carbapenemases
    • Enterobacteriaceae, p. aeruginosa, a. baumanii produce extended spectrum b-lactamases (ESBLs) and or carbapenemases
    • Act via enzymatic hydrolysis to break open the b-lactam ring and inactivate b-lactam antibiotics

New antibiotics: Fidaxomicin (Difcid)

- Macrolide antimicrobial
- Inhibits RNA polymerase, specifically at sigma subunit responsible for promoter recognition
- Active against Gram positive bacteria, bactericidal against *C. difficile*
- Administered 200 mg orally BID for 10 days
Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Where does Difcid fall in CDI treatment algorithm?

- Should be considered in patients with recurrent CDI with non-NAP1/BI/027 strain
- Not effective for systemic infections
- Investigational in severe or refractory CDI
- Cost of treatment $3360 (in contrast, Vancomycin is $1273, generic metronidazole $21.90)
Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection

Fecal Microbiota Transplant (FMT) takes off

- July 2013: FDA rescinds rule that FMT requires an IND for refractory CDI
- “Why I donated my stool”
  – NY Times July 6, 2013
CDC: Fungal infections linked to steroid injections

[Map showing the distribution of fungal infections across different states in the USA]
Antifungals: spinal paraspinal infections with contam methylpred

- Source of outbreak contaminated methylprednisilone acetate from a single compounding pharmacy in New England (next to a facility that processed construction debris)
- 23 states, 14,000 patients may have been exposed
- 48 died, 720 treated for persistent infections
- Recommended treatment: 3-6 months of voriconazole and amphoteracin

Exserohilum rostratum
Antifungal resistance

• Echinocandin resistance rising among *C. glabrata* isolates
  – Caspofungin, micafungin, anidulafungin
    • Generally very potent against *Candida* spp
    • First line for *C. glabrata*
  – Resistance should be suspected in patients with
    • recent exposure to echinocandins
    • candidemia that develops while on echinocandin
Empiric antifungals

- Amongst patients with intra-abdominal infection, “isolation of fungi was associated with steroid use, pulmonary disease, and a gastro-duodenal or small bowel source”
- IAI Guidelines from Surgical Infection Society/IDSA
  35. Empiric antifungal therapy for Candida is not recommended for adult and pediatric patients with community-acquired intra-abdominal infection (B-II).
  48. Antifungal therapy for patients with severe community-acquired or health care-associated infection is recommended if Candida is grown from intra-abdominal cultures (B-II).
  49. Fluconazole is an appropriate choice for treatment if Candida albicans is isolated (B-II).
  50. For fluconazole-resistant Candida species, therapy with an echinocandin (caspofungin, micafungin, or anidulafungin) is appropriate (B-III).
  51. For the critically ill patient, initial therapy with an echinocandin instead of a triazole is recommended (B-III).
  52. Because of toxicity, amphotericin B is not recommended as initial therapy (B-II).

Antifungal prophylaxis

- Meta-analysis in 2005 demonstrated >50% decrease in rate of Candida infections among surgical ICU patients who received prophylaxis...

![Figure 1. Impact of fluconazole prophylaxis on candidal infections. CI, confidence interval.](image)

Antifungal prophylaxis

• ...but no impact on mortality

Figure 2. Effect of fluconazole prophylaxis on mortality. CI, confidence interval.
Prophylactic antifungals

• IDSA Guidelines: “should be considered in critically ill patients with risk factors for candidiasis”
  – neutropenic patients
  – Stem cell transplants
  – New liver or pancreas transplants
  – ICUs with >10% rate of candidiasis

• 3 RCTS demonstrating decreased rates of fungal infection with prophylaxis, no long term effect on resistance

  Garbino et al. Int Care Med 2002;28:1708-1717
Procalcitonin: It’s not THE answer

• 1200 patients in 9 Danish ICUs randomized to standard care or procalcitonin-driven (1.0 ng/mL threshold) strategy for escalation of diagnosis, treatment
• No difference in 28-d mortality
• Procalcitonin group
  – LOS one day longer
  – Significant trend to renal failure
  – Received more broad spectrum abx overall, did not receive early appropriate abx more often

Procalcitonin: It’s not THE answer

• **Not** sufficiently accurate to consistently differentiate bacterial from viral pneumonias, or any other infection
  – 10% false negative rate in identifying bacterial superinfection of viral pneumonia
  – Insensitive to mycoplasma pneumonia
  – Uncertainty of performance in diagnosis of VAP/HAP