Bacterial Infections in Neutropenic Patients and HSCT Recipients

Kieren A. Marr MD
Professor of Medicine and Oncology
Director, Transplant and Oncology ID
Johns Hopkins University School of Medicine

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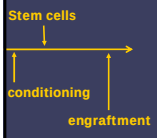
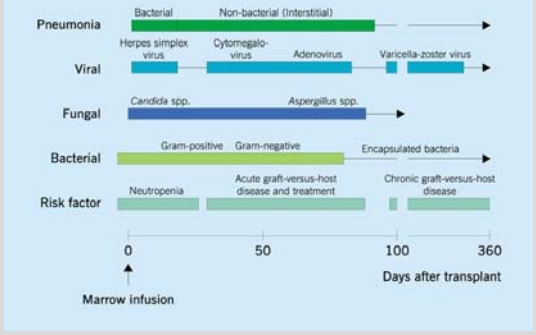
Outline

- Risks- changes in therapy
- Bacterial Infections: update in a select population
  - Overall epidemiology
  - Gram – negative bacteria
  - Gram – positive bacteria
  - *Clostridium difficile* disease
  - Risks: new developments
- NOT discussed: empirical treatment

Course of BMT

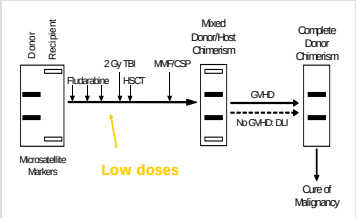


- Conditioning therapy
  - Spectrum: myeloablative to non-myeloablative
    - reduced toxicities
- Infusion of stem cells
  - Self origin: Autologous
  - Other: Allogeneic
    - HLA match important
  - Source of stem cells
    - Peripheral blood, marrow, cord blood
  - Manipulation of stem cell product
    - CD34-selected, T cell depleted
- Infection risks
  - Periods of immune impairment
    - Neutropenia (early)
    - T cell (late)
  - GI tract mucositis
  - GVHD and therapy
  - Intravascular lines



Time line, and incidence of OI's changed with preventative therapy and type of BMT

Non-myeloablative



- Different conditioning regimens
- Much less neutropenia and early mucositis
- GVHD encouraged (Graft vs. Malignancy effect)
- Infection risks associated with
  - GVHD and therapy
  - Long-term intravascular access
- Infections predominate LATE after BMT

Invasive fungal infections
CMV
Respiratory viruses
Catheter-related bacteria
Encapsulated bacteria

Nosocomial Bloodstream Infections in US Hospitals: 1995-2002

Rank	Pathogen	BSI per 10,000 admissions	% BSI			% Crude Mortality		
			Total (n=20,978)	ICU (n=10,515)	Non-ICU (n=10,515)	Total	ICU	Non-ICU
1.	CoNS	15.8	31.3	35.9	26.6	20.7	25.7	13.8
2.	*S. aureus*	10.3	20.2	16.8	23.7	25.4	34.4	18.9
3.	*Enterococcus* spp.	4.8	9.4	9.8	9.0	33.9	43.0	24.0
4.	*Candida* spp.	4.6	9.0	10.1	7.9	39.2	47.1	29.0
5.	*E. coli*	2.8	5.6	3.7	7.6	22.4	33.9	16.9
6.	*Klebsiella* spp.	2.4	4.8	4.0	5.5	27.6	37.4	20.3
7.	*P. aeruginosa*	2.1	4.3	4.7	3.8	38.7	47.9	27.6
8.	*Enterobacter* spp.	1.9	3.9	4.7	3.1	26.7	32.5	18.0
9.	*Serratia* spp.	0.9	1.7	2.1	1.3	27.4	33.9	17.1
10.	*A. baumannii*	0.6	1.3	1.6	0.9	34.0	43.4	16.3

Wisplinghoff H, et al. *Clin Infect Dis.* 2004;39:309-317.

Bacterial Infections: Hematology

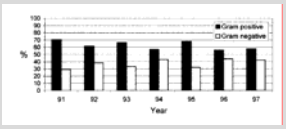
- Population – based studies don't tell whole story
  - Changes over time
  - Evolving epidemiology based on differences in host, differences in supportive care
- Time-dependent changes:
  - Decrease in gram-negative bacteremias during 1990's
    - Rebound increase in Gram – neg: Resistance
  - Increased problems with gram+ Resistance

Prophylaxis

- Highly 'pre-treated' population
- Multiple studies have shown better outcomes with some antibacterial prophylaxis
  - β-lactams
  - Quinolones
    - Decreased fever, bacteremias
    - But increased breakthrough resistance
- Practices change epidemiology in institutional- host dependent fashion

Bacteremia

- European Organization for Research and Treatment of Cancer
  - 1970's: gram-negative bacteria caused 70% of bloodstream infections, 40% mortality
  - 1980's: gram positive bacteria caused 70%, gram – negative 30% [1]
- University of Florida: 519 BMT [2]
  - 29.5% patients developed bacterial infection
  - Incidence decreased 1991 to 1997
    - Decreased in Streptococci and Staphylococci
    - Resistance in Strept: β-lactam, carbapenem
  - *Pseudomonas* high mortality 40%



[1] Eur J Cancer 26: 569-74 (1990)
[2] Collin et al. Clin Infect Dis 2001; 33: 947-53

Multidrug-Resistant Bacterial Organisms Causing Major Clinical Problems.*

Organism and Antibiotic Resistance	Common Mechanism of Resistance	Recent, Resurrected, and Future Antimicrobial Agents with Potential Clinical Use
Hospital-associated MRSA†		
Vancomycin (both VISA and VRSA)	Thickening of cell wall (not fully elucidated); change in the last amino acid of peptidoglycan precursors	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Daptomycin	Associated with changes in cell wall and cell membrane (not fully elucidated)	Linezolid, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Linezolid	Mutations in the 23S ribosomal RNA genes; rarely, acquisition of a methyltransferase gene (*cfr*)	Daptomycin, quinupristin–dalfopristin, tigecycline, ceftobiprole, ceftaroline, dalbavancin, telavancin, oritavancin, iclaprim
Vancomycin-resistant *Enterococcus faecium*‡		
Ampicillin (common)	Mutation and overexpression of *pbp5*	Linezolid, quinupristin–dalfopristin, daptomycin, tigecycline
High-level resistance to aminoglycosides	Acquisition of aminoglycoside-modifying enzymes, ribosomal mutations (streptomycin)	No alternative for a reliable bactericidal effect alone or in combination
Linezolid	Mutations in the 23S ribosomal RNA genes	Quinupristin–dalfopristin, daptomycin, tigecycline
Daptomycin	Unknown	Linezolid, quinupristin–dalfopristin, tigecycline
Quinupristin–dalfopristin	Enzymes that inactivate quinupristin–dalfopristin, target modification	Daptomycin, linezolid, tigecycline
Escherichia coli, Klebsiella species, and enterobacter species§		
Oxyimino-cephalosporins (ceftriaxone, cefotaxime, ceftazidime, and cefepime)	Extended-spectrum β-lactamases (includes hyperproduction of the AmpC enzymes by Enterobacteriaceae family)	Carbapenems, tigecycline
Carbapenems	Production of carbapenemases, decreased permeability	Polymyxins, tigecycline
Acinetobacter species¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins
Pseudomonas aeruginosa¶		
Carbapenems	Decreased permeability, increased efflux, and production of carbapenemases	Polymyxins

Arias and Murray New Eng J Med 2009; 360(5) 439-43

MDR-gram negative bacteremia

- 13 centers in Brazil: March – Nov 2004
  - Day 0 until engraftment or death
  - Resistance to 2 drug classes: MDR
  - 411 pts: prophylaxis 34% (β-lactam, quin)
  - Bacteremia 91 (27%)
    - 47% gram-positive, 37% gram-negative
    - 37% of gram-negative bacteria MDR
      - *K. pneumoniae*, *P. aeruginosa*, *Enterobacter* spp., *E. coli*, *B. cepacia*, *S. maltophilia*, *Acinetobacter* spp., *C. freundii*
      - Risks: 3rd generation cephalosporins, clustering in hospitals

Empirical therapy considerations

[1] Oliveira et al. BMT 2007 39; 775-781

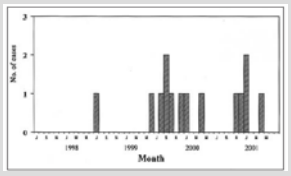
Pseudomonas aeruginosa

- Most common cause of bacterial pneumonia before day 100[1]
- FHCRC review (1990 – 2001) [2]
  - 95 / 5772 patients (1.65%)
    - 2% allogeneic, 1% autologous
  - 63 days after HCT (5-1435)
    - Bulk during GVHD; 28% during neutropenia
  - Copathogens common: 48% (IFI, CMV, polymicrobial bacterial infection)
  - 16% developed recurrent disease after 2 weeks of antibiotics (mortality 60%): GVHD
    - Longer therapy should be considered

[1] Lossos et al Transplantation 1995 60: 672-78
[2] Hakki et al. BMT 2007 39, 687-93

Stenotrophomonas maltophilia

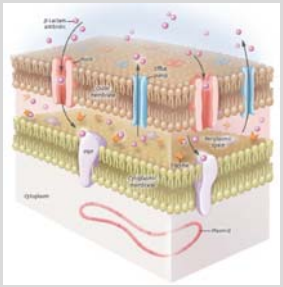
- Resistance to carbapenems
- Bloodstream infection, pneumonia
- Poor outcomes[1]
- Risks in case-control study at Barnes Jewish Hospital [2]
  - Mucositis, diarrhea, metronidazole, many antibiotics used



[1] Cherif et al. Hematol J 2003; 4(6): 420-6
[2] Apisarnthanarak et al. Infect Control and Hosp Epid 2003; 24: 269-74

Acinetobacter baumannii

- Natural habitat water and soil, hot and humid climates
  - Nosocomial: burns, wounds, pneumonia
  - Outbreaks in hospitals and facilities
  - Multidrug resistance



Munoz-Price and Weinstein New Eng J Med 2008; 358: 1271-81

Acinetobacter baumannii

- Neutropenia = risk for death

Table 3 Independent risk factors for in-hospital mortality for 46 patients with *Acinetobacter baumannii* bacteraemia

Risk factor	Odds ratio (95% CI)	*P* value
Elevated APACHE II score[†]	1.333 (1.076–1.652)	0.008
Neutropenia	38.211 (3.225–452.673)	0.004

[†]Per 1 point increase in score. APACHE, acute physiology and chronic health evaluation.

- Not simply related to drug resistance
  - Underlying disease severity, toxicities

Table. Risk factors and outcome for 27 neutropenic cancer patients with bacteremia due to multidrug-resistant (MDR) or drug-susceptible *Acinetobacter baumannii* infection

Characteristic	All patients, no. (%) (N = 27)	Patients with drug-susceptible *A. baumannii*, no. (%)* (n = 12, 44%)	Patients with MDR *A. baumannii*, no. (%)* (n = 15, 56%)
Risk for bacteremia			
Central venous catheter	19 (70.4)	9 (75.0)	10 (66.7)
Acute leukemia	11 (40.7)	6 (50.0)	5 (33.3)
Previous prophylaxis with quinolones	14 (51.9)	8 (66.7)	6 (40.0)
Previous therapeutic treatment with cephalosporins	15 (55.6)	8 (66.7)	7 (46.7)
Previous therapeutic treatment with carbapenems	8 (29.6)	4 (33.3)	4 (26.7)
Outcome			
Septic shock	4 (14.8)	2 (16.7)	2 (13.3)
Death	2 (7.4)	1 (8.3)	1 (6.7)

*Insignificant difference between patients with drug-susceptible infection and those with MDR infection (p≥0.05 by univariate analysis).

Choi et al. Intern Med J 2005; 35: 599-603
Krcmery and Kalavasky Emer ID 13(6) 2007

MRSA

- Classically, hospital – associated MRSA relatively low incidence in hematologic population, in absence of outbreak
- Single UK HCT center: 41/776 (5%); 9% in unrelated donor allogeneic HCT
  - Increased during outbreak in 2004
- Colonization and persistent carriage risk factor for infection [2]

[1] Shaw et al. Bone Marrow Transplant 2007; 39: 623-29
[2] Kato et al. Ann Hematol 2003 82: 310-12

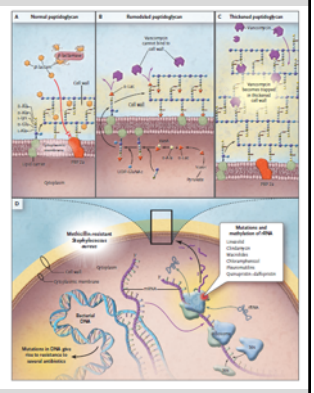
S. aureus

- 1994 – 1996 DUMC
- 430 – MSSA / MRSA bacteremia
  - 122 (28%) cancer
  - 52 non-neutropenic
    - Device-related: 42%
    - Tissue infection: 44%
    - Unidentified focus: 13%
    - IE: 15%
  - MRSA 20 patients (38%)

gopal et al. J Clin Oncol 2000

MRSA: Issues

- High-virulence "community-acquired" MRSA causing hospital infection
  - Skin, soft tissue infection in healthy people, bloodstream infection, necrotizing pneumonia, abscess formation
  - Into the hospital-colonization pre-therapy



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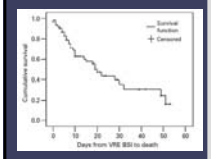
Vancomycin Resistant Enterococcus



[1] Avery et al. Bone Marrow Transplant 2005: 35: 497-99
[2] Dubberke et al. Bone Marrow Transplant 2006: 38: 813-19

- 281 HCT recipients at Cleveland Clinic: 1997 – 2003[1]
  - Early VRE infection in 2.6% patients, poor outcomes
- Leukemia / HCT at Barnes Jewish (1996 – 2002)[2]
  - Incidence bloodstream 0.6 – 2.1 / 1000 patient days
  - Dependent on infection control (gowns)
  - 334 patients colonized: 13% BSI
    - 70% infected were colonized prior
  - 78% hospitalized in prior 30 days
  - Survival poor: GVHD, pneumonia, antifungals, high APACHE II

Vancomycin Resistant Enterococcus

Calderwood et al. Infect Control Hosp Epi 2008 29: 1019-25

- Active surveillance study at University of Chicago HCT unit[1]
  - Sequential cultures upon admission
  - Prevalence rate: 11.2% current BMT; 67.3% previous HCT, 24% nontransplant
  - Risk for conversion: voriconazole, trimethoprim-sulfamethoxazole, carbapenem, URD HCT

Question

- 42 yr old M with AML 12 days after therapy with mucositis, neutropenia 12 days, fever for 6 days
  - Levofloxacin prophylaxis- ceftazidime empirically, added vancomycin (1 day)
- Gram-positive coccus in blood culture
- After 24 hours, patient became hypotensive and developed ARDS, and a diffuse erythemetous rash
- Which organism is the most likely etiology ?
  1. *Streptococcus pneumoniae*
  2. Coagulase-negative *Staphylococcus*
  3. *Enterococcus faecalis*
  4. *Streptococcus mitis*
  5. *Stomatococcus mucilaginosus*

Viridans Streptococci
Epidemiology and Clinical Presentation

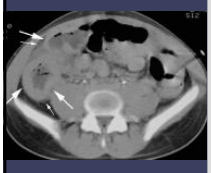
- Important cause of bacteremia in neutropenic cancer patients
- Risk factors: severe neutropenia, oral mucositis, high-dose cytosine arabinoside, antimicrobial prophylaxis with TMP-SMX or a fluoroquinolone
- Can present with fever, flushing, chills, stomatitis, pharyngitis
- After 24-48 hours, hypotension in 1/3 of cases
- Rash, shock, ARDS in 1/4 of cases (similar to toxic shock)
- Endocarditis unusual (<10%)
- Mortality high (15-20%)

Streptococci

- *S. pneumoniae*
  - MD Anderson[2]
    - 1989 – 2005: incidence 7/1000 HCT
    - Late complication: median 443 days
    - Lymphoma, steroids risks
  - Population-based surveillance in Toronto (1994 – 2005)[3]
    - 347 / 100,000 person yrs (vs. 11.5 / 100,000 in general population
    - Serotypes would be protected in vaccine (not given)
    - High rates of Tm/Slf resistance
  - Allogeneic HSCT: timing of vaccination

[1] Prabhu et al. Eur J Clin Microb ID 2005 24: 832-38
[2] Youssef et al. Medicine 2007 86(2): 69-77
[3] Kumar et al. Bone Marrow Transplant 2008 41: 743-47

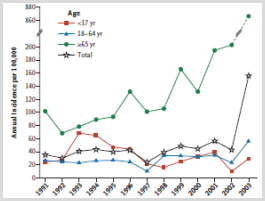
GI Infections



- Diarrhea is a common complaint
  - Most non-infectious
  - Tips for infections
    - Bloody, fever, abdominal pain
- Colitis
  - Neutropenic enterocolitis
  - *C. difficile* colitis
  - CMV, other Herpes viruses (not common)

Clostridium difficile disease

- Little data in HCT or neutropenic population
- 119 patients (auto, allo)
  - 7 / 109 (6%) CDAD [1]
- Incidence subsequent to toxigenic strain (NAP-1) likely increased
  - Multiple risks predict problem[2]
    - Quinolone resistance
    - Antibiotic-induced changes in flora
    - Low humoral immune response to circulating toxin A (IgG)



[1] Tomblyn et al. Bone Marrow Transplant 2002 30: 517-19
[2] Kelly and LaMont New Eng J Med 2008; 359: 1932-40

C. difficile disease

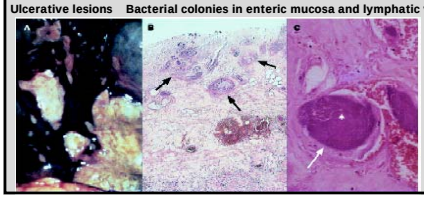
- Risks for CDAD ↑ neutropenia, HSCT
  - Incidence, risks unknown
  - Certain drugs may potentiate risks
- Autologous PBSCT (n=242, 1996-2001)[1]
  - Incidence 15%
  - Risks: cephs, vanco
  - Paclitaxel with mobilization: lower incidence
- 2003-2004 case-control[2]
  - Incidence cancer floor 2.4/1,000 pt-days
  - Cases: older; lung cancer (3x) antibiotics 22x higher (cephalosporins); IL-2 7x
- Recent small retrospective study[3]:
  - 1st allogeneic HSCT 2003-2007 (n=26)
    - 88.5% had diarrhea
    - 30% had CDAD diagnosed (n=7)
    - AML (n=6); imipenem

[1] Arango et al. BMT 2006 37, 517-521
[2]Gifford and Kirkland. Eur J Clin Microbiol Infect Dis 2006; 25(12): 751-5
[3]Leung et al. Infect Control Hosp Epid 2010 31(3): 313-15

Neutropenic Enterocolitis

- Neutropenic enterocolitis (typhlitis)
  - Necrotizing inflammation with transmural infection of damaged bowel wall
  - Mixed infection with gram-negative, gram-positive, anaerobic bacteria
  - Can be accompanied by bacteremia
    - Mixed, Anaerobic (*C. septicum*, *C. tertium*, *B. cereus*[1])
  - Medical and surgical management

Ulcerative lesions **Bacterial colonies in enteric mucosa and lymphatic vessels**



Ginsburg et al, Amer J Hematol 72 (2003)
Cornely Lancet 358:9296 (2001)

Risks for bacterial infection

- Neutropenia, mucositis, intravascular catheters
  - Different risks associated with conditioning
- Genetic risks
  - HLA-matched siblings (Korea)[1]
    - Polymorphism in P2X7 receptor: plasma membrane R for ATP involved in IL-1 processing
      - associated with survival, bacteremia
  - FHCRC: case-control study alloHCT
    - Polymorphism in LPS binding protein (promoter) associated with gram-negative bacteremia and mortality
  - Paris: non-T depleted (n=192)
    - Polymorphism in PTPN22 gene (protein tyrosine phosphatase): negative regulator of T cell activation
  - Polymorphism 2q21.3 (lactase phlorizin hydrolase) associated with pneumonia, TRM[4]

[1] Lee et al. Haematologica 2007; 92(5)
[2] Chien et al. Blood 2008; 111: 2462-69
[3] Azarian et al. Transplantation 2008; 85: 1859-62
[4] Hauser et al. Blood 2008 112(5): 2156-59

Conclusions

- Epidemiology
  - Always evolving
  - Institutional infection control issues
  - Additional pressures (prevention)
- Issues of great concern
  - Resistance (both gram – and +)
  - Some practices should differ
    - Longer course therapies for *P. aeruginosa* pneumonia
  - CDAD not well understood
    - Risks and outcomes, factors that dictate recurrence
- New understanding of infectious risks