

Infections in Hematopoietic Stem Cell Transplantation Recipients in the Pre-Engraftment Period

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Abstract: *Introduction:* The recipients of the hematopoietic stem cell transplantation (HSCT) are at increased risk of a variety of infections due to their immunocompromised state. The severity of the immunocompromise differs depending upon host, underlying disease, comorbidities, type of transplantation, conditioning regimen, and immunosuppressive drugs. Pre-engraftment period is attended by neutropenia, mucosal barrier disruption, broad spectrum antibiotic usage and invasive procedures like central lines.

Aim: We sought to evaluate the type and frequency of the infections in the pre-engraftment period in our transplant center.

Methods and Results: We reviewed 17 HSCT cases done in our center over 24 months from August, 2011 upto August, 2013 which included 11 autologous and 6 allogeneic HSCT cases. We found a total of 20 febrile neutropenic episodes with 12 bacterial and 6 fungal infections. Eighteen of the 73 cultures were positive (24.65%). Nine out of 17 patients (52.94%) had at least one culture positive. Eight out of 11 bacteria were ESBL producing (extended spectrum beta lactamase) and one organism was only sensitive to colistin. Only 2 of the 12 bacteria were gram positive (16.67%). Only one stool test was positive for *Clostridium difficile*. We had only one culture documented fungal infection (*Aspergillus sinusitis*) and 5 presumed *Aspergillus* infections.

Conclusion: The incidence of febrile neutropenia is similar to other centers in India and Western world, though the organisms are different. Gram negative bacteria continue to be the major threat to hematopoietic cell transplant recipients especially in the early post-transplant period in India.

Keywords: Stem cell transplantation, Infections, Fungal.

INTRODUCTION

The recipients of the hematopoietic stem cell transplantation (HSCT) are at increased risk of a variety of infections due to their immunocompromised state. The severity of the immunocompromise differs depending upon host, underlying disease, comorbidities, type of transplantation, conditioning regimen, and immunosuppressive drugs. Allogeneic HSCT has manifold increased risk than autologous HSCT. The post transplantation infections are roughly divided into pre-engraftment, immediate post engraftment (upto 3 months) and late post engraftment (more than 3 months). The mechanism of immunosuppression is different in different periods post transplantation. Pre-engraftment period is attended by neutropenia, mucosal barrier disruption, broad spectrum antibiotic usage and invasive procedures like central lines [1]. The common organisms expected during this period are gram positive and gram negative bacteria, gut organisms, viruses like *Herpes simplex*

virus, respiratory and enteric viruses and fungi like *Candida* and *Aspergillus* species.

Aim

To evaluate the types and frequency of the infections in the pre-engraftment period in our transplant center.

METHODS

The patient record files and the final microbiology reports were reviewed. All the transplantations were done in HEPA filtered, positive pressure rooms, with all standard recommended precautions, 1:1 nursing and proper central line care (double/triple lumen tunneled). All patients underwent baseline blood and nasal swab cultures and received treatment if indicated prior to entry into the transplantation unit.

Antimicrobial Prophylaxis

Acyclovir was started at day +1 and continued until engraftment in case of allogeneic transplant recipients. Fluconazole prophylaxis was used in all patients (allogeneic as well as autologous) till engraftment.

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Trimethoprim + sulfamethoxazole was started after stable engraftment in allogeneic transplant recipients. All patients used medicated mouth washes, betadine water perianal care, soap water and alcohol hand rub.

Definitions of Infections

On documentation of an oral temperature of 100.4 F or 100 F for 1 hour, blood cultures and if indicated other targeted cultures were taken and empirical antibiotics started. First antibiotic used was cefoperazone + sulbactam. If the fever did not resolve in 2-3 days antibiotics were escalated to carbapenems or as per bacterial sensitivities and serum galactomannan checked on clinical or chest X-ray suspicion. Antifungal used for treatment if indicated was amphotericin-B. We reviewed the microbiology results including bacterial, fungal, viral and other organisms from wide range of the clinical specimens including blood, urine, stool, throat swabs, endotracheal tube secretions, and other specimens.

RESULTS

We reviewed 17 HSCT cases done in our center over 24 months from Aug 2011 upto August 2013 which included 11 autologous and 6 HSCT cases. The indications for the transplantation were multiple myeloma for eight, non-Hodgkin lymphoma for two, Hodgkin lymphoma for one, chronic myeloid leukemia (CML) for one, Sickle cell disease for one, aplastic anemia for two (one with paroxysmal nocturnal hemoglobinuria- PNH), hemophagocytic histiocytosis (HLH) for one and acute myeloid leukemia for one. There were 10 males and 7 females. The median age was 41 years (range from 7 years to 71 years).

The conditioning regimen used were high dose melphalan for multiple myeloma, BEAM (carmustine, etoposide, cytarabine, melphalan) for lymphoma, and busulfan/cyclophosphamide with or without antithymocyte globulin for allogeneic transplantation.

Mean engraftment was on day 12 of the transplantation in autologous and day 16 in the allogeneic transplantation. Engraftment was not reached in the three patients who died.

Bacterial Infections

We found a total of 11 bacterial infections (Table 1) out of the 20 febrile episodes (55%). A total of 73 blood/urine/endotracheal secretions/swabs cultures were sent for the evaluation of the post transplantation/

pre-engraftment febrile neutropenia in addition to the number of follow up cultures to document resolution of the previous infection. Eighteen of the 73 cultures were positive (24.65%). Nine out of 17 patients (52.94%) had at least one culture positive. Eight out of 12 bacteria were ESBL producing (extended spectrum beta lactamase) and one organism was only sensitive to Colistin. The source of the positive cultures were blood (11/18, 61.1%), urine (2/18, 11.1%), throat swab (1/18, 5.5%) and endotracheal secretions (4/18, 22.2%). Only 2 of the 12 bacteria were gram positive (16.67%). The patients who died had multidrug resistant gram negative bacterial infections (*E. coli*, *Acinetobacter* and *Klebsiella species*). All the transplantation subjects had diarrhea at least once during the hospitalization. Ova and cysts, culture, *Clostridium difficile* toxin were checked in all the cases. All of these were negative except one case of *Clostridium difficile* diarrhea which resolved after oral vancomycin.

Fungal Infections

Serum Galactomannan was checked in each episode of febrile neutropenia and also routinely weekly in case of allogeneic transplantations. Six of the 20 febrile neutropenic episodes were positive for serum galactomannan with one of the patients having fungal sinusitis documented with culture (*Aspergillus species*) and treated with liposomal amphotericin-B.

Routine viral screening for *HSV*, *CMV*, *HIV*, HBsAg and Anti-*HCV* was done prior to the transplantation. We did not see any reactivation of *CMV* or *HSV*. We had one death amongst autologous transplant patients and two deaths amongst allogeneic transplantation patients, all of which were due to multi drug resistant bacterial infections.

DISCUSSION

The major cause of the mortality following hematopoietic stem cell transplantation is infection. In the pre-engraftment period, mucositis, low neutrophils due to the conditioning regimen, immunosuppressive drugs and central venous lines increase the chances of the serious infections.

Bacterial Infections

Due to the defective phagocytosis, bacterial infections are very common. Common gram positive bacteria [2] include *Coagulase Negative Staphylococcus*, *Staphylococcus Aureus*, *Streptococci*, and *Enterococci*. Common gram negative bacteria

Table 1: Bacterial Culture Positive Febrile Neutropenias

S. No.	Organism Isolated	Post Transplant day	Clearance/ Outcome	Source	Sensitivity Pattern	Resistance Pattern	Duration of Antibiotics, Dose and Name
1	<i>Coagulase negative staphylococcus</i>	7	Resolved	Blood	Amoxicillin/clavulinate, Cefazolin, Vancomycin, Teicoplanin, Clindamycin, Linezolid, Cefipime, Ciprofloxacin	Erythromycin Co-trimoxazole	Cefipime 2 grams IV Q12H x7d
2	<i>Klebsiella pneumonia</i> (ESBL)	2	Resolved	Blood	Amikacin, Meropenum, Imepenum, Piperacillin/tazobactam (Int), Cefoperazone/sulbactam(Int)	Ceftazidime, Ceftriaxone, Ciprofloxacin, Ofloxacin, Tobramycin, Netilmycin, Cefotaxime, Aztreonam, Cefoperazone	Cefoperazone/ sulbactam(Int) 2gms IV Q12H x 14 days Plus Amikacin IV 750 mg IV Q24H x 14 days
3	<i>Coagulase negative staphylococcus</i>	4	Resolved	Blood	Amoxicillin/clavulinate, Erythromycin, Cefazolin, Clindamycin, Cefuroxime, Cefipime, Ciprofloxacin, Co-trimoxazole	None	Cefoperazone/ sulbactam(Int) 2gms IV Q12H x 11 days
4	<i>Pseudomonas aeruginosa</i>	28	Resolved	Sinus aspiration	Gentamycin, Amikacin, Ceftazidime, Ciprofloxacin, Tobramycin, Imepenum, Piperacillin/tazobactam, Cefoperazone/sulbactam, Cefipime	None	Imepenum IV 500 mg Q8H x 12 dias
5	<i>E. Coli</i> (ESBL)	31	Resolved	Urine	Amikacin, Imepenum, Piperacillin/tazobactam, Cefoperazone/sulbactam,	Gentamycin, Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Cefotaxime, Tobramycin, Cefipime, Ceftizoxime, Aztreonam, Cefoperazone	Imepenum IV 500 mg Q8H x 12 days
6	<i>E. Coli</i> (MDR)	3	Death	Blood	Colistin	Gentamycin, Amikacin, Ceftazidime, Ceftriaxone, Ciprofloxacin, Cefotaxime, Tobramycin, Cefipime, Ceftizoxime, Piperacillin/tazobactam, Aztreonam, Cefoperazone/sulbactam, Meropenum, Imipenum	Colistin 6 M IU iv Q12H x 7d
7	<i>Klebsiella pneumonia</i>	3	Resolved	Throat swab	Gentamycin, Amikacin, Meropenum, Imipenum, Ertapenum	Ceftazidime, Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Cefotaxime, Tobramycin, Cefipime, Cetizoxime, Aztreonam, Cefoperazone	Meropenum 2 grams IV Q8H x 16 days
8	<i>E. Coli</i>	6	Resolved	Urine	Gentamycin, Amikacin, cefoperazone / sulbactam, Piperacillin / Tazobactam, Imipenum, Meropenum, Ertapenum	Ceftazidime, Ceftriaxone, Cefotaxime, Cefipime, Ceftizoxime, Cefoperazone	Meropenum 2 grams IV Q8H x 13 days
9	<i>Acinetobacter baumannii</i> (MDR)	17	Death	Endotracheal tube secretion	Colistin Tigecycline	Ceftazidime, Ceftriaxone, Cefotaxime, Cefipime, Cefoperazone/sulbactam, Gentamycin, Amikacin, Ofloxacin, Co-trimoxazole, Tobramycin, Netilmycin,	Meropenum 2 grams IV Q8H x 6 d Plus Colistin 6 M IU IV Q12H x 3 days

(Table 1). Continued..

S. No.	Organism Isolated	Post Transplant day	Clearance/ Outcome	Source	Sensitivity Pattern	Resistance Pattern	Duration of Antibiotics, Dose and Name
10	<i>Klebsiella pneumoniae</i> (MDR)	14	Death	Throat swab	Colistin Tigecycline	Ceftazidime, Ceftriaxone, Cefotaxime, Cefipime, Cefoperazone/sulbactam, Gentamycin, Amikacin, Ofloxacin, Co-trimoxazole, Tobramycin, Netilmicin, Meropenem	Meropenem 2 grams IV Q8H x 6 d Plus Colistin 6 M IU IV Q12H x 3 days
11	<i>Klebsiella pneumoniae</i> (MDR)	4	Death	Endotracheal tube suction	Colistin Tigecycline	Ceftazidime, Ceftriaxone, Cefotaxime, Cefipime, Cefoperazone/sulbactam, Gentamycin, Amikacin, Ofloxacin Co-trimoxazole Tobramycin Netilmicin Meropenem	Meropenem 2 grams IV Q8H x 4 days Plus colistin 6 M IU IV Q12H

Table 2: All the Observed Infections

Bacterial	Gram positive	3	<i>Coagulase negative staphylococcus</i>	2
			<i>Clostridium difficile</i>	2
	Gram negative	9	<i>Klebsiella P.</i>	4
			<i>E. coli</i>	3
			<i>Pseudomonas A.</i>	1
			<i>Acinetobacter</i>	1
Viral	None			
Fungal	<i>Candida</i>	None		
	<i>Aspergillus</i>	6	Presumed	5
			Culture positive	1
Parasite	None			

[1] include *Enterobacteraceae* like *E. coli*, *Enterobacter*, *Klebsiella* species; others include *Pseudomonas* species. Anaerobes are not very uncommon and include *Clostridium* species. Woo PC, et al. from Hong Kong suggested in their study [3] that bacillus may be responsible for the culture negative febrile neutropenias.

Viral Infections

Reactivation of *Herpes simplex (HSV)* is common and is comparable between allogeneic and autologous transplantation [4]. The median time of reactivation is about 3 weeks [5] and *HSV-1* is more common than *HSV-2*. Other viruses include respiratory viruses like

Respiratory syncytial virus, Influenza and Parainfluenza viruses.

Fungal Infections

Fungal infections are significantly more common in allogeneic as compared to the autologous transplantation. *Candida* and *Aspergillus* species are the commonest killers. *Candida* used to be the commonest before the advent of routine triazole prophylaxis [6, 7] post transplantation though part of this achievement has been blunted by appearance of the resistant *Candida* strains like *C. krusei* and *C. glabrata* [8-10]. *Aspergillus* and *Fusarium* are the common mold infections, though more common in allogeneic than autologous transplantation [11, 12].

B. George *et al.* [13] presented a large retrospective series from India in 2004 of 297 allogeneic transplantation patients. This study included even the post engraftment period and reported 415 documented infections among 304 transplants. All patients developed febrile neutropenia which is fairly constant in over the board studies. We had 66.67% bacterial infections, which is almost double as compared to their series though gram negative bacteria topped our list too at 75% as compared to their 80%). The pattern of gram negative organisms is significantly different as *Klebsiella* and *E. coli* together constituted 58.33% amongst the gram negative group. The major bacterial group in their series was non-fermenting gram negative bacteria at 24.9%. These differences could be attributed to the different hospital flora in these studies. We did not see any viral infections as compared to their study, because their study included the post-engraftment follow up period too. The *Aspergillus* was the most common fungal infection in their study too but *Candida* and *Zygomycetes* were also seen and our study had only *Aspergillus* fungal infections. This may be because of the less number of the patients in our study.

Gudiol C, *et al.* [14] has presented an interesting study of pre-engraftment versus post engraftment blood stream infections in hematopoietic stem cell transplant recipients. They concur with the different etiological factors in the two settings and have indicated worse outcome in the late infections as per their high case fatality ratios. Another fact in concordance with earlier studies remains that Gram positive infections are more prevalent than Gram negative bacterial infections which has been consistently shown to be different in Indian subcontinent as evidenced by the above study by B George, *et al.* [13].

Kinnebrew, *et al.* [15] reviewed a 13 year observational data from Memorial Sloan Kettering Cancer Center of hematopoietic stem cell transplant recipients. Fecal specimens from 37 patients (39%) were found to harbor *C. difficile*. Early-transplant *Clostridium difficile* infection (CDI) was diagnosed in 16 of 94 (17%) patients undergoing allogeneic-HSCT. This is a significant percentage of patients in this critical period. Though we did *Clostridium difficile* testing in all patients with diarrhea, we found only one positive case in our study.

The mortality in our study was related to the multi drug resistant (MDR) bacteria and thus raises concerns regarding the prevalence of the MDR bacteria. We understand from our study that the spectrum of infections may be different in different setting with regard to the local flora.

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