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

C. difficile Infection: Minimizing the Impact

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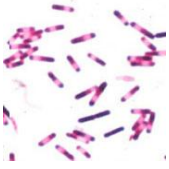
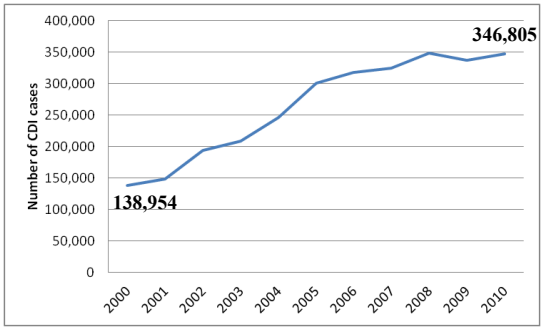
Clostridium difficile Infection

- 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

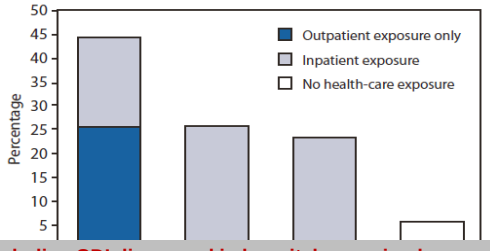


Total Number of Cases in U.S. Hospitals



Source: AHRQ HCUP data. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf.

CDI Onset in Nursing Homes and the Community

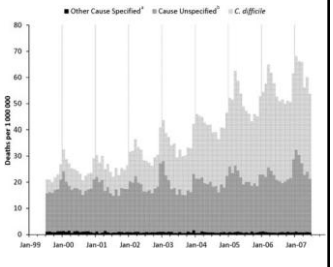


Including CDI diagnosed in hospitals, nursing homes, the community, and recurrent CDI: likely over 700,000 CDI cases in US in 2010

CDC. *MMWR*. 2012;61(09):157-162.

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**

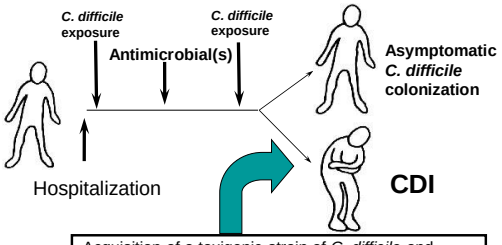


Pépin J, et al. *Can Med Assoc J*. 2005;173:1037-42.
Dubberke ER, et al. *Clin Infect Dis*. 2008;46:497-504.
Dubberke ER, et al. *Emerg Infect Dis*. 2008;14:1031-8.
Hall AJ, et al. *Clin Infect Dis*. 2012;55:216-23.

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)

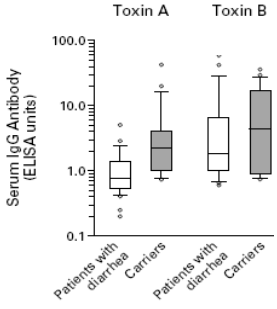


Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic antibody response results in CDI.

Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-1036.
Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

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



Loo VG, et al. *N Engl J Med*. 2011;365:1693-703.
Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

Additional Risk Factors

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

Hookman. *World J Gastroenterol.* 2009;15:1554-1580.
Cohen SH, et al. *Infect Control Hospital Epidemiol.* 2010;31(5):431-455.
Schaier M, et al. *Nephrol Dial Transplant.* 2004;19:2432-2436.

C. difficile Diagnostics

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

Diagnostics Available

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

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

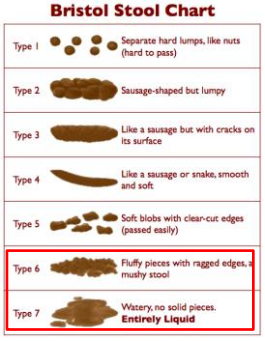
Peterson LR, et al. *Clin Infect Dis*. 2007;45:1152-1160.

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

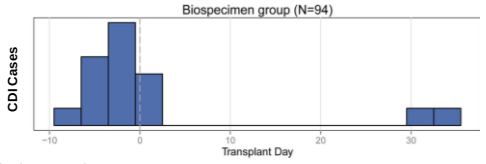
- Including clinically significant diarrhea with gold standard*:
  - No impact on sensitivity
  - Specificity of NAATs decreased from ~98% to ~89% ($p < 0.01$)
    - Positive predictive value decreased to **~60%** (25% drop)



*Recovery of toxigenic *C. difficile* from stool NAATs, nucleic acid amplification tests
Dubberke ER, et al. *J Clin Microbiol*. 2011;49:2887-2893.

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



Kinnebrew MA, et al. *PLoS One*. 2014;9:e90158.

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

Disease Severity	No. of patients cured/ no. of patients treated (%)			P value
	Metronidazole	Vancomycin	Total	
Mild	37/41 (90)	39/40 (98)	76/81 (94)	0.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	0.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

Zar FA, et al. *Clin Infect Dis*. 2007;45: 302-7.
Lawrence SJ, et al. *Clin Infect Dis*. 2007;45:1648.

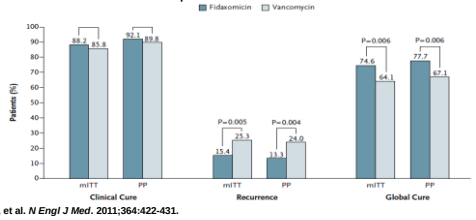
CDI Treatment Stratified by Severity

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

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31:431-455.

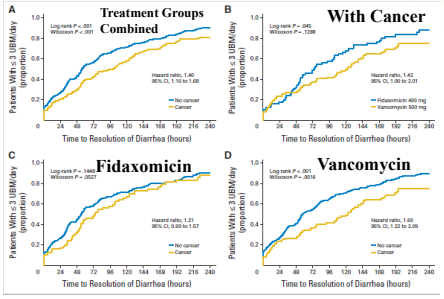
Fidaxomicin

- 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



Louie TJ, et al. *N Engl J Med*. 2011;364:422-431.

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)

Cornely OA, et al. *J Clin Oncol.* 2013;31:2493-2499.

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

Clinical scenario	*Recommended treatment*
First recurrence	Treat as first episode according to disease severity
Second recurrence	Treat with oral vancomycin taper and/or pulse dosing

Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31:431-455.

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

Method	Resolution
Colonoscope	55/62 (88.7%)
Enema	105/110 (95.4%)
Gastric or duodenal tube	55/72 (76.4%)
Rectal catheter	44/46 (95.6%)
>1 method	19/21 (90.5%)
Not reported	6/6 (100%)

Gough E, et al. *Clin Infect Dis*. 2011;53:994-1002.

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

Method	Number prior episodes	Resolution
Single infusion of feces	3 (1-5)	13/16 (81%)
Vancomycin only	3 (1-4)	4/13 (31%)
Vancomycin and lavage	2 (1-9)	3/13 (23%)

Van Nood E, et al. *N Engl J Med*. 2013;368:407-415.

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

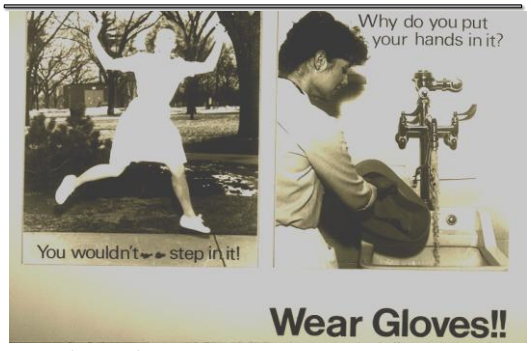
Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2009;30:57-66.

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

Clabots CR, et al. *J Infect Dis*. 1992:166:561-7.
Chang VT, Nelson K. *Clin Infect Dis*. 2000:31:717-22.
McFarland LV, et al. *N Engl J Med*. 1989:320:204-10.
Shaughnessy MK, et al. *Infect Control Hosp Epidemiol*. 2011:32:201-6.

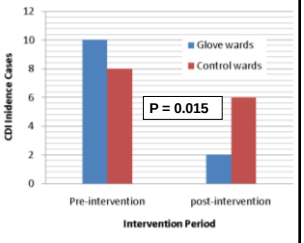
Healthcare Workers Should *NOT* Handle Stool With Bare Hands



Picture courtesy from Stuart Johnson

A-I Recommendation: Wear Gloves When Handling Stool

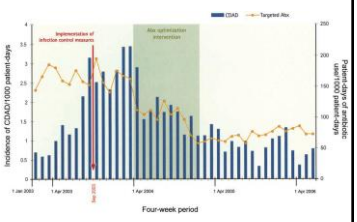
- Four wards randomized
- Intervention
  - Education: gloves when handling body substances (stool)
  - Gloves placed bedside
- Reduction in CDI on glove wards
  - Also colonization



Johnson S, et al. *Am J Med*. 1990;88:137-140.

A-II Recommendation: Antimicrobial Stewardship

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



Valiquette L, et al. *Clin Infect Dis*. 2007;45 (Suppl 2):S112-121.
Fowler S, et al. *J Antimicrob Chemother*. 2007;59:990-995.

Conclusions

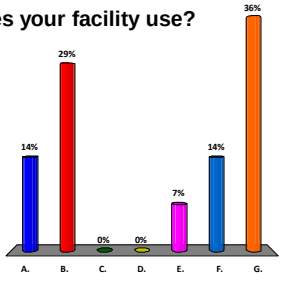
- CDI incidence and severity have increased
- New diagnostics available
  - Unclear if "more sensitive" tests are better
  - Particularly problematic after chemotherapy
- Treat CDI based on severity
  - Data with limitations, but consistent with historical observations
- Prevention
  - Diagnose and isolate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

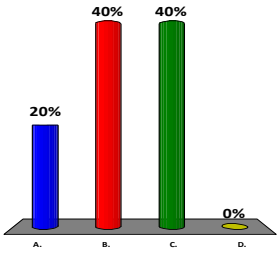


Clinical Consideration

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



THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Gram-Positive Bacteria: New Approaches To An Old Problem

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Department of Infectious Diseases,
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Common Sites of Infection in Cancer Patients

Site of Infection*	% Frequency
Respiratory Tract	35–40
Blood Stream	15–25
Urinary Tract	5–15
Skin and Skin Structure	5–10
Gastrointestinal Tract	5–10
Other Sites	5–10

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

Nesher L, Rolston KV. *Infection.* 2014;42:5-13.

Current Spectrum of Bacterial Infection in Cancer Patients

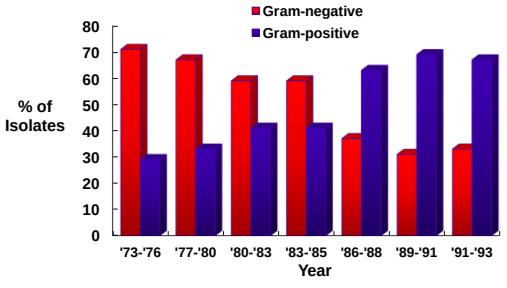
Most databases (e.g., SCOPE) or organizations (e.g., EORTC) focus only on monomicrobial bloodstream infections (ignoring other sites and polymicrobial infections)

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

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

Yadegarynia D, et al. *Clin Infect Dis*. 2003;37:1144-1145.
Wisplinghoff H, et al. *Clin Infect Dis*. 2003;36:1103-1110.
Zinner SH. *Clin Infect Dis*. 1999;29:490-494.

EORTC-IATCG: Trends in Single Organism Bacteremia, 1973–1993



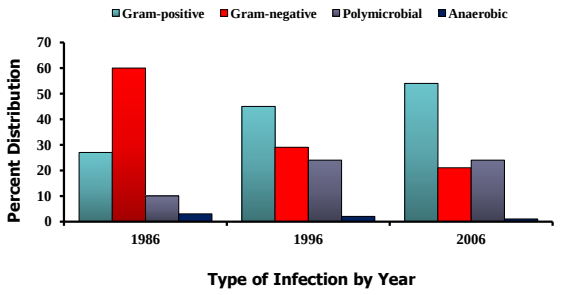
Zinner SH. *Clin Infect Dis*. 1999;29:490-494.

Surveillance and Control of Pathogens of Epidemiologic Importance – SCOPE

	No. (%) of Patients Per Year		
Pathogen	1995 (n = 390)	1998 (n = 451)	2000 (n = 411)
Gram-positive	241 (61.8)	251 (55.7)	312 (75.9)
Gram-negative	84 (21.5)	164 (36.4)	59 (14.4)
Anaerobic	7 (1.8)	10 (2.2)	6 (1.5)
Fungi	58 (14.9)	26 (5.8)	34 (8.3)

Wisplinghoff H, et al. *Clin Infect Dis*. 2003;36:1103-1110.

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



*Approximately 90% of patients studied.
Adapted from Rolston KV, et al. ECCMID 2003. Glasgow, Scotland. Poster 678.

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

Organism	% Frequency
Coagulase-negative staphylococci	20–50
Staphylococcus aureus	10–30
Viridans group streptococci (VGS)	3–27
Enterococcus species	5–15
Micrococcus species	5–8
Corynebacterium species	2–5
Beta-haemolytic streptococci	4–6
Bacillus species	4–6

Nesher L, Rolston KV. *Infection*. 2014;42:5-13.

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

Organism	% Frequency
Aerococcus species	<3% respectively
Streptococcus pneumoniae	
Stomatococcus mucilaginosus	
Listeria monocytogenes	
Rhodococcus equi	
Lactobacillus species	Intrinsically resistant to vancomycin
Leuconostoc species	
Pediococcus species	

Nesher L, Rolston KV. *Infection*. 2014;42:5-13.

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 mucilaginous*
- *Enterococcus* species (including VRE)

Organisms Associated with Impaired Cell-Mediated Immunity

- *Listeria monocytogenes*
- *Rhodococcus equi*

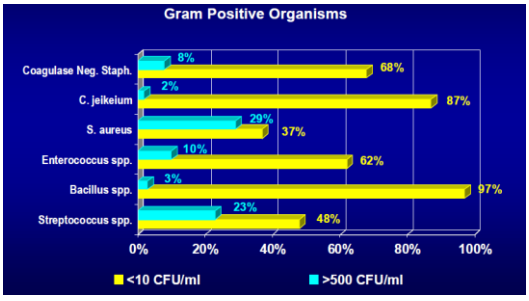
VRE, vancomycin-resistant enterococci

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

Dubois D, et al. *J Clin Microbiol*. 2010;48:941-945.
Szabados F, et al. *J Med Microbiol*. 2010;59:787-790.
Cherkaoui A, et al. *J Clin Microbiol*. 2011;49:3004-3005.

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



Rolston KV, et al. Presented at the 40th ICAAC, 2000. Abstract #729.

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

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

*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.

Matar MJ, Tarrand J, Raad I, Rolston KV. *Am J Infect Control.* 2006 Oct;34(8):534-6.

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
Freifeld A, et al. *Clin Infect Dis*. 2011;52:e56-93.

Current Options for Treatment of Gram-Positive Infections

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

Freifeld A, et al. *Clin Infect Dis*. 2011;52:e56-93.

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)

Sakoulas G, et al. *J Clin Microbiol*. 2004;42(6):2398-2402.
Rodvold KA, et al. *Clin Infect Dis*. 2014;58 (Suppl 1):S20-27.

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

Organism	Year (No. tested)	MIC_{50}*	MIC_{90}*	No. (%) with MIC ≥1.0*	
MSSA**	1985 (30)	0.06	0.12	1 of 30 (3)	p=0.0001
	2004–2005 (25)	2.0	2.0	25 of 25 (100)	
MRSA†	1985 (25)	0.12	0.25	2 of 25 (8)	p=0.0001
	2004–2005 (28)	2.0	2.0	25 of 28 (89)	

*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

Organism	Year (No. tested)	MIC:MBC Ratio*			
		≤1:8	1:16	≥1:32	
MSSA**	1985 (10)	10	0	0	p=0.0007
	2004–2005 (10)	2	4	4	
MRSA†	1985 (10)	10	0	0	p=0.0007
	2004–2005 (10)	2	8	0	

*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

MIC (μg/mL)	% Response	
≤0.5	55.6	p=0.02
1.0 or 2.0	9.5	

Treatment failures despite in vitro susceptibility

Sakoulas G, et al. *J Clin Microbiol*. 2004;42(6):2398-2402.

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

	Vancomycin MIC (mg/L)
Susceptible	from <4.0 to ≤2.0
Intermediate	from 8.0–16.0 to 4.0–8.0
Resistant	from >32.0 to ≥16.0
Tolerant	MBC ≥32 times the MIC

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

Still Uncommon

Rybak M, et al. *Expert Opin Pharmacother*. 2013;14:1919-1932.
Nesher L, Rolston KV. *Infection*. 2014;42:5-13.

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

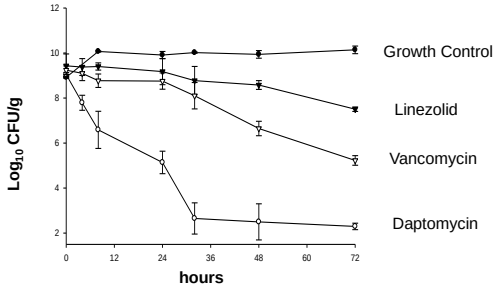
VGS, viridans group streptococci

Current Options for the Treatment of Gram-Positive Infections

Daptomycin

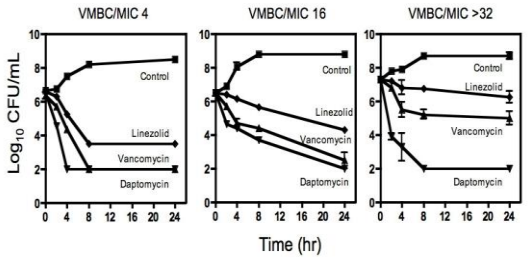
- Bactericidal, concentration-dependent lipopeptide
- FDA-approved for cSSSI, *S. aureus* bacteremia & (R)-sided endocarditis
- Higher doses (8–10 mg/kg/d) may be better for MRSA, VRE infections
- Not suitable for pneumonia, CNS infections
- CPK elevations occur occasionally but rhabdomyolysis is rarely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

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



Tedesco K, Rybak MJ. Presented at the 42nd ICAAC 2003. Abstract #A-1151.

Bactericidal Activity of Various Agents against *S. aureus*



Presented at the 44th ICAAC, Washington, DC, 2005. Abstract #E-807).

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/mm^3)
- 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%)

Rolston KV, et al. *Support Care Cancer*. 2014:22;7-14.

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

Raad I, et al. *Clin Infect Dis*. 2005;40:374-80.
Rybak JM, et al. *Expert Opin Pharmacother*. 2013;14:1919-32.

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

File TM, et al. *Clin Infect Dis*. 2010;51:1395-1405.
Corey R, et al. *Clin Infect Dis*. 2010;51:641-650.

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

O'Riordan W, et al. *Clin Infect Dis*. 2014;58(Suppl I):S43-50.

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

Tice A. *Clin Infect Dis*. 2012;54 (Suppl 3):S239-243.

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%

Noel GJ, et al. *Antimicrob Agents Chemother.* 2012;56:5650-5654.
Macone AB, et al. *Antimicrob Agents Chemother*. 2014;58:1127-1135.

Activity of Selected Older Agents Against Gram-Positive Organisms

Agents*	
Trimethoprim/sulfamethoxazole	
Clindamycin	
Doxycycline	
Minocycline	
Quinolones - good streptococcal activity	
Rifampin	Generally used in combination regimens
Gentamicin	

*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

Rybak M, et al. *Expert Opin Pharmacother*. 2013;14:1919-1932.
Rodvold KA, et al. *Clin Infect Dis*. 2014;58(Suppl 1):S20-S27.

Combination Regimens for Gram-Positive Infections

Vancomycin →	**gentamicin, rifampin, beta-lactams (nafcillin, ceftaroline)**
Daptomycin →	**nafcillin, ceftaroline, ampicillin, trimethoprim/sulfamethoxazole**
TMP/SMX →	**rifampin, minocycline, daptomycin**

McConeghy KW, et al. *Clin Infect Dis*. 2013;57(12):1760-1765.
Steed ME, et al. *Antimicrob Agents Chemother*. 2012;56(11):5709-5714.
Gould IM, et al. *Intl J Antimicrob Agents*. 2013;42:202-210.

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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Director, Transplantation-Oncology Infectious Diseases Program
Chief, Infectious Diseases Translational Research Laboratory
Professor of Medicine, Pediatrics, and Microbiology & Immunology
Weill Cornell Medical Center
New York, NY

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/mm^3).

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

Epidemiologic trend toward a predominance of Gram-negative pathogens in the neutropenic patients

Common Gram-negative pathogens

Escherichia coli
Klebsiella species
Pseudomonas aeruginosa
Stenotrophomonas maltophilia
Enterobacter species
Citrobacter species
Acinetobacter species

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*$_{KPC}$)**
  - *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*$_{KPC}$): 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

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

- New Delhi Metallo-beta lactamase-1 (NDM-1): a local clone emerges with worldwide aspirations (Marra A: Future Microbiol. 2011;6:137-41)
- 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.

Lancet Infect Dis. 2010;10:597-602.

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

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 *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

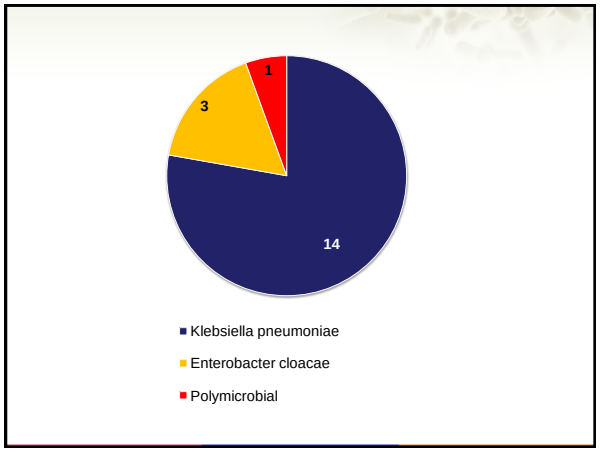
- We therefore studied the emergence of CRE in patients with hematologic malignancies in a large, oncology-hematopoietic stem cell transplant (HSCT) center located in an endemic area (2007-2010).
- Eighteen patients with hematologic malignancies developed CRE bloodstream infections (BSIs).

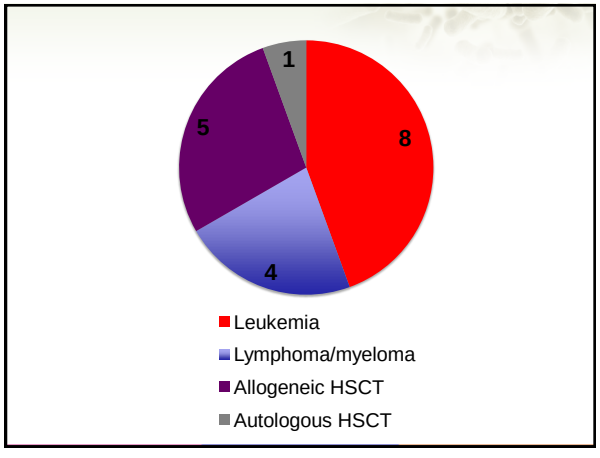
Satlin M et al, *Leuk Lymphoma*. 2013.

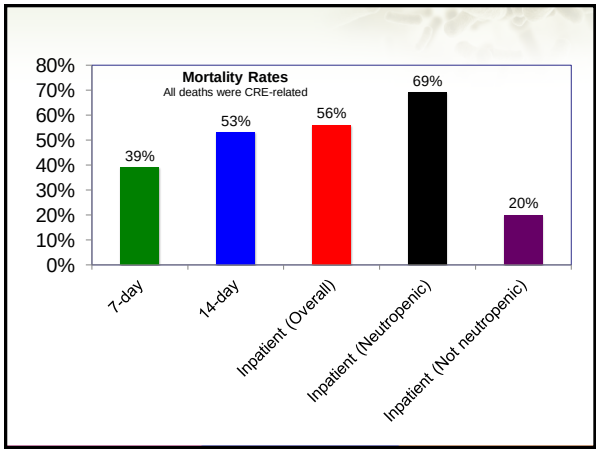
Emergence of Carbapenem-resistant Enterobacteriaceae as a Cause of Bloodstream Infections in Patients with Hematologic Malignancies

- Thirteen patients (72%) were neutropenic at BSI onset. Initial empirical antimicrobial therapy was active *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.

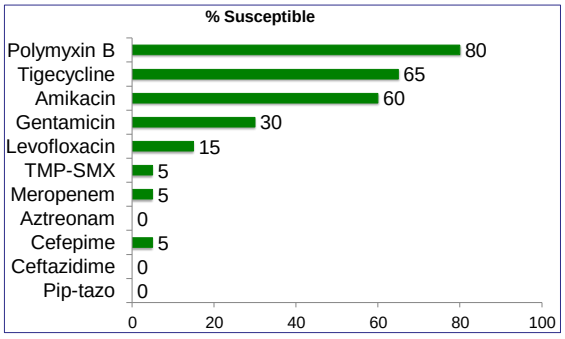
Satlin M et al, *Leuk Lymphoma*. 2013.


1
3
14
Klebsiella pneumoniae
Enterobacter cloacae
Polymicrobial


1
5
8
4
Leukemia
Lymphoma/myeloma
Allogeneic HSCT
Autologous HSCT


Mortality Rates
All deaths were CRE-related
80%
70%
60%
50%
40%
30%
20%
10%
0%
39%
53%
56%
69%
20%
7-day
14-day
Inpatient (Overall)
Inpatient (Neutropenic)
Inpatient (Not neutropenic)

Phenotypic Characteristics of CRE Isolates



Investigational Antimicrobial Agents against GNRs

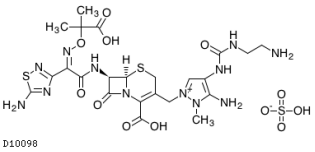
- β-Lactamase Inhibitor Combinations
  - Ceftolozane + Tazobactam
  - Avibactam (NXL-104)
    - w/ Ceftazidime
    - w/ Ceftaroline
- MK-7655
  - w/ Imipenem-cilastatin
- Key target enzymes
  - Class A β-lactamases (e.g., KPCs)
  - Class C β-lactamases (e.g., ampC)
- None of these inhibitor combinations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



D10098

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, 4/>32 µg/mL) against many 601 MDR strains but not against the 86 XDR strains (MIC50, >32 µg/mL).

Farrel, AAC 2013.

Ceftolozane/tazobactam

- Robustly powered phase III trials in the treatment of complicated urinary tract infections and complicated intra-abdominal infections.
- 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

Supported by an educational grant from Cubist Pharmaceuticals

Jointly sponsored by Vemco MedEd and Center for Independent Healthcare Education