A local physician calls your pharmacy to ask your advice about treatment of one of his patients (an otherwise healthy individual) who has a skin infection. The MD is concerned that he cover CA-MRSA. You should recommend:

1. oral vancomycin
2. oral linezolid
3. oral clindamycin
4. oral trimethoprim/sulfamethoxazole

The most common type of vancomycin resistance encountered in hospitals is:

1. vancomycin-resistant *S. aureus*
2. vancomycin-intermediate *S. aureus*
3. vancomycin-resistant enterococci
4. vancomycin-resistant *S. epidermidis*

Which of the following is/are common side effects of vancomycin?

1. nephrotoxicity
2. ototoxicity
3. red man syndrome
4. allergic reactions
5. seizures
Agents for Gram-positive Infections
John A. Bosso, Pharm.D.

Which of the following is the most troublesome side effect of linezolid?

1. renal toxicity
2. neurologic disorders including seizures
3. blood dyscrasias including thrombocytopenia
4. diarrhea

Daptomycin should not be used for:

1. endocarditis
2. complicated skin and skin structure infections
3. pulmonary infections
4. bacteremia

IMPORTANT GRAM-POSITIVE PATHOGENS

• Staphylococcus aureus
• Coagulase-negative staphylococci
• Streptococcus pneumoniae
• Enterococci

Traditional Treatment of Gram-positive Infections

• Staphylococci - β-lactams / macrolides / tetracyclines
• S. pneumoniae - β-lactams / macrolides / tetracyclines
• Enterococci - ampicillin / aminoglycosides
Vancomycin-spectrum of activity

- Gram-positive pathogens
  - Staphylococci (including MRSA), enterococci
  - Some anaerobes (C. difficile, microaerophilic streptococci, but not B. fragilis)

Vancomycin - resistance

- Related to overuse
- That of clinical relevance mostly seen with enterococci at this time
- Decreased susceptibility in Staphylococcus aureus reported in 1997
- Resistance in S. aureus reported in 2002

Glycopeptide Resistance in S. aureus

- First clinical strain demonstrating a vancomycin-intermediate phenotype (VISA or GISA) recovered in Japan in 1996, and in the US in 1997
  - Vancomycin MIC = 6-8 µg/mL
  - So far, all clinical VISA isolates are MR
- Mechanism: produce excess non-cross-linked D-alanyl-D-alanine which captures vanco molecules
- Heterogeneous resistance isolates also exist
  - hVISA
  - Negative for VanA, B, C

Vancomycin Susceptibility Interpretive Breakpoints: Then and Now

<table>
<thead>
<tr>
<th></th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-2006</td>
<td>≤ 4</td>
<td>8 - 16</td>
<td>≥ 32</td>
</tr>
<tr>
<td>2006</td>
<td>≤ 2</td>
<td>4 - 8</td>
<td>≥ 16</td>
</tr>
</tbody>
</table>
Agents for Gram-positive Infections
John A. Bosso, Pharm.D.

Glycopeptide Resistance in *S. aureus*

- In vitro-derived strains
  - Modifications in PBP2
  - Increased cell wall thickness
  - Decreased coagulase activity
  - Appearance of novel, or increased production of, proteins with molecular masses of 35, 37, or 39 kDa
  - Decreased lysostaphin sensitivity
  - ? related to alterations in cross-link structure
  - Negative for VanA, B, C

Activity of Various Antibiotics Against VISA

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MU50 (µg/mL)</th>
<th>MI strain (µg/mL)</th>
<th>NJ strain (µg/mL)</th>
<th>MR-494 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>0.75</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>16</td>
<td>8</td>
<td>2</td>
<td>0.25</td>
</tr>
<tr>
<td>LY333328</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Amp/sulbactam</td>
<td>64</td>
<td>32</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>32</td>
<td>64</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Rifampin</td>
<td>2048</td>
<td>1024</td>
<td>2048</td>
<td>0.0075</td>
</tr>
<tr>
<td>Trovaflaxacin</td>
<td>2</td>
<td>0.5</td>
<td>1</td>
<td>0.015</td>
</tr>
<tr>
<td>Clinafloxacin</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Sivencid</td>
<td>0.5</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td>4</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>


The First Case of VRSA

- Isolated from a catheter exit site in a 40 yo with diabetes, peripheral vascular disease & chronic renal failure
- Treated with multiple course of abx including vanco for chronic foot ulcerations
- MIC>128 µg/ml
- Contained vanA and meca genes
- Susceptible to chloro, linezolid, minocycline, Q/D, tetracycline & TMP/SMX

Enterococci: Glycopeptide Resistance

- High level glycopeptide resistance
  - First isolate (*E. faecium*) recovered in France in 1986
  - MICs are usually in excess of 256 µg/mL
  - Resistance of this type is plasmid-mediated, inducible, and associated with the appearance of a new 39 kDa cytoplasmic membrane protein known as VanA

MMWR 2002 (7/5):51:565-7
Vancomycin Resistance

Vancomycin Tolerance in *S. pneumoniae*

- Absence or malfunction of *vnc* S gene which renders *S. pneumoniae* less susceptible to vancomycin
- Problem in triggering autolysis
- Mutant strains appear to be better DNA scavengers
  - Promote more antibiotic resistance
  - A community pathogen with this capability is a significant problem


Vancomycin - pharmacokinetics

- Absorption
  - Minimal oral (enhanced with AAC)
  - Painful IM
  - 50-65% intraperitoneal
- Distribution
  - Therapeutic conc. in pericardium, synovium, pleura, ascitic fluids, heart, liver, kidney
  - Poor CNS penetration (improved with inflamed meninges)
  - PPB: 30-55%

Bacterial Eradication vs AUC/MIC

Clinical Success vs AUC/MIC

<table>
<thead>
<tr>
<th>Clinical Success vs AUC/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table IV. Odds ratios for clinical success</strong></td>
</tr>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Vancomycin AUC/MIC ratio 5.50</td>
</tr>
<tr>
<td>MSSA vs. pathogen</td>
</tr>
<tr>
<td>Single-dose intravenous</td>
</tr>
<tr>
<td>Baseline serum albumin</td>
</tr>
<tr>
<td>&lt; 1 g/L</td>
</tr>
<tr>
<td>Medications (CI)</td>
</tr>
</tbody>
</table>

Vancomycin Treatment Guidelines

- **HAP/VAP**
  - ATS: 15 mg/Kg Q12H, dosage range 15-20 mg/L

- **Meningitis**
  - IDSA: 15-20 mg/L

- **Endocarditis**
  - BSAC: 1 Gm Q12H, dosage range 10-15 mg/L
  - AHA: 15 mg/Kg Q12H, dosage range 10-15 mg/L

- No evidence offered that:
  - Initial dose will produce desired trough
  - That higher troughs are more effective
  - That higher troughs are safe

Vancomycin - pharmacokinetics

- **Elimination**
  - Renal (glomerular filtration)
  - Removed by hemodialysis (9-50%)
  - Crystalline degradation products cross react with FPA (TDx assay)

- **Pharmacodynamics**
  - Cidal titers of 1:8 reportedly important with staphylococcal infections
  - PAE: 1 hr > 8 hr
  - AUC/MIC (>400) is predictive parameter

Vancomycin: Pulmonary Penetration

- **FIG. 1. Relationship between vancomycin concentrations in plasma and ELF.** Symbols: ◦, patients with ELF levels &lt; 3.4 mg/ml; ●, patients with ELF levels ≥ 3.4 mg/ml.


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Vancomycin - side effects

- Red Man Syndrome
  - Infusion rate-dependent
  - Histamine related
    - Diphenhydramine 50mg
    - Hydroxyzine 50 mg
  - Symptoms: erythema of face, neck & upper torso, pruritis, hypotension, tachycardia
- Ototoxicity and nephrotoxicity

Ototoxicity

- Incidence: 54 cases in 30+ years of use
- Definite causality: ?14 cases where other agents not described or not given
- Reversible in the vancomycin only cases
- Concentrations: range 17-62 mg/L

Nephrotoxicity

- History: ?Due to impurities in original formulation
- Incidence: 167 cases in literature (82 case reports)
- Definite causality: 3 cases where vanco monotherapy used, 18 cases where other agents not noted
- Concentrations: range >10 mg/L but no clear relationship
- Nephrotoxicity of other agents augmented?
Vancomycin Intolerance

- anaphylaxis
- rash (not red man syndrome)
- hematologic SE
- hearing loss
- ? synergistic nephrotoxicity (with amgly)
- fever

THE USE CONTROVERSY

Acceptable Uses:
1. serious infexns with β-lactam-resistant G+ organisms
2. serious G+ infexn in face of serious β-lactam allergy
3. when AAC fails metronidazole tx
4. prophylaxis for endocarditis (with hi risk procedures)
5. prophylaxis for surg implantation of prosthetic materials or devices at institutions with hi rates of MRSA +/or MRSE

Use discouraged for:
1. routine surgical prophylaxis
2. empiric tx of most febrile neutropenic patients
3. bacteremia with MRSE (only 1 + Cx)
4. use in patients without β-lactam resistant G+
5. prophylaxis for infexn of catheters or vasc grafts
6. selective GI decontamination
7. eradication of MRSA colonization
8. primary tx of AAC
9. routine prophylaxis for VLBW infants
10. routine prophylaxis in CAPD

Vancomycin Use by Country

Days of Therapy Per Person Per Year

United States
Japan
France
Australia
Finland
Austria
Canada
Italy
Germany
Taiwan
Sweden
United Kingdom
Korea
New Zealand
Czech Republic
Poland
South Africa
Argentina
Thailand

PHMPR732.gmpos.bosso.rev7.07
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THE MONITORING CONTROVERSY

1. lack of documented correlation between serum concentrations and therapeutic efficacy
2. lack of documented correlation between serum concentrations and toxicity
   a. ototoxicity
   b. nephrotoxicity

WHEN MONITORING MAY BE PRUDENT*

1. patients receiving vanco/aminogly combos
2. anephric patients undergoing hemodialysis
3. patients on unusually high doses
4. patients with rapidly changing renal function


OTHER ISSUES WITH VANCOMYCIN

• Vancomycin kills bacteria at a slower rate (than β-lactams)
• Higher mortality with vancomycin treated patients
• Independent risk factor for Gram-negative bacteremia
• Independent risk factor for VRE

Higher Vancomycin Doses: the newest Rage

• rationale is to address increasing MICs (among S. aureus) and poor penetration into some tissues
• dosing of ~15mg/kg designed to achieve trough concentrations of 15-20 mg/L
• Supporting data (in vitro or in vivo)?
Agents for Gram-positive Infections

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---

**Quinupristin/Dalfopristin**

- Referred to as streptogramins
- Derivatives of pristinamycin compounds
- RP 59500 30:70 (w/w)
  - Quinupristin RP 57669 (pristinamycin Iₐ)
  - Dalfopristin RP 54476 (pristinamycin IIₐ)
- Each component alone is bacteriostatic
- Combination is synergistic resulting in bactericidal activity against gram-positives such as *S. aureus*

**Pharmacokinetics/Pharmacodynamics**

- Most common dosage regimens: 7.5 mg/kg q 8–12 h
- Quinupristin: Cmax 2.9±0.6, T₁/₂ h = 0.9±0.1
- Dalfopristin: Cmax 7.2±1.9, T₁/₂ h = 0.7±0.4
- Both *Q* and *D* have active metabolites
- Concentration-independent once 4–5 x MIC with a long PAE

---

**Probability of Vancomycin Target Attainment (AUC/MIC Ratio > 400) in Susceptible *S. aureus* vs. GISA**


**Quinupristin/Dalfopristin (Synercid®)**

- Q/D ratio of 30:70 w/w
- MOA: Inhibits protein synthesis at two unique steps
- Each component alone is bacteriostatic
- Combination is synergistic and bactericidal against most gram-positives
Agents for Gram-positive Infections
John A. Bosso, Pharm.D.

### Quinupristin/Dalfopristin In Vitro Activity

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; µg/ml</th>
<th>Range (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S aureus</em> (MS)</td>
<td>0.6</td>
<td>0.03–16.0</td>
</tr>
<tr>
<td><em>S aureus</em> (MR)</td>
<td>0.7</td>
<td>0.03–4.0</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MS and MR</em></td>
<td>0.5</td>
<td>0.03–4.0</td>
</tr>
<tr>
<td><em>S pneumoniae</em> (<em>erythro and PCN–R</em>)</td>
<td>0.8</td>
<td>0.125–4.0</td>
</tr>
<tr>
<td><em>Streptococci spp</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>E faecium</em> (VSE, VRE)</td>
<td>1.0</td>
<td>0.25–8.0</td>
</tr>
<tr>
<td><em>E faecalis</em> (VSE, VRE)</td>
<td>0.3</td>
<td>0.25–32.0</td>
</tr>
</tbody>
</table>

*Mean weighted (MIC<sub>90</sub>)


### Quinupristin/Dalfopristin Safety

- Phlebitis: 75.1% (947 patients)
- Arthralgia-myalgia: 3%–12%
- Elevated hepatic enzymes: 2%
- Headache: 1.6%
- Nausea/vomiting: 4.6%, 2.7%
- Diarrhea: 2.7%

### ARTHRALGIAS/MYALGIAS

- **Interventions**
  - Increasing the dosing interval from q8h to q12h if the infection is under control
  - Decreasing the dose from 7.5 mg/kg to 5.0 mg/kg in hepatic insufficiency

- **Anecdotal Interventions**
  - Acetaminophen or NSAIDs first, provided there are no contraindications in the particular patient
  - Lorazepam has been used successfully in some patients
  - Stronger analgesics, including morphine, are an option if continuation of Synercid is necessary because of a lifesaving situation

### DRUG INTERACTIONS

- CYP 3A4 is significantly inhibited. In *in vitro* studies, Synercid inhibited the CYP 3A4 metabolism of cyclosporin A, midazolam, nifedipine, and terfenadine
- A dosage reduction of cyclosporin A may be necessary
- Clinical interactions with drugs metabolized by other P450 isoenzyme pathways are not expected
Quinupristin/Dalfopristin

- Indications:
  - VREF infections
  - Skin and skin structure infections
- Cost:
  - For 500 mg vial: ~$85

Quinupristin/Dalfopristin
Reconstitution/Dilution

- Supplied as 500mg vials (freeze-dried powder)
- Reconstitute with 5 ml D5W or sterile water
  - 30 min. stability
- Further dilute in 250 ml D5W (mini-bag)
  - May be further diluted (i.e., 500-750 ml) to avoid venous reactions
- DO NOT reconstitute/dilute with normal saline

Linezolid (Zyvox®)

- New synthetic class
  - MOA: inhibits protein synthesis
  - Conc-independent
- Broad spectrum Gram-positive activity
  - PO or IV

Linezolid - Mechanism of Action

Linezolid binds specifically to the 50S Ribosomal subunit and inhibits the formation of a functional initiation complex. Data on file = Pharmacia & Upjohn.
Agents for Gram-positive Infections
John A. Bosso, Pharm.D.

Linezolid Activity Against Gram-positive Organisms

<table>
<thead>
<tr>
<th>Species</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae (79)</td>
<td>1</td>
<td>1</td>
<td>0.25-2</td>
</tr>
<tr>
<td>E. faecalis (1,137)</td>
<td>2</td>
<td>4</td>
<td>1-4</td>
</tr>
<tr>
<td>E. faecium (452)</td>
<td>2</td>
<td>4</td>
<td>0.5-4</td>
</tr>
<tr>
<td>S. aureus (1,020)</td>
<td>2</td>
<td>4</td>
<td>1-4</td>
</tr>
<tr>
<td>MRSA (451)</td>
<td>2</td>
<td>4</td>
<td>1-4</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>1</td>
<td>&gt;4</td>
<td>0.5-4</td>
</tr>
</tbody>
</table>

Noskin et al. (1999) AAC 43:2059

Linezolid - pharmacokinetics

- Oral Bioavailability: 100%
- Food Effect: Slight decrease in rate, but no effect on extent of absorption
- Volume of Distribution: 40 to 50 L
- C<sub>max</sub> (steady state): 10.8 µg/mL (400 mg PO) 21.2 µg/mL (600 mg PO)
- Protein Binding: 31%
- Elimination Half-Life: 5 to 7 hours
- Clearance: total=100-200 mL/min renal 30-50 mL/min
- no dosage adjustment for renal or hepatic impairment

Linezolid - metabolism

- Partly metabolized by liver
- Not metabolized by cytochrome P450 enzymes
- Does not inhibit the activity of the major human P450 drug metabolizing enzymes

Linezolid: Adverse Effects & Drug Interactions

- The most common AE’s reported in clinical trials (incidence < 5%):
  - Headache
  - Nausea
  - Diarrhea
- Weak MAOI; avoid foods rich in tyramine and co-administration with other MAOI’s
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**Linezolid - Indications for Use**

- Vancomycin-resistant *E. faecium*
- Nosocomial pneumonia*
- Complicated skin and skin structure infections
- Uncomplicated skin and skin structure infections
- Community-acquired pneumonia*
- Not indicated for treatment of catheter-related BSI or infections with Gram-negatives

*Including concurrent bacteremia

**Linezolid: Formulations & Costs***

- **IV**
  - RTU bags, 2 mg/mL, 200 mg ($28.75), 400 mg, 600 mg ($57.50)
- **Oral**
  - Film-coated tablets, printed Linezolid, 400 mg, 600 mg
  - Bottles of 20, 100 tablets ($42.50/tab)
  - Unit dose pack, 30 tablets
  - Blisters of 10
  - Oral suspension for reconstitution, 100 mg / 5 mL bottle of 240 mL ($42.50/dose)

***AWP

**Substantially Abnormal Values for Selected Hematology Assays**

<table>
<thead>
<tr>
<th>Assay</th>
<th>WBC</th>
<th>RBC</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td></td>
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<td>Linezolid</td>
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<td></td>
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</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Daptomycin (Cubicin®)**

- Lipopeptide similar to the glycopeptides
- Active against PRSP, MRSA, VISA, VRE
- Narrow therapeutic index limits dose that can be administered safely
  - Therapeutic dose: 3 mg/kg
  - Neuromuscular toxicity (myalgia, weakness, increased creatinine phosphokinase levels) seen at 4 mg/kg q12h
- Excretion is renal, so dose reductions are necessary in patients with renal impairment

Chambers HF. Presented at the 37th Annual Meeting of the Infectious Diseases Society of America, 1999.
Daptomycin

- Rapidly bactericidal (acts on cell membrane)
  - Concentration-dependent killer
- No CYP450 drug interactions
- $t_{1/2} \sim 8.5$ hr
- 87-94% PPB
- Synergy with aminoglycosides
- MM SE not seen with 8mg/kg qd dosing

Daptomycin in vitro Activity

<table>
<thead>
<tr>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
<th>Dapto</th>
<th>Vanco</th>
<th>Q/D</th>
<th>Linezo</th>
<th>Clinda</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>&gt;32</td>
</tr>
<tr>
<td>VRE. faecalis</td>
<td>4</td>
<td>&gt;128</td>
<td>16</td>
<td>2</td>
<td>&gt;32</td>
</tr>
<tr>
<td>VRE. faecium</td>
<td>2</td>
<td>&gt;128</td>
<td>2</td>
<td>2</td>
<td>&gt;32</td>
</tr>
</tbody>
</table>


Daptomycin

- Common side effects
  - Constipation (6.2%)
  - Nausea (5.8%)
  - There is a lingering concern about muscular toxicity due to results of early trials with high/more frequent dosing
    - This does not appear to be an issue with approved dosing although PI recommends monitoring of CPK (weekly), muscle pain and weakness

Daptomycin

- Approved & marketed 2003
  - cSSSI's
  - Newest Indications
    - bacteremia & endocarditis

Agents for Gram-positive Infections
John A. Bosso, Pharm.D.
Tigecycline (Tygacil®)

- A glycyclcycline (semi-synthetic derivative of doxycycline)
- In vitro activity vs:
  - Resistant Gram-positives
  - Mycoplasma, Legionella, Ureaplasma
  - Gram-negative aerobes
  - Anaerobes
- Resistance via non-specific efflux pumps
- Approved for tx of cSSI & cIAI
  - sNDA filed for CAP (summer ’07)

Tigecycline Indications

<table>
<thead>
<tr>
<th>cSSI</th>
<th>cIAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complicated skin and skin structure infections (cSSSIs) in adults caused by susceptible strains of:</td>
<td></td>
</tr>
<tr>
<td>- E. coli</td>
<td></td>
</tr>
<tr>
<td>- E. faecalis*</td>
<td></td>
</tr>
<tr>
<td>- S. aureus (including MRSA)</td>
<td></td>
</tr>
<tr>
<td>- S. agalactiae</td>
<td></td>
</tr>
<tr>
<td>- S. anginosus group</td>
<td></td>
</tr>
<tr>
<td>- S. pyogenes</td>
<td></td>
</tr>
<tr>
<td>- B. fragilis</td>
<td></td>
</tr>
<tr>
<td>• Complicated intra-abdominal infections (cIAIs) in adults caused by susceptible strains of:</td>
<td></td>
</tr>
<tr>
<td>- C. freundii</td>
<td></td>
</tr>
<tr>
<td>- E. cloacae</td>
<td></td>
</tr>
<tr>
<td>- E. coli</td>
<td></td>
</tr>
<tr>
<td>- K. oxytoca</td>
<td></td>
</tr>
<tr>
<td>- K. pneumoniae</td>
<td></td>
</tr>
<tr>
<td>- E. faecalis*</td>
<td></td>
</tr>
<tr>
<td>- S. aureus†</td>
<td></td>
</tr>
<tr>
<td>- S. anginosus group</td>
<td></td>
</tr>
<tr>
<td>- Bacteroides group</td>
<td></td>
</tr>
<tr>
<td>- C. perfringens</td>
<td></td>
</tr>
<tr>
<td>- P. micra</td>
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</tbody>
</table>

In Vitro Activity Against Common Pathogens

<table>
<thead>
<tr>
<th>Gram-positive Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus*†</td>
</tr>
<tr>
<td>E. faecium</td>
</tr>
<tr>
<td>E. faecalis</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus anginosus group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gram-negative Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli*</td>
</tr>
<tr>
<td>K. pneumoniae*</td>
</tr>
<tr>
<td>K. oxytoca*</td>
</tr>
<tr>
<td>Citrobacter freundii*</td>
</tr>
<tr>
<td>Enterobacter cloacae*</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. fragilis group*</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
<tr>
<td>Peptostreptococcus spp.</td>
</tr>
<tr>
<td>C. perfringens*</td>
</tr>
</tbody>
</table>

*Vancomycin-susceptible isolates only.
†Methicillin-susceptible isolates only.

Clinical efficacy has been demonstrated for susceptible strains in cIAI* and cSSI†.

In Vitro Activity Against Other Pathogens

<table>
<thead>
<tr>
<th>Resistant Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellicillin-resistant S. aureus (MRSA)</td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus* (VRE)</td>
</tr>
</tbody>
</table>
  - E. faecium |
  - E. faecalis |
| Acinetobacter baumannii |

Tigecycline is not affected by gram-negative bacteria that produce ESBLs.

Clinical efficacy has been demonstrated for susceptible strains in cIAI* and cSSI†.
Agents for Gram-positive Infections
John A. Bosso, Pharm.D.

Tigecycline Pharmacology

- Linear pharmacokinetics
- $C_{\text{max}} = 0.87 \, \mu g/mL$
- $C_{\text{min}} = 0.13 \, \mu g/mL$
- $AUC_{0-24h} = 4.7 \, \mu g\cdot h/mL$
- $t_1/2 = 42$ hours
- $V_d = 639 \, L$, significant tissue uptake

Steady-State Serum Concentrations

![Steady-State Serum Concentrations](image)


Tigecycline Metabolism and Excretion

- Eliminated unchanged primarily by the biliary/fecal route
- Does not affect the activity of cytochrome P450 (CYP) isoforms
- Has a low potential for drug interactions
  - Not metabolized by and does not inhibit or induce CYP450

Excretion

![Excretion](image)

The clinical significance of pharmacokinetic parameters is unknown. Data on file, Wyeth Pharmaceuticals Inc.

Tigecycline Dosing

- **Standard dose**
  - Initial dose of 100 mg IV followed by 50 mg IV q12h
  - Indicated in patients ≥18 years of age
  - PK not altered by age, sex, or race
- **Renal impairment**
  - No dosage adjustment necessary
  - Not dialyzable
- **Hepatic impairment**
  - No dosage adjustment necessary in patients with mild to moderate impairment
  - In patients with severe hepatic impairment (Child-Pugh C), the initial dose is 100 mg IV followed by 25 mg IV q12h

Some Common Treatment-Emergent Adverse Events in Phase III Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tigecycline (N = 1415)</th>
<th>Comparator* (N = 1382)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>29.5</td>
<td>15.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.5</td>
<td>15.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12.7</td>
<td>10.8</td>
<td>0.127</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6.1</td>
<td>6.2</td>
<td>0.937</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>1.8</td>
<td>3.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Rash</td>
<td>2.4</td>
<td>4.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Infection</td>
<td>8.3</td>
<td>5.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Bilirubinemia</td>
<td>2.3</td>
<td>0.9</td>
<td>0.004</td>
</tr>
<tr>
<td>ALT</td>
<td>5.6</td>
<td>4.7</td>
<td>0.305</td>
</tr>
<tr>
<td>AST</td>
<td>4.3</td>
<td>4.4</td>
<td>0.926</td>
</tr>
</tbody>
</table>

*Vancomycin plus aztreonam (cSSSI), imipenem-cilastatin (cIAI), or linezolid (resistant pathogens).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, m-ITT = modified intention to treat.

Data on file, Wyeth Pharmaceuticals Inc.
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EXPERIMENTAL AGENTS FOR GRAM-POSITIVE INFECTIONS

Dalbavancin

- IV glycopeptide
- Long half-life (~ 8.5 d)
  - Once weekly administration
- Complicated and uncomplicated SSSIs
  - Including those with MRSA
- As of 8/04, in phase 3 trials

Oritavancin (LY333328)

- A glycopeptide
- Active vs a variety of Gram-positives including VRE
- Bactericidal, concentration-dependent
- Long PAE
- Non-renal elimination (only 3%)
- Long terminal $t_{1/2}$ ~250 hr

Oritavancin (LY333328)

- Clinical status (8/06)
- Undergoing clinical trials for:
  - Skin and skin structure infections
  - Bacteremia
- Outlicensed to InterMune
- FDA requesting additional safety data
Agents for Gram-positive Infections
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Telvancin (TD 6424)
- A glycopeptide antibiotic
- Cell wall active, blocking peptidoglycan cross-linking
- May also inhibit synthesis of phospholipids
- Bactericidal
- Concentration-dependent activity
- Currently in Phase II and III trials

Other Possibilities
- Ramoplanin
  - A glycolipodepsipeptide
  - A PO formulation targeted at prevention of VRE
  - Phase III trials
- Ketolides

Case Study - MRSA Vertebral Osteomyelitis
A 27 year old male undergoes operative decompression of L4-L5 and L-5-S1 disks and vancomycin is subsequently initiated for MRSA wound infection but discontinued due to adverse reactions. Linezolid, quinupristin-dalfopristin, Q-D/rifampin all initiated and discontinued over the next week due to adverse reactions. A core biopsy of L4-L5 (off antibiotics) revealed vertebral osteomyelitis with MRSA susceptible to prior antibiotics except rifampin.

What treatment possibilities remain?
What do you recommend?