Clostridium difficile Infection

- Gram-positive, spore-forming rod
- Obligate anaerobe
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
  - C. difficile infection (CDI, formerly CDAD)
    - Toxigenic C. difficile in stool ≠ CDI
Total Number of Cases in U.S. Hospitals


CDI Onset in Nursing Homes and the Community

Including CDI diagnosed in hospitals, nursing homes, the community, and recurrent CDI: likely over 700,000 CDI cases in US in 2010


Increasing CDI Severity

- Sherbrooke, Quebec, outbreak, 2003
  - 16.7% attributable mortality
- St. Louis, endemic, 2003
  - 5.7% attributable mortality
  - 2.2 times more likely readmitted
  - 1.6 times more likely discharged to LTCF

The “Epidemic” Strain

- Several methods of molecular typing
  - NAP1
  - BI
  - 027
- Virulence factors
  - tcdC mutation: more toxin A and B production
  - Binary toxin
- Fluoroquinolone resistance
  - New competitive advantage for old strain?

Current Pathogenesis Model for *C. difficile* Infection (CDI)

- Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic antibody response results in CDI.

Other Key Risk Factors

- Strain
  - New acquisitions that went on to develop CDI
    - NAP1: 55%
    - Non-NAP1: 29%
- Advanced age
- Severity of underlying illness
- Immune response
  - Pre-existing antibodies protective
  - Antibody response lower risk recurrent CDI
Additional Risk Factors

- Gastric acid suppression
  - Proton pump inhibitors and H2 blockers
- Immunosuppression
- Inflammatory bowel disease
- Gastrointestinal surgery
- Chemotherapy

C. difficile Diagnostics

- Critical role in:
  - C. difficile epidemiology
  - Treatment
  - Infection prevention and control
- Diagnostic test utilization also important
  - Patient selection

Diagnostics Available

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantage(s)</th>
<th>Disadvantage(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin testing</td>
<td>Rapid, simple, inexpensive</td>
<td>Least sensitive method, assay variability</td>
</tr>
<tr>
<td>Toxin Enzyme immunoassay (EIA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue culture cytotoxicity</td>
<td>More sensitive than toxin EIA, associated with outcomes</td>
<td>Labor intensive; requires 24–48 hours for a final result, special equipment</td>
</tr>
<tr>
<td>Organism identification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate dehydrogenase (GDH) EIA</td>
<td>Rapid, sensitive</td>
<td>Not specific, toxin testing required to verify diagnosis</td>
</tr>
<tr>
<td>Nucleic acid amplification tests (NAAT)</td>
<td>Rapid, sensitive, detects presence of toxin gene</td>
<td>Cost, special equipment, may be “too” sensitive</td>
</tr>
<tr>
<td>Stool culture</td>
<td>Most sensitive test available when performed appropriately</td>
<td>Confirm toxin production; labor-intensive; requires 48–96 hours for results</td>
</tr>
</tbody>
</table>
Flaws in Diagnostic Literature Interpretation

- Lack of clinical data
  - Detection of \( C. \) difficile, not diagnosis of CDI
    - Enhanced sensitivity for \( C. \) difficile detection may decrease specificity for CDI
- Focus on sensitivity and specificity
  - Not negative predictive value and positive predictive value

Types of False-Positive Tests for CDI

- Toxigenic \( C. \) difficile present but no CDI
  - Concern of more sensitive tests
    - GDH
    - NAAT
    - Culture
- Assay result positive but toxigenic \( C. \) difficile not present
  - Tests that detect non-toxigenic \( C. \) difficile
    - GDH alone
    - Culture alone
  - Function of assay performance
    - Repeat testing (Toxin EIAs)

Enhanced Sensitivity May Decrease Specificity

- Including clinically significant diarrhea with gold standard*:
  - No impact on sensitivity
  - Specificity of NAATs decreased from ~98% to ~89% (p < 0.01)
    - Positive predictive value decreased to ~60% (25% drop)

*Recovery of toxigenic \( C. \) difficile from stool
NAATs, nucleic acid amplification tests

Bristol Stool Chart

- Type 1: Normal stool
- Type 2: Soft stool
- Type 3: Medium stool
- Type 4: Hard stool
- Type 5: String mealy stool
- Type 6: Very hard or no stool
- Type 7: Entirely liquid

More Difficult After Chemotherapy

- 94 patients undergoing allogeneic HCT
  - Stool collected pre-transplant and then weekly until discharge/day 35
  - Study PCR on all stools: 37 (39%) colonized
- Clinical testing based on treating physicians
  - Clinical lab PCR: 16 (17%) positive
- All cases mild
- No CDI related adverse events
- Strongest predictors of "CDI" myeloablative conditioning and pre-transplant colonization

Diagnostic Approach after Chemotherapy

- No studies differentiate between chemotherapy-induced diarrhea and CDI
- Considerations
  - Diarrhea severity out of proportion to chemotherapeutic agent/mucositis
  - Concomitant abdominal pain
  - Assay used

CDI Treatment

- Historically two main treatments
  - Metronidazole
  - Oral vancomycin (not intravenous)
- Response rates equal until 2000
  - Initial cure in 85% to 95%
  - Recurrence in 15% to 30%
Vancomycin vs. Metronidazole for Severe CDI

- First double-blind trial of metronidazole vs. vancomycin

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>No. of patients cured/ no. of patients treated (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metronidazole</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Mild</td>
<td>37/41 (90)</td>
<td>39/40 (98)</td>
</tr>
<tr>
<td>Severe</td>
<td>29/38 (76)</td>
<td>30/31 (97)</td>
</tr>
<tr>
<td>All</td>
<td>66/79 (84)</td>
<td>69/77 (97)</td>
</tr>
</tbody>
</table>


CDI Treatment Stratified by Severity

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Leukocytosis (WBC &lt;15,000 cells/μL) or SCr level ≤1.5 times premorbid level</td>
<td>Metronidazole 500 mg 3 times per day PO for 10–14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Leukocytosis (WBC ≥15,000 cells/μL) or SCr level ≥1.5 times premorbid level</td>
<td>Vancomycin 125 mg 4 times per day PO for 10–14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500 mg 4 times per day PO or by nasogastric tube plus metronidazole 500 mg IV q 8 hrs</td>
</tr>
</tbody>
</table>


Fidaxomicin

- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram-negatives
  - Sparing of Bacteroides spp., Bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Patients with multiple recurrences were excluded

Fidaxomicin in Oncology Patients

Clinical cure: fidaxomicin 85%, vancomycin 74% (p=0.065)
Recurrence: fidaxomicin 14%, vancomycin 30% (p=0.018)
Sustained clinical response: fidaxomicin 74%; vancomycin 52% (p=0.003)

Management of Recurrent CDI

- CDI recurrence is a significant challenge
- Rates of recurrent CDI:
  - 20% after first episode
  - 45% after first recurrence
  - 65% after two or more recurrences

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>Treat as first episode according to disease severity</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Treat with oral vancomycin taper and/or pulse dosing</td>
</tr>
</tbody>
</table>

Alternative/Adjunctive Therapies

- **Probiotics**: RCTs of *Lactobacillus* and *Saccharomyces boulardii* without benefit
- **Cholesterol binders**: no better than placebo
- **Rifaximin**: “Chaser” to prevent recurrence,
  - Caveat: rapid development of resistance
- **Nitazoxanide**: non-inferior to metronidazole and vancomycin in small trials, no clear advantage
- **IVIG**: severe or recurrent, mixed results
Fecal Microbiota Therapy (FMT)

- **Theory:** Restoration of fecal flora and colonization resistance
- **First report in 1958**
- **Several recent reviews of published reports**

<table>
<thead>
<tr>
<th>Method</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscope</td>
<td>55/62 (88.7%)</td>
</tr>
<tr>
<td>Enema</td>
<td>105/110 (95.4%)</td>
</tr>
<tr>
<td>Gastric or duodenal tube</td>
<td>55/72 (76.4%)</td>
</tr>
<tr>
<td>Rectal catheter</td>
<td>44/46 (95.6%)</td>
</tr>
<tr>
<td>&gt;1 method</td>
<td>19/21 (90.5%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>6/6 (100%)</td>
</tr>
</tbody>
</table>


FMT RCT

- **At least one relapse**
- **Open label**
  - 4–5 days of vancomycin, bowel prep, FMT (duodenal tube)
  - 14 days of oral vancomycin
  - 14 days of vancomycin with bowel prep at day 4–5

<table>
<thead>
<tr>
<th>Method</th>
<th>Number prior episodes</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single infusion of feces</td>
<td>3 (1-5)</td>
<td>13/16 (81%)</td>
</tr>
<tr>
<td>Vancomycin only</td>
<td>3 (1-4)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>Vancomycin and lavage</td>
<td>2 (1-9)</td>
<td>3/13 (23%)</td>
</tr>
</tbody>
</table>


CDI Prevention in Hospitals

- **Decrease risk of transmission**
  - Rapid identification and diagnosis of patients with CDI
  - Contact precautions
    - Gloves/gowns
    - Dedicated patient equipment
  - Environment decontamination

- **Decrease risk of CDI if transmission occurs**
  - Antimicrobial stewardship

Healthcare Workers: Primary Source of Transmission

- Healthcare worker hand contamination after caring for CDI patient
  - 59% hand contamination regardless of any direct patient contact
  - No hand contamination if gloves worn

- Recent study found patients admitted to an ICU room that previously housed a CDI patient at increased risk for CDI (p=0.01)
  - 89% of new CDI cases not admitted to a CDI room


Healthcare Workers Should NOT Handle Stool With Bare Hands

Why do you put your hands in it?
You wouldn’t step in it!

Wear Gloves!!

Picture courtesy from Stuart Johnson

A-I Recommendation: Wear Gloves When Handling Stool

- Four wards randomized
- Intervention
  - Education: gloves when handling body substances (stool)
  - Gloves placed bedside
- Reduction in CDI on glove wards
  - Also colonization

A-II Recommendation: Antimicrobial Stewardship

- Reduce use of “high risk” antimicrobials
- Reduce unnecessary antimicrobial use
- Effective in outbreak and non-outbreak settings


Conclusions

- CDI incidence and severity have increased
- New diagnostics available
  - Unclear if “more sensitive” tests are better
  - Particularly problematic after chemotherapy
- Treat CDI based on severity
  - Data with limitations, but consistent with historical observations
- Prevention
  - Diagnose and isolate
  - Compliance with contact precautions

Clinical Consideration

Please consider your answer. Voting is not offered to online users.
You have the option to see polling results from the live program.

What C. difficile assay does your facility use?

A. Culture
B. Toxin EIA
C. Cytotoxicity cell assay
D. GDH then toxin EIA
E. GDH then PCR
F. PCR/NAAT
G. Not sure
Clinical Consideration

A patient with multiple myeloma develops diarrhea d8 after autologous HCT. She has grade 2 mucusitis. There is new fever and abdominal cramping (5/10 pain). Her creatinine recently increased from 0.8 to 1.2, ANC is 200. *C. difficile* toxin EIA is positive.

What do you do?

A. Start metronidazole IV
B. Start vancomycin 125 mg po QID
C. Start vancomycin 250 mg po QID
D. Watch and wait, if symptoms develop start immodium

---

Gram-Positive Bacteria: New Approaches To An Old Problem

Kenneth V. Rolston, MD
Professor, Department of Infectious Diseases, Infection Control and Employee Health
University of Texas MD Anderson Cancer Center
Houston, TX

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Common Sites of Infection in Cancer Patients

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>% Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Tract</td>
<td>35–40</td>
</tr>
<tr>
<td>Blood Stream</td>
<td>15–25</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>5–15</td>
</tr>
<tr>
<td>Skin and Skin Structure</td>
<td>5–10</td>
</tr>
<tr>
<td>Gastrointestinal Tract</td>
<td>5–10</td>
</tr>
<tr>
<td>Other Sites</td>
<td>5–10</td>
</tr>
</tbody>
</table>

*Approximately 15%–20% of patients have multiple sites of infection (e.g., pneumonia + bacteremia): these are not always caused by the same organism.

Current Spectrum of Bacterial Infection in Cancer Patients

Most databases (e.g., SCOPE) or organizations (e.g., EORTC) focus only on monomicrobial bloodstream infections (ignoring other sites and polymicrobial infections).

Monomicrobial BSIs are predominantly Gram-positive (70%–80%).

Infections at other sites and polymicrobial infections are predominantly Gram-negative.


---


<table>
<thead>
<tr>
<th>Year</th>
<th>Gram-negative</th>
<th>Gram-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>73-76</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>77-80</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>81-83</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>84-85</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>86-88</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>89-91</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>91-93</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>


---

**Surveillance and Control of Pathogens of Epidemiologic Importance – SCOPE**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>1995 (n = 390)</th>
<th>1998 (n = 451)</th>
<th>2000 (n = 411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive</td>
<td>241 (61.8)</td>
<td>251 (55.7)</td>
<td>312 (75.9)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>84 (21.5)</td>
<td>164 (36.4)</td>
<td>59 (14.4)</td>
</tr>
<tr>
<td>Anaerobic</td>
<td>7 (1.8)</td>
<td>10 (2.2)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Fungi</td>
<td>58 (14.9)</td>
<td>26 (5.8)</td>
<td>34 (8.3)</td>
</tr>
</tbody>
</table>

Epidemiology of Bacterial Infections in Patients with Hematologic Malignancies* (1986 – 2006)

<table>
<thead>
<tr>
<th>Year</th>
<th>Gram-positive</th>
<th>Gram-negative</th>
<th>Polymicrobial</th>
<th>Anaerobic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td></td>
<td>20</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>1996</td>
<td>70</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>2006</td>
<td>60</td>
<td>30</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

*Approximately 90% of patients studied.

Gram-Positive Organisms
An Emerging Problem

Some reasons for the re-emergence of Gram-positives:
- Increasing use of catheters and other medical devices
- Antimicrobial prophylaxis/therapy directed primarily at Gram-negatives
- Chemo/radiation causing cutaneous and mucosal damage
- Misuse of antimicrobial agents, both in humans and in agriculture/animal husbandry
- Environmental changes
- Better microbiological techniques

Spectrum of Gram-Positive Infections in Cancer Patients

<table>
<thead>
<tr>
<th>Organism</th>
<th>% Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>20–50</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>10–30</td>
</tr>
<tr>
<td>Viridans group streptococci (VGS)</td>
<td>3–27</td>
</tr>
<tr>
<td><em>Enterococcus</em> species</td>
<td>5–15</td>
</tr>
<tr>
<td><em>Micrococcus</em> species</td>
<td>5–8</td>
</tr>
<tr>
<td><em>Corynebacterium</em> species</td>
<td>2–5</td>
</tr>
<tr>
<td>Beta-haemolytic streptococci</td>
<td>4–6</td>
</tr>
<tr>
<td><em>Bacillus</em> species</td>
<td>4–6</td>
</tr>
</tbody>
</table>

Spectrum of Gram-Positive Infections in Cancer Patients (cont’d)

<table>
<thead>
<tr>
<th>Organism</th>
<th>% Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerococcus species</td>
<td>&lt;3% respectively</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Stomatococcus mucilaginosus</td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
</tr>
<tr>
<td>Rhodococcus equi</td>
<td></td>
</tr>
<tr>
<td>Lactobacillus species</td>
<td></td>
</tr>
<tr>
<td>Leuconostoc species</td>
<td></td>
</tr>
<tr>
<td>Pediococcus species</td>
<td></td>
</tr>
</tbody>
</table>

Intrinsically resistant to vancomycin


Gram-Positive Organisms
An Emerging Problem

Organisms Colonizing the Skin
- Coagulase-negative staphylococci
- Staphylococcus aureus
- Bacillus species
- Corynebacterium jeikeium

Oral/gastrointestinal Pathogens
- Viridans group streptococci
- Stomatococcus mucilaginosus
- Enterococcus species (including VRE)

Organisms Associated with Impaired Cell-Mediated Immunity
- Listeria monocytogenes
- Rhodococcus equi

VRE, vancomycin-resistant enterococci

Early Identification of Microorganisms Using Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS)

- Relatively new technology for identification of microorganisms
- Decreases time to identification (from days to hours)
- Lower minimal microorganism concentration required to detect bacteremia compared to standard methods
- Useful for identification of aerobic Gram-positive and Gram-negative bacteria, some anaerobes, and fungi
- Earlier identification should lead to earlier administration of targeted/specific therapy and may improve outcomes, especially in neutropenic patients

Comparison of Frequencies of High-Grade and Low-Grade Bacteremias


Intestinal Colonization and Subsequent VRE Infection in Patients with Hematologic Malignancies and HSCT Recipients

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No.</th>
<th>(%) with Intestinal Colonization</th>
<th>(%) with Bacteremia**</th>
<th>(%) with Other Sites of Infection†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>955</td>
<td>56 (5.9)</td>
<td>17 (30)*</td>
<td>17 (30)</td>
</tr>
<tr>
<td>HSCT</td>
<td>654</td>
<td>32 (4.7)</td>
<td>9 (28)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>507</td>
<td>11 (2.2)</td>
<td>3 (27)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2115</td>
<td>99 (4.7)</td>
<td>29 (29)</td>
<td>32 (32)</td>
</tr>
</tbody>
</table>

*Two additional patients with VRE colonization developed VRE bacteremia. Vancomycin-susceptible E. faecalis were recovered from their fecal swabs.

**Positive predictive value for development of bacteremia = 29.3%; negative predictive value = 99.9%.

†These included 28 episodes of urinary tract infection and 4 episodes of surgical wound infection.


Types of Antibacterial Therapy in Cancer Patients

- **Antimicrobial Prophylaxis**
  - Directed primarily against Gram-negative bacilli (fluoroquinolones are used most often)

- **Empiric Therapy**
  - Coverage with agents like vancomycin is generally not recommended (few exceptions)

- **Targeted Therapy**
  - Directed against specific pathogens based on culture & susceptibility data
Indications for Empiric Therapy in Febrile Neutropenic Patients with Agents Active Against Gram-Positive Pathogens

- Hemodynamic instability/severe sepsis
- Documented pneumonia
- Blood culture positive for GPO prior to the availability of susceptibility data
- Clinically suspected catheter-related infection
- Documented colonization with resistant GPOs
- Severe mucositis, quinolone prophylaxis

GPO: Gram-positive organism

Current Options for Treatment of Gram-Positive Infections

- Vancomycin
- Daptomycin
- Telavancin
- Linezolid
- Ceftaroline
- Tigecycline
- Fosfomycin
- Quinupristin/Dalfopristin
- Trimethoprim/Sulfamethoxazole
- Clindamycin
- Macrolides
- Doxycycline/Minocycline
- Rifampin
- Gentamicin

Specific Gram-Positive Therapy in Febrile Neutropenic Patients

- MRSA – consider early addition of vancomycin, linezolid, or daptomycin
- VRE – Consider early addition of linezolid or daptomycin
- It may be prudent to add vancomycin when viridians group streptococci or pneumococci are suspected/documented until susceptibility data become available

Therapeutic Options for Resistant Gram-Positive Organisms

Vancomycin is still the workhorse despite emerging problems:
- MIC creep – gradual rise in MICs over time
- Slow responses/clinical failures when vancomycin MIC is >0.5 µg/mL
- Increased nephrotoxicity when aiming for trough concentrations of 15–20 µg/mL (diminished bactericidal activity, tolerance by heteroresistant strains)


In Vitro Activity of Vancomycin Against S. aureus Isolates from 1985 and 2004 - 2005

<table>
<thead>
<tr>
<th>Organism</th>
<th>Year (No. tested)</th>
<th>MIC50</th>
<th>MIC90</th>
<th>No. (%) with MIC ≥1.0*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA**</td>
<td>1985 (30)</td>
<td>0.06</td>
<td>0.12</td>
<td>1 of 30 (3)</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (25)</td>
<td>2.0</td>
<td>2.0</td>
<td>25 of 25 (100)</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (28)</td>
<td>2.0</td>
<td>2.0</td>
<td>25 of 28 (89)</td>
</tr>
<tr>
<td>MRSA†</td>
<td>1985 (25)</td>
<td>0.12</td>
<td>0.25</td>
<td>2 of 25 (8)</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (28)</td>
<td>2.0</td>
<td>2.0</td>
<td>25 of 28 (89)</td>
</tr>
</tbody>
</table>

*p=0.0001

*All MIC values in µg/mL.
**MSSA – methicillin-susceptible Staphylococcus aureus
†MRSA – methicillin-resistant Staphylococcus aureus
MD Anderson Cancer Center, unpublished data.

Bactericidal Activity of Vancomycin Against S. aureus Isolates from 1985 and 2004 - 2005

<table>
<thead>
<tr>
<th>Organism</th>
<th>Year (No. tested)</th>
<th>MIC:MBC Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤1:8 1:16 ≥1:32</td>
</tr>
<tr>
<td>MSSA**</td>
<td>1985 (10)</td>
<td>10    0    0</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (10)</td>
<td>2     4     4</td>
</tr>
<tr>
<td>MRSA†</td>
<td>1985 (10)</td>
<td>10    0    0</td>
</tr>
<tr>
<td></td>
<td>2004–2005 (10)</td>
<td>2     8     0</td>
</tr>
</tbody>
</table>

*p=0.0007

*All MIC values in µg/mL.
**MSSA – methicillin-susceptible Staphylococcus aureus
†MRSA – methicillin-resistant Staphylococcus aureus
MD Anderson Cancer Center, unpublished data.
MRSA Bacteremia
Vancomycin MICs and Response

Isolates from 30 patients with MRSA bacteremia were tested

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>55.6%</td>
</tr>
<tr>
<td>1.0 or 2.0</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

Treatment failures despite in vitro susceptibility


Revised CLSI Interpretive Criteria (Susceptibility and Resistance) Breakpoints for Vancomycin

<table>
<thead>
<tr>
<th>Vancomycin MIC (mg/L)</th>
<th>Susceptible from &lt;4.0 to ≤2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>from 8.0–16.0 to 4.0–8.0</td>
</tr>
<tr>
<td>Resistant</td>
<td>from &gt;32.0 to ≥16.0</td>
</tr>
<tr>
<td>Tolerant</td>
<td>MBC ≥32 times the MIC</td>
</tr>
</tbody>
</table>

Therapeutic Options for Resistant Gram-Positive Bacteria

- Vancomycin – less effective against MSSA (45%–50% of S. aureus isolates are MSSA)
- Increasing levels of vancomycin resistance among enterococci
  - Enterococcus faecium – ~83%
  - Enterococcus faecalis – ~10%
- Intrinsic resistance to vancomycin among
  - Leuconostoc species
  - Lactobacillus species
  - Pediococcus species

Current Options for Targeted Gram-Positive Therapy

**Linezolid**
- First oxazolidinone agent
- Active against MRSA, VRE, VGS
- Available for parenteral and oral administration
- Myelosuppressive, especially with prolonged therapy, bacteriostatic
- Drug interactions, costly
- Has been compared to vancomycin for empiric therapy in neutropenic patients

Current Options for the Treatment of Gram-Positive Infections

**Daptomycin**
- Bactericidal, concentration-dependent lipopeptide
- FDA-approved for cSSSI, *S. aureus* bacteremia & (R)-sided endocarditis
- Higher doses (8-10 mg/kg/d) may be better for MRSA, VRE infections
- Not suitable for pneumonia, CNS infections
- CPK elevations occur occasionally but rhabdomyolysis is rarely seen

Bactericidal Activity of Daptomycin, Vancomycin and Linezolid Against MRSA Simulated Vegetations

Bactericidal Activity of Various Agents against *S. aureus*

![Graph showing bactericidal activity](image)


---

**Daptomycin For Gram-Positive Infections in Neutropenic Patients**

- Data from a 3-year (2006–2009) retrospective, multicenter, observational registry (CORE)
- All patients (n=186) were neutropenic (ANC ≤500/mm³)
- Bacteremia (78%); cSSSI (8%); UTI (6%)
- VRE (57%), MRSA (20%), CoNS (19%)
- 31% were failures of vancomycin therapy
- Overall response rate (159 of 186 – 85%)


---

**Newer Therapeutic Options for Gram-Positive Infections**

**Dalbavancin**

- Long-acting lipoglycopeptide (half-life 150-250 hours)
- Active against most Gram-positive organisms (MRSA, hVISA, VISA, and some VRE)
- 1 g initial dose followed by 500 mg 1 week later
- Approved last week by the FDA for cSSSIs
- Encouraging data for catheter-related BSIs
- Not evaluated in neutropenic cancer patients

Newer Therapeutic Options for Gram-Positive Infections

**Telavancin:**
- Bactericidal, once-daily, lipoglycopeptide
- Active against many Gram-positive organisms, including MRSA, but not VRE
- Approved in the US for SSSIs and hospital-acquired/ventilator-associated pneumonia
- Not evaluated in cancer patients


Newer Therapeutic Options for Gram-Positive Infections

**Ceftaroline:**
- Novel broad-spectrum cephalosporin.
- Active against many Gram-positives, including MRSA and *S. pneumoniae*
- Active against many Gram-negative rods, including Enterobacteriaceae, but not *P. aeruginosa*
- Approved for community-acquired bacterial pneumonia and acute bacterial SSSIs

New Investigational Options for Gram-Positive Infections

**TEDIZOLID**
- Next-generation oxazolidinone
- More potent in vitro activity against a broad spectrum of Gram-positive organisms compared with linezolid
- Active against wild-type and linezolid-resistant strains
- Good oral bioavailability and low risk of hematologic suppression
- Non-inferior to linezolid in Phase 3 trial of ABSSSIs

Investigational Options for Gram-Positive Infections

Oritavancin
- Bactericidal lipoglycopeptide
- Active against most Gram-positive pathogens
  - Staphylococci (including CoNS and MRSA)
  - Enterococcus species
  - Streptococcus species
- Prolonged half-life (195–360 h)
- Several single-dose studies underway
- No need for dose adjustments or for monitoring drug levels


Investigational Options for Gram-Positive Infections

OMADACYCLINE
- New class (aminomethylcyclines), semi-synthetic derivatives of minocycline
- Active agents against many Gram-positive organisms, including staphylococci, enterococci, beta-haemolytic streptococci, Streptococcus pneumoniae
- Was compared to linezolid in a phase 2 study of cSSSI
- Was well tolerated with a response rate of 83.3%


Activity of Selected Older Agents Against Gram-Positive Organisms

<table>
<thead>
<tr>
<th>Agents*</th>
<th>Quinolones - good streptococcal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Generally used in combination regimens</td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
</tr>
</tbody>
</table>

*Most are available for both oral and parenteral administration
Alternative Option for Resistant Gram-Positive Infections

Quinupristin/dalfopristin
- Now used mainly for MRSA salvage therapy
- *Enterococcus faecalis* – intrinsic resistance
- Increasing resistance among *E. faecium*
- Many adverse events including
  - severe myalgias and arthralgias
  - infusion-related and infection-site reactions


Combination Regimens for Gram-Positive Infections

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>gentamicin, rifampin, beta-lactams (nafcillin, ceftaroline)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>nafcillin, ceftaroline, ampicillin, trimethoprim/sulfamethoxazole</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>rifampin, minocycline, daptomycin</td>
</tr>
</tbody>
</table>


Gram-Positive Infections in Cancer Patients

Summary
- Predominant bacterial pathogens (45%–80%)
- Increasing levels of resistance to standard agents, including vancomycin (VRE, MRSA, VGS)
- Currently available therapeutic options have significant gaps in coverage, toxicity, or other problems
- Combination regimens may be necessary
- Several promising agents are in advanced stages of development, but most have not been evaluated in neutropenic cancer patients
- Infection control and antimicrobial stewardship efforts remain important
Gram-Negative Bacteria:
Emerging Pathogens and
Global Public Health
Threat

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What is the Magnitude of Infection in
Patients with Hematological Malignancies

- >80% of patients with hematologic malignancies will develop fever during chemotherapy cycles associated with neutropenia.
- Bacteremia occurs in 10%–25% of all febrile neutropenic episodes.
- Most episodes develop in the setting of prolonged or profound neutropenia (ANC, <100 neutrophils/mm³).

What are the Organisms Currently Recovered from Febrile Neutropenic Patients?

- Early in the development of cytotoxic chemotherapy, during the 1960s and 1970s, Gram-negative pathogens predominated.
- During the 1980s and 1990s, Gram-positive organisms became more common in association with expanded use of vascular catheters.

**Common Gram-positive pathogens**
- Coagulase-negative staphylococci
  - *Staphylococcus aureus* (MSSA, MRSA, VISA)
- Enterococcus species (VRE)
- Viridans group streptococci
- *Bacillus* spp.
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
Emergence of Gram-negative Bacterial Pathogens in Hematological Malignancies

<table>
<thead>
<tr>
<th>Epidemiologic trend toward a predominance of Gram-negative pathogens in the neutropenic patients</th>
<th>Common Gram-negative pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>Klebsiella species</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Stenotrophomonas maltophilia</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>Citrobacter species</td>
</tr>
<tr>
<td>Acinetobacter species</td>
<td></td>
</tr>
</tbody>
</table>

What is the Current Management of Fever and Neutropenia in High-risk Patients with Hematological Malignancies?

- High-risk patients with hematological malignancies require hospitalization for IV empirical antibiotic therapy.
- The rationale for current empirical antibacterial therapy is to provide effective Gram-negative coverage, particularly against *Pseudomonas aeruginosa*.
- Monotherapy with an anti-pseudomonal beta-lactam agent is the current standard of care.

What is the Current Management of Fever and Neutropenia in High-risk Patients with Hematological Malignancies?

### Standards for Single Agent Therapy

- **Anti-pseudomonal cephalosporin**
  - ceftazidime
  - cefepime
- **Anti-pseudomonal penicillin**
  - piperacillin-tazobactam
- **Carbapenem**
  - meropenem
  - imipenem-cilastatin
What is the Role for Aminoglycoside Therapy for the Initial Empirical Antibacterial Therapy of Febrile Neutropenic Patients with Hematological Malignancies?

- Multiple randomized trials and several meta-analyses support the use of single anti-pseudomonal agents for initial therapy of febrile neutropenic patients with hematological malignancies.
- Recent meta-analysis found a therapeutic advantage of beta-lactam monotherapy over beta-lactam plus aminoglycoside combinations for initial therapy of febrile neutropenic patients.
  - Significantly fewer adverse events and less morbidity
  - Similar survival rates

What is the Approach to Treatment of Gram-Negative Bacteremia?

- Understanding local unit-based antimicrobial spectrum is critical in this decision.
- For units with relatively few resistant GNRs, single agent anti-pseudomonal beta-lactam or carbapenem antimicrobial therapy is appropriate.

What is the Approach to Treatment of Gram-Negative Bacteremia?

- For units with resistant GNRs, combination therapy with anti-pseudomonal beta-lactam or carbapenem antimicrobial therapy plus an aminoglycoside provides broad initial coverage of possible multidrug-resistant pathogens.
- If organism is later found to be susceptible to anti-pseudomonal beta-lactam or carbapenem, then the aminoglycoside or fluoroquinolone can be discontinued.
What are the Challenges of Emerging Resistant Gram-Negative Bacteria in Patients with Hematological Malignancies?

- Extended-spectrum beta-lactamase (ESBL)
  - Escherichia coli
  - Klebsiella species
- Carbapenemase producers (bla<sub>KPC</sub>)
  - Escherichia coli
  - Klebsiella species
- Multiple mechanisms (pumps, porins, beta-lactamases)
  - Pseudomonas aeruginosa

What are the Challenges of Emerging Resistant Gram-Negative Bacteria in Patients with Hematological Malignancies?

- Metallo-beta-lactamase producers (L1, L2)
  - Stenotrophomonas maltophilia
- Stably derepressed beta-lactamase producers
  - Enterobacter species
  - Citrobacter species
- Integron-mediated resistance (multiple mechanisms)
  - Acinetobacter species

What is the Current Approach to Emerging Gram-Negative Bacteria in Patients with Hematological Malignancies?

- Extended-spectrum beta-lactamase (ESBL)
  - Escherichia coli
  - Klebsiella species
- Loss of all beta-lactam antimicrobial agents
- Initial Treatment: carbapenem

- Carbapenemase producers (bla<sub>KPC</sub>):
  - CRE
    - Escherichia coli
    - Klebsiella species
  - Loss of all beta-lactam antimicrobial agents and carbapenems
  - Initial Treatment: colistin or polymyxin + carbapenem or tigecycline
What is the Current Approach to Emerging Gram-Negative Bacteria in Patients with Hematological Malignancies?

- Multiple mechanisms (pumps, porins, beta-lactamases)
  - *Pseudomonas aeruginosa*
- Loss of all beta-lactam antimicrobial agents and carbapenems
- Initial Treatment: guided by *in vitro* susceptibility

- Metallo-beta-lactamase producers (*L1, L2*)
  - *Stenotrophomonas maltophilia*
- Loss of all beta-lactam antimicrobial agents and carbapenems
- Initial Treatment: TMP/SMX
- Alternative: tigecycline

- Metallo-beta-lactamase producers (*L1, L2*)
  - *Stenotrophomonas maltophilia*
- Loss of all beta-lactam antimicrobial agents and carbapenems
- Initial Treatment: TMP/SMX
- Alternative: tigecycline

What is the Current Approach to Emerging Gram-Negative Bacteria in Patients with Hematological Malignancies?

- Stably derepressed beta-lactamase producers (**AmpC**)
  - *Enterobacter species*
  - *Citrobacter species*
  - *Serratia marcescens*
- Loss of all beta-lactam antimicrobial agents
- Initial Treatment: carbapenem

- Integron mediated resistance (multiple mechanisms)
  - *Acinetobacter species*
- Initial Treatment: colistin or polymyxin plus tigecycline

What is the Magnitude of this Problem Globally?
Global Emergence of Carbapenem-resistant Enterobacteriaceae (CRE)

- *Klebsiella pneumoniae* carbapenemase (KPC) producers in New York City and Israel
- 21% of *Klebsiella pneumoniae* isolates reported to the Center for Disease Control and Prevention in 2006-2007 from NYC were carbapenem-resistant
- CRE reported in >35 states and 30 countries
- Carbapenem resistance among Enterobacteriaceae in the USA is most commonly caused by KPC

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK

- Clones of CRE historically have resided in hospitals or long-term care facilities.
- They now have the capability of thriving in the community and quickly spreading across countries and continents in relation to accessible, rapid global travel.
- Common conditions favor the organism
  - profligate antibiotic use
  - poor infection control procedures
- Local problem of resistance can rapidly become a worldwide health crisis.

Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies

- Local problem of resistance can rapidly become a worldwide health crisis.
Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies

- Expansion of CRE into patients with hematologic malignancies would have ominous implications.
- Enterobacteriaceae are the most common causes of Gram-negative BSIs in this patient population.
- Recommended empirical antimicrobial agents for the management of fever in these patients do not have \textit{in vitro} activity against CRE.

Satlin M et al, IDSA, 2011.

Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies

- We therefore studied the emergence of CRE in patients with hematologic malignancies in a large, oncology-hematopoietic stem cell transplant (HSCT) center located in an endemic area (2007-2010).
- Eighteen patients with hematologic malignancies developed CRE bloodstream infections (BSIs).


Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies

- Thirteen patients (72%) were neutropenic at BSI onset. Initial empirical antimicrobial therapy was active \textit{in vitro} in two patients (11%).
- A median of 55 hours elapsed between culture collection and receipt of an active agent.
- Ten patients (56%) died during hospitalization.
- All deaths were CRE-related.

Klebsiella pneumoniae
Enterobacter cloacae
Polymicrobial

Leukemia
Lymphoma/myeloma
Allogeneic HSCT
Autologous HSCT

Mortality Rates
All deaths were CRE-related

39% 53% 56% 69% 20%
Phenotypic Characteristics of CRE Isolates

% Susceptible

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>% Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin B</td>
<td>80</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>65</td>
</tr>
<tr>
<td>Amikacin</td>
<td>60</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>30</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>15</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>5</td>
</tr>
<tr>
<td>Meropenem</td>
<td>5</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>0</td>
</tr>
<tr>
<td>Cefepime</td>
<td>5</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>0</td>
</tr>
</tbody>
</table>

Investigational Antimicrobial Agents against GNRs

- β-Lactamase Inhibitor Combinations
  - Ceftolozane + Tazobactam
  - Avibactam (NXL-104)
    - w/ Ceftazidime
    - w/ Ceftaroline
- MK-7655
  - w/ Imipenem-cilastatin
- Key target enzymes
  - Class A β-lactamases (e.g., KPCs)
  - Class C β-lactamases (e.g., ampC)
- None of these inhibitor combinations are active against metallo beta-lactamases (e.g., NDM)

Investigational Antimicrobial Agents with Enhanced Activity against Gram-negative Bacilli

- CB-182.804 (neoteric polymyxin; significant synergy with rifampin)
- Bis-Indole antimicrobials
- CHIR-090 (LpxC inhibitor)
- AN-33656 (boron-containing protein synthesis inhibitor)
Ceftolozane/tazobactam

- Novel antimicrobial agent with activity against *Pseudomonas aeruginosa* (including drug-resistant strains) and
- Other common Gram-negative pathogens
- Most extended-spectrum-β-lactamase (ESBL)-producing Enterobacteriaceae strains

Farrel, AAC 2013.

Ceftolozane/tazobactam

- Ceftolozane/tazobactam was the most potent (MIC50/90, 0.5/2 μg/mL) agent tested against *P. aeruginosa*.
- Demonstrated good activity against 310 MDR strains (MIC50/90, 2/8 μg/mL) and 175 XDR strains (MIC50/90, 4/16 μg/mL).
- Exhibited high overall activity (MIC50/90, 0.25/1 μg/mL) against Enterobacteriaceae and retained activity (MIC50/90, >32 μg/mL) against many 601 MDR strains but not against the 86 XDR strains (MIC50, >32 μg/mL).

Farrel, AAC 2013.

Ceftolozane/tazobactam

- Potential for treatment of GNRs and empirical antibacterial therapy in febrile neutropenic patients.
Summary

- Resistant GNR infection are emerging risk factors for severe morbidity and high mortality.
- Expanding regional and global threat
- Expansion into immunocompromised patients with cancer and HSCT
- Critical public health need for
  - improved detection of MDR GNR colonization and infection
  - effective preventive measures
  - development of novel antimicrobial agents

BACTERIAL INFECTIONS IN PATIENTS WITH CANCER

New Challenges
- New Opportunities

Supported by an educational grant from Cubist Pharmaceuticals
Jointly sponsored by Vemco MedEd and Center for Independent Healthcare Education