Clinical Risk Factors for Infection and Antibiotic Resistance in BMT Patients

Allison Bock[1], Qing Cao[2] & Daniel Weisdorf[3]
[1]College of Biological Sciences, University of Minnesota, Minneapolis, MN, USA;
[2]Masonic Cancer Center, University of Minnesota, Minneapolis, MN;
[3]Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN

Infection is a Leading Cause of Mortality and Morbidity in Blood and Marrow Transplantation (BMT) Patients

- Incidence of bacteremia, bacterial isolates in the blood, ranges from 20-62% in BMT patients, often with a higher incidence during the first 30 days when most patients are neutropenic (absolute neutrophil count, ANC <500ul)[1,2,3]
- Many of the overall risks BMT patients face occur within these first 30 days post-transplant and are a consequence of the patient's decreased immune defense ability
- Mortality rates for infection differ significantly by institution and bacterial organism, emphasizing the importance of hospital conditions and antibiotic selection
- Gram positive organisms account for the majority of infection, with coagulase negative *Staphylococcus* (CNS) being the most frequently isolated organism
- However, Infection by gram negative organisms is associated with a higher case-fatality rate and more serious clinical consequences and complications such as sepsis, pneumonia, and shock[3]
- There are some reports of a reemergence in infection by gram negative organisms that is associated with multi-drug resistance (MDR)[4]

Study Goal

- The relative importance of clinical features on the incidence and timing of post-transplant bacterial infections is uncertain, but a detailed analysis could better guide prevention and therapy.
- This study also examined the antibiotic sensitivity profiles of the BMT patients and the contemporaneous hospital-wide microbiology laboratory antibiotic sensitivity profiles to describe the bacterial isolate susceptibility changes in the BMT population compared to the general hospital population

Patients and Management of Infection

- We retrospectively analyzed 834 adult patients who received a BMT at the University of Minnesota between January 2005 and October 2010
- All patients with at least one positive bacterial blood culture within the first 100 days post-transplant were considered to have bacteremia
- BMT patients without bacteremia during the six year period were defined as controls
- All patients received the broad spectrum quinolone, levofloxacin for prophylaxis (500mg/day). If allergic, patients were given penicillin or a related beta-lactam antibiotic
- Empiric antibiotic regimens started at the onset of fever include ceftazidime, vancomycin, and tobramycin with a modification after the identification of the bacterial organism

Antibiotic Sensitivity Testing of BMT and Hospital Bacterial Isolates

- Antibiotic sensitivities were done on the first positive blood culture taken from the BMT patient, and all relevant hospital blood isolate data was obtained from the microbiology laboratory at University of Minnesota Medical Center-Fairview (UMMC)
- Antibiotic sensitivities were determined using the Vitiek Automated Microbiology System or a microdilution minimum inhibitory concentration (MIC) procedure
- The sensitivities from BMT patients were compared with hospital wide sensitivities that are analyzed yearly at UMMC

Results

Infection by antibiotic resistant gram negative bacteria is more frequent in BMT patients compared to the general hospital population

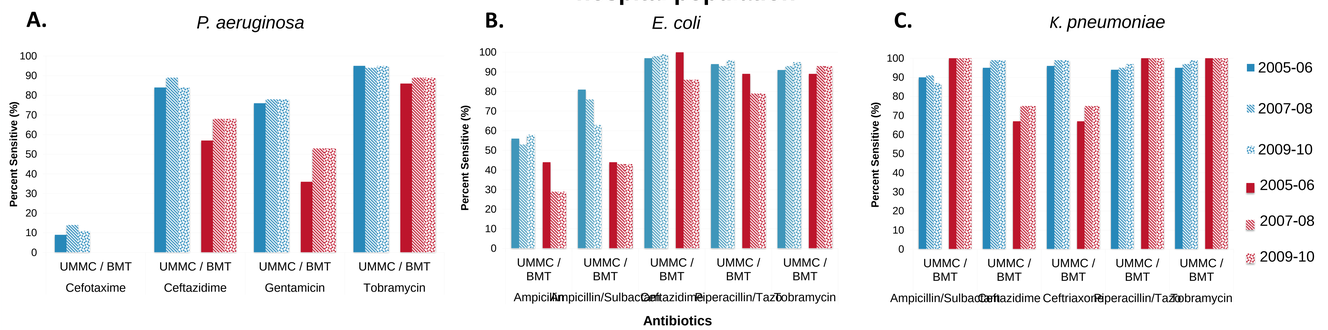

Figure 1. The sensitivity of *P. aeruginosa, E. coli, and K. pneumoniae* blood isolates from hospital wide and BMT patients between 2005 and 2010. A) Ceftazidime and gentamicin alone are not sufficient empiric therapy treatment for infections by *P. aeruginosa* for both BMT and hospital patients. **B)** Ampicillin is not effective for use against *E. coli* for both BMT and hospital patients. Resistance to ceftazidime and piperallin/tazobactam increases in BMT patients in latter four years. **C)** Ceftazidime and ceftriaxone alone are not sufficient empiric therapy treatment for infections by *K. pneumoniae* in BMT patients. Piperacillin/tazobactam and tobramycin remain effective against *K. pneumoniae* for both BMT and hospital wide patients.

Resistance to the prophylactic antibiotic, levofloxacin, is common in BMT patients

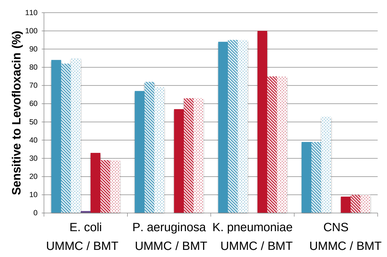

Figure 2. The sensitivity of *E. coli, P. aeruginosa, K. pneumoniae*, and *Coag Neg Staph* (CNS) blood isolates to levofloxacin from hospital wide and BMT patients between 2005 and 2010.

Clinical Features of Patients

Features	without Bacteremia By day 100	with Bacteremia By day 100	P-value
All	472 (58%)	341 (42%)	
Gender			.11
Male	299 (62%)	196 (56%)	
Female	186 (38%)	153 (44%)	
Recipient age			
Median (range)	51 (18-74)	48 (18-74)	<.01
Donor Type			<.01
Sibling	104 (21%)	91 (26%)	
Self (Autologous)	213 (44%)	66 (19%)	
Unrelated	16 (3%)	20 (6%)	
Related non-sibling	152 (31%)	172 (49%)	
Cell Source			<.01
Sibling	104 (21%)	91 (26%)	
Self M/P	213 (44%)	66 (19%)	
Related non-sibling M/P	16 (3%)	20 (6%)	
Unrelated M/P	18 (4%)	20 (6%)	
UCB	134 (28%)	152 (44%)	
GVHD II-IV			<.01
NO	388 (80%)	238 (68%)	
YES	97 (20%)	111 (32%)	
Time to ANC recovery for engrafted patients			
Median (range)	11 (0-42)	13 (0-42)	<.01
Diagnosis prior to BMT			<.01
Non-malignant disorders	18 (5%)	12 (4%)	
Acute Leukemia	131 (27%)	158 (45%)	
Other Leukemia	55 (12%)	58 (17%)	
Lymphoma (Non-Hodgkin's)	121 (25%)	59 (17%)	
Lymphoma (Hodgkin's)	49 (10%)	16 (5%)	
Other Malignancy	110 (23%)	46 (14%)	

Multivariate Analysis

A.

	Allo/Auto		GVHD III-IV	
All Bacteremias	**Relative Risk (95% CI)**	**P-value**	**Relative Risk (95% CI)**	**P-value**
Overall (0-100 days)	3.07 (2.30-4.11)	**<0.01**	1.77 (1.29-2.41)	**<0.01**
Month 1 (0-30)	2.09 (1.52-2.87)	**<0.01**	1.83 (.61-5.49)	0.28
Month 2 (31-60)	6.79 (3.32-13.9)	**<0.01**	1.5 (.95-2.38)	0.08
Month 3 (61-100)	59.95 (8.27-435)	**<0.01**	1.53 (0.99-2.36)	0.06
All excluding CNS				
Overall (0-100)	3.87 (2.53-5.93)	**<0.01**	1.89 (1.24-2.87)	**<0.01**
Month 1 (0-30)	2.85 (1.75-4.62)	**<0.01**	1.27 (.13-12.4)	0.84
Month 2 (31-60)	6.95 (2.59-18.7)	**<0.01**	1.73 (1.00-3.01	0.05
Month 3 (61-100)	34.54 (4.75-251)	**<0.01**	1.41 (0.74-2.69)	0.3

B.

	Day 0-100		Day 0-30	
Risk Factor	**Relative Risk (95% CI)**	**P-value**	**Relative Risk (95% CI)**	**P-value**
Reduced Intensity (RIC)	1		1	
Myeloablative	1.43 (1.13-1.80)	**<0.01**	1.70 (1.24-2.34)	**<0.01**
Sib M/P	1		1	
Non-sibling RD M/P	1.39 (0.90-2.14)	0.14	1.55 (0.85-2.82)	0.15
URD M/P	1.22 (0.84-1.76)	0.3	1.17 (0.70-1.96)	0.55
URD Cords	1.22 (0.98-1.53)	0.08	1.19 (0.88-1.61)	0.26
GVHD III-IV	1.57 (1.15-2.15)	**<0.01**	1.54 (0.51-4.70)	0.44

Table 1. Multivariate analysis for impact of clinical features on infection risk and timing. A) Allogeneic transplants have a significantly higher risk overall and independently in the first three months post-transplant for infection by all bacterial species and infection excluding CNS in comparison to autologous transplants. The development of GVHD is also a significant risk factor for infection overall in both infection groups. **B)** Among allogeneic transplants, myeloablative conditioning is associated with a significantly higher risk of bacteremia by an bacterial species overall and in the first 30 days post transplant. Development of acute GVHD III-IV is also a significant risk factor overall for bacteremia by any bacterial species.

Cumulative Incidence of Bacteremia by 100 Days Post-Transplant

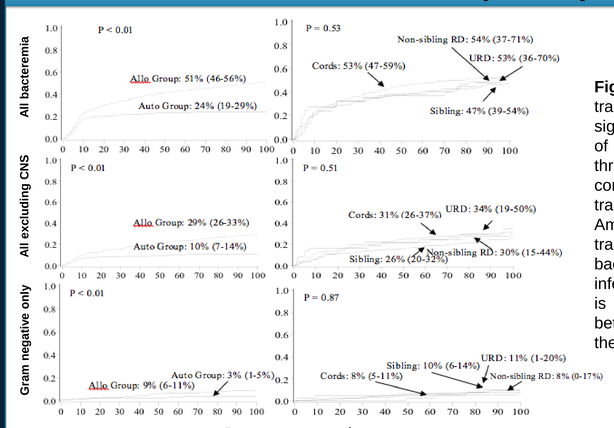

Figure 3. Allogeneic transplant recipients have a significantly higher incidence of bacteremia in each of the three infection groups compared to autologous transplant recipients (left). Among allogeneic transplants, the incidence of bacteremia is similar in each infection group (right). There is no major difference between donor type in any of the groups.

Conclusions

- Allogeneic transplants and patients receiving myeloablative conditioning regimens have a substantially higher risk of developing infection compared to autologous transplant recipients and those receiving RIC
- The development of acute GVHD grade III-IV was a significant risk factor for all bacteremia overall (0-100 days post-transplant)
- Further, infection risk is similar for allogeneic transplants from a sibling, non-sibling related donor, or unrelated donor
- Resistance to levofloxacin is more frequent in BMT patients
- For the three most frequent gram negative organisms (*E. coli, P. aeruginosa, K. pneumoniae*), ampicillin, ceftazidime, gentamicin, or ceftriaxone alone are insufficient empiric therapy treatments
- Thus, prescription of tobramycin or other aminoglycosides may be necessary for initial empiric therapy

References

1. Collin, B.A., Leather, H.L., Wingard, J.R. & Ramphal, R. Evolution, Incidence, and Susceptibility of Bacterial Bloodstream Isolates from 519 Bone Marrow Transplant Patients. *Clinical Infectious Diseases* **33**, 947 - 953 (2001).
2. Mitchell, A.E. *et al.* Gram-negative bacteraemia (GNB) after 428 unrelated donor bone marrow transplants (UD-BMT): risk factors, prophylaxis, therapy and outcome. *Bone Marrow Transplant* **33**, 303-310 (2003).
3. Frère, P. *et al.* Bacteremia after hematopoietic stem cell transplantation: incidence and predictive value of surveillance cultures. *Bone Marrow Transplant.* **33**, 745-749 (2004).
4. Oliveira, A.L. *et al.* Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant.* **39**, 775-781 (2007)