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# Infections among allogeneic bone marrow transplant recipients in India

B George, V Mathews, A Srivastava and M Chandy

*Department of Haematology, Christian Medical College, Vellore, Tamil Nadu, India*

**Summary:**

**Infections are a major cause of morbidity and mortality in patients undergoing high-dose therapy and allogeneic bone marrow transplantation (BMT) despite prophylaxis, use of growth factors and newer antimicrobial drugs. We report the clinical profile of infections among 297 patients who underwent 304 allogeneic transplants between 1986 and December 2001. All patients developed febrile neutropenia. There were 415 documented infections among 304 transplants. This included bacterial (34.9%), viral (42.9%), fungal (15.9%) and other infections (6.3%) including tuberculosis. Bacterial pathogens were mainly Gram-negative bacteria (80%) as compared to Gram-positive (20%) bacteria. The common Gram-negative bacteria were *nonfermenting Gram-negative bacteria* (*NFGNB*) (24.9%), *Pseudomonas* (17.9%), *Escherichia coli* (17.9%) and *Klebsiella* (9.7%). The major source of positive cultures was blood (53.7%) followed by urine (25.5%) and sputum (8.9%). In all, 133/304 (43.7%) transplants had 178 documented viral infections. The common viral infections were due to cytomegalovirus, herpes group of viruses and transfusion-related hepatitis; and 60/304 (19.7%) transplants had 66 documented fungal infections. Common fungi included *Aspergillus* species (69.7%), *Candida* (22.2%) and *Zygomycetes* (8.1%). Tuberculosis was documented in 2.3% of the transplants. Catheter infections were suspected or documented in 7.8% of the transplants (24/304). The incidence of infections in this series from developing countries is not significantly different from reports from the West.**
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Infections following allogeneic bone marrow transplantation (BMT) contribute to morbidity and mortality in the peri and post transplant period. During the first 30 days after BMT, sepsis is mainly related to neutropenia, mucositis and reactivation of dormant herpes simplex. Acute graft-versus-host disease (GVHD) and therapy for GVHD contribute to sepsis in the 30–100 day period. Following this, delayed immune reconstitution contributes to Gram-positive infections. Host defenses are profoundly altered due to the conditioning regimen, use of implanted venous catheters, administration of prolonged immunosuppressive drugs and reactivation of infection. Bacterial and fungal infections in the post transplant period contribute to 15% of post transplant mortality. There is a concern that transplants in developing countries may be associated with a higher incidence of infections related to the poor quality of the environment around the transplant center.

We have attempted to look at the pattern of infections in our center over the past 15 years and compare this data with published literature from the Western world.

## Patients and methods

All patients who underwent allogeneic BMT at the Christian Medical College Hospital between October 1986 and December 2001 were included in this study. The medical records of these patients were analyzed for data pertaining to infection including cultures, biopsy and autopsy reports. All patients had six antigen HLA-matched sibling or family donors.

### *Transplant*

All patients were nursed in HEPA-filtered rooms. Water used for the patient and the unit was boiled and cooled. Food for the patient was usually terminally pressure-cooked prior to consumption. Dual lumen Hickman Broviac catheters inserted surgically under general anaesthesia acted as venous accesses. These venous catheters were dressed twice a week from insertion till discharge from Vellore by trained nursing staff. Once the patient was discharged from the hospital, they remained in Vellore for a period of 4–8 weeks in apartments/houses close to the hospital for easy access.

*Antimicrobial prophylaxis.* Acyclovir was administered at the dose of 15 mg/kg/day intravenously starting on day +1 and switched to oral by day 14. This was continued for 3–6 months as cytomegalovirus (CMV) prophylaxis. Sulfamethoxazole/Trimethoprin for *Pneumocystis carinii* prophylaxis was started once the WBC count was above 3000/mm$^3$ with an ANC >1500/mm$^3$. Intravenous

Correspondence: Dr B George, Department of Haematology, Christian Medical College, Vellore 632004, Tamil Nadu, India;
E-mail: biju@cmcvellore.ac.in
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immunoglobulin (i.v.Ig) was administered at a dose of 400 mg/kg on day +7, +21, and subsequently was given monthly for affordable patients till 12 months post BMT. GVHD prophylaxis consisted of Cyclosporine (2.5 mg/kg/day i.v.) from day −4, while short-course Methotrexate was administered on days +1, +3, +6 and +11 post BMT followed by folinic acid rescue.

### *Documentation of infection*

The patient was considered to be febrile if a body temperature of $\geqslant 38.2^{\circ}C$ was documented.

*Bacterial infections*: Bacterial infections were documented on positive culture from any sites – blood, urine, sputum, pus, abscess and catheter. Urine culture was considered to be significant if the colony count was more than $100\,000/mm^3$ or if colony counts $<100\,000/mm^3$, but considered to be significant if the patient was already on antibiotics. Sputum culture was significant in the presence of pulmonary findings or X-ray infiltrates.

*Fungal infections*: All fungal infections were documented as probable, possible and proven fungal infections based upon the CDC criteria.[1]

*Viral infections*: The diagnosis of herpes simplex and zoster was made on clinical grounds, while tissue invasion was proven on biopsy and histology. The diagnosis of invasive CMV disease was based on tissue diagnosis. PCR for CMV antigen was carried out by day +30 for all patients since 1998. Adenovirus detection was based on ELISA.

*Tuberculosis*: The diagnosis of tuberculosis was based on biopsy showing granulomas positive for AFB and/or cultures being positive.

### *Antimicrobial therapy*

Broad-spectrum antibiotics were started immediately after the temperature rose above $38.2^{\circ}C$ or higher or for documented or suspected bacterial infections. Blood cultures were drawn prior to the initiation of antibacterial therapy. X-ray examination of the chest was also carried out. Our first-line antibiotic therapy for febrile neutropenia consists of cefotaxime, gentamicin and fluconazole. If the fever persists or the patient is toxic, this is rapidly escalated to ceftazidime or imipenem and amoxycillin/calvulinic acid or vacomycin. Fluconazole is changed to amphotericin if fever persists or in the presence of pulmonary infiltrates. Stool and throat surveillance cultures were performed once a week and guide antibiotic policy, particularly if there are resistant bacteria. Ganciclovir was started if the patient became PCR positive for CMV and was on immunosuppressive therapy for the treatment of acute GVHD.

## Results

A total of 297 patients had 304 allogeneic transplants between October 1986 and December 2001. This included 211 males (69.4%) and 93 females (31.6%). Recipients included 164 children (<15 years) and 140 adults with an average age of 17.3 years (range: 0.5–51 years). The graft source was bone marrow in 266/304(87.5%), G-CSF-mobilized stem cells in 37/304(12.1%) and cord blood in one patient (0.4%). Indications for BMT include thalassaemia major (50.8%), acute lymphoblastic leukemia (14.7%), chronic myeloid leukemia (13.1%), aplastic anemia (11%), acute myeloid leukemia (4.2%), myelodysplastic syndrome (4.7%) and others (including PNH, PRCA, DBA) (1.5%).

*Infections*: There were 415 documented infections in 304 transplants. This included 145 bacterial (34.9%), 178 viral (42.9%), 66 fungal (15.9%) and 26 other infections (6.3%). There was no difference in the incidence of infections between patients transplanted for malignant and nonmalignant indications. Fungal infections were, however, seen to be lower among pediatric patients as compared to adults (Table 1).

*Bacterial infections*: In all, 111/304 (36.5%) transplants had 145 documented bacterial infections. The majority of bacterial infections (55%) occurred in the first 30 days following BMT. The organisms identified were mainly Gram-negative bacteria (80%) with few Gram-positive organisms (20%) (Table 2). The common gram-negative bacteria identified included *NFGNB* (24.9%), *Pseudomonas* (17.9%), *E. coli* (17.9%) *and Klebsiella* (9.7%).The gram-positive organisms were *Staphylococcus aureus* (5.5%) and *Coagulase negative staphylococci* (8.9%). Positive bacteriological cultures were obtained from blood (53.7%) followed by urine (25.5%) and sputum (8.9%) (Table 3). Majority of the organisms causing bacteremia were gram-negative organisms (81%), commonly *NFGNB* and *Pseudomonas*. The overall incidence of bacterial infections seems to be slowly decreasing over the years, although infections by gram-positive organisms seems to be slowly increasing (31.1% after 1996 compared to 9.6% between 1991 and 1995).

*Viral Infections*: In all, 133/304(43.7%) transplants had 178 documented viral infections (Table 4). The common pathogens include CMV, herpes group of viruses, adenovirus and transfusion-related hepatitis viruses.

**Table 1** Patient profile and distribution of infection

| | *Bacterial infections* | *Viral infections* | *Fungal infections* |
|---|---|---|---|
| Overall ($n=304$) | 111 (36.5%) | 133 (43.7%) | 60 (19.7%) |
| Malignant disorders ($n=113$) | 43 (38.1%) | 45 (39.8%) | 24 (21.2%) |
| Nonmalignant disorders ($n=191$) | 68 (35.6%) | 88 (46%) | 36 (18.8%) |
| Adults ($n=140$) | 50 (35.7%) | 56 (40%) | 40 (28.5%) |
| Children ($n=164$) | 61 (37.1%) | 77 (46.9%) | 20 (12.1%) |

**Table 2** Bacterial infections – organisms identified

| | | | |
|---|---|---|---|
| Gram-negative organisms | 116 (80%) | Gram-positive organisms | 29 (20%) |
| *Nonfermenting GNB* | 36 (24.8%) | *Coagulase negative staphylococci* | 13 (8.9%) |
| *Pseudomonas* | 26 (17.9%) | *Staphylococcus aureus* | 8 (5.5%) |
| *Escherichia coli* | 26 (17.9%) | *Enterococcus* | 5 (3.5%) |
| *Klebsiella* | 14 (9.7%) | Others | 3 (2.1%) |
| Others | 14 (9.7%) | | |

**Table 3** Bacterial infections – sources of positive culture

| | |
|---|---|
| Blood | 78 (53.7%) |
| Urine | 37 (25.5%) |
| Sputum | 13 (8.9%) |
| Pus | 5 (3.5%) |
| Catheter site | 4 (2.8%) |
| Others | 8 (5.6%) |

**Table 4** Viral infections – pathogens

| | |
|---|---|
| Cytomegalovirus | 69 (38.8%) |
| Herpes simplex | 37 (20.8%) |
| Hepatitis C | 30 (16.8%) |
| Hepatitis B | 17 (9.5%) |
| Herpes zoster | 15 (8.4%) |
| Adenovirus | 6 (3.3%) |
| Others | 4 (2.4%) |

**Table 5** Sites of fungal infection

| | |
|---|---|
| Lungs | 34 (51.5%) |
| Disseminated | 10 (15.5%) |
| GIT | 5 (7.5%) |
| Blood | 4 (6.0%) |
| CNS | 4 (6.0%) |
| Others – skin, catheter, sinus, heart, ear | 9 (13.5%) |

*CMV*: CMV infection was detected in 69/304 (22.6%) of transplants. Of these, 56/69 (81.1%) patients were positive for CMV by PCR. CMV disease was confirmed by biopsy in 16/69 (23.1%). Sites of involvement included gastrointestinal tract (31.2%), lungs (25%), liver (6.3%) and also a disseminated form (37.5%). CMV infection was documented at a median of 48 days post transplant (pre BMT – 121 days). Documented CMV infection was seen mainly in patients on immunosuppressive medication for acute GVHD. Among the 16 patients who had documented CMV disease, nine (56%) have expired.

*Herpes simplex and zoster infection*: Herpes simplex infection was seen in 37/304 (12.1%) transplants. The majority (87%) had only oral herpes simplex. Tissue infiltration was seen in the GIT and as genital ulcers. Herpes zoster was seen in 15/304 (4.9%) of the transplants. The average time of infection was 133 days (day −3 to 365 days).

*Hepatitis B infection*: Hepatitis B was detected in 17/304 (5.5%) of transplants. In 9/17 (52.9%), hepatitis B was diagnosed prior to BMT, while in 8/17 (47.1%), hepatitis B infection was diagnosed after BMT. In all, one patient died of hepatic encephalopathy related to hepatitis B; two patients had donors who were hepatitis B positive (HbSAg positive but HBV DNA negative), but there was no seroconversion post BMT in both the patients.

*Hepatitis C infection*: Hepatitis C was detected in 30/304 (9.8%) transplants. In all, 25/30 (83.3%) patients were positive for Hepatitis C prior to BMT, and 5/30 (16.7%) developed Hepatitis C following BMT. There was no worsening of hepatic dysfunction attributable to Hepatitis C.

*Adenovirus infections*: Adenoviral infections were seen in 6/304 (1.9%) of all transplants. Adenovirus was isolated from urine in four (66.6%) and one each from lungs and stool. Almost all patients had a self-limiting illness, except for the patient with adenoviral pneumonia where it was fatal.

*Fungal infections*: Fungal infections were documented in 60/304 (19.7%) transplants. The common organisms identified were *Aspergillus* species (69.7%), *Candida* species (22.2%) and *Zygomycetes* (8.1%). For infections due to aspergillus, all patients fulfilled the CDC criteria of either proven or possible fungal infection. Majority of the infections were seen in the early and mid recovery phase of BMT (<100 days post BMT). Only a few (12%) occurred more than 100 days post BMT with all being on chronic immunosuppressive therapy for GVHD. The most common site of fungal infection was the lung (51.5%). Other sites included the central nervous system, isolation from blood (candida), gastrointestinal tract, skin, catheter related and a disseminated form (Table 5).

*Tuberculosis*: In total, 9/304 (2.3%) of transplants developed tuberculosis. This included a disseminated form in five (55.5%), involvement of the bone in two patients (22.2%) and involvement of the lung and the lymph node in one patient each. All patients were on steroids for GVHD when they developed tuberculosis. All patients have responded well to antituberculous therapy.

*Parasitic Infections*: Two patients had infections with *Plasmodium vivax* and one with *Plasmodium falciparum* infection during BMT. All patients were treated successfully. *Cryptosporidium* was identified in the stool in nine patients (2.9%). *Ascaris* infection was seen in four patients (1.3%). Infections due to *P. carinii* infections were not seen in any transplant recipients.

*Catheter-related infections*: In all, 24/304 (7.8%) transplants had either suspected (55%) or documented (45%) catheter infections. Organisms included *Staphylococcus aureus* (45.4%), *Coagulase negative staphylococci* (27.3%) and *Candida albicans* (27.3%).

**Table 6** Day 100 mortality related to infection

| *Cause of mortality* | *Number (%)* |
|---|---|
| (A) Bacterial infections | 4 (8.9%) |
| (B) Fungal infections | 34 (75.5%) |
| GVHD with fungal infection | 12 |
| Relapse with fungal infection | 1 |
| Graft failure with fungal infection | 5 |
| Isolated fungal infection | 16 |
| (C) CMV disease | 7 (15.6%) |
| GVHD with CMV disease | 6 |
| Isolated CMV disease | 1 |

*Mortality*: Out of 304 transplants, 120 (39.4%) have expired, with 84 (27.6%) expiring in the first 100 days following BMT. Infection-related 100-day mortality was seen in 45 out of the 304 transplants (14.8%) The major causes included fungal pneumonia and CMV infection (Table 6).

## Discussion

Infections are a major cause of morbidity and mortality in patients following allogeneic BMT. In our study, we have tried to evaluate the clinical profile of various infections following allogeneic BMT, and ascertain whether infections following BMT in a developing country in the tropics were similar to economically advanced countries.

In all, 251/304(82.5%) transplants had clinical or microbiologically significant bacterial, fungal or viral infection with all patients developing febrile neutropenia. The incidence rates reported in western studies have varied between 60 and 90% depending on the transplant center.[2]

The incidence of bacterial infections of 36.5% is similar to western data[3,4] where rates ranging between 35 and 50% have been reported. Gupta *et al*[5] from a referral center in North India have reported similar infection rates among transplant patients. Data from developing countries though limited are similar, with 40–50% of patients developing bacterial infections.[6] Gram-negative bacteria are still the major organisms, although recently the incidence of gram-positive organisms seems to be on the increase, consistent with western data.[7] The decrease in the incidence of documented bacterial infections related to early and aggressive use of antibiotics in treating febrile neutropenia in transplant recipients has also reflected in a decreased mortality attributable to bacterial infections over the years.[3,4,7]

Viral pathogens seem to be the major organisms causing infections among Indian transplant recipients. The incidence of herpes simplex and herpes zoster infections (8–10%) are similar to incidences worldwide.[8,9] CMV infection was common (38.8%), with histological or microbiological evidence of CMV disease seen in 9.5% of patients. Limited data from Asia reveal incidences varying from 1.7 to 16%, although CMV is the main causative organism associated with interstitial pneumonitis (36–60%).[10,11] Early diagnosis of CMV antigenemia using PCR and preemptive therapy with ganciclovir, especially in patients 'at risk', may help in reducing the risk of CMV disease.[12,13]

The incidence of hepatitis B and hepatitis C seems to be similar to western data.[14,15] Reactivation and hepatic dysfunction due to hepatitis B or C was uncommon among transplant recipients. Reactivation can be seen in 8–12% of patients with hepatitis B during BMT and rare case reports exist with hepatitis C. The use of HbSAg-positive, but HBV DNA-negative donors did not result in seroconversion in any of our patients.

Data on fungal infections from various transplant centers around the world suggest an incidence varying between 4 and 30%.[16,17] Studies from Asian countries like Israel have observed an increasing incidence of fungal isolates from BMT units[18] similar to the data from our center (19.7%). Infections due to *Candida* infections have decreased over the years probably due to the early institution of fluconazole for the treatment of febrile neutropenia. Invasive fungal infections due to aspergillus are still a major cause of morbidity affecting 14.5% of transplants. Steroid therapy for GVHD and prolonged neutropenia secondary to graft failure or rejection were identified as the main predisposing factors[19,20] in the majority of fungal infections.

Tuberculosis was surprisingly uncommon (2.3%) among transplant recipients.[21] Studies from developing countries, including Turkey and Hong Kong, have reported incidences varying between 1 and 12%.[22–24] In view of the low incidence in India, INAH prophylaxis during BMT may not be essential.

Parasitic infections including malaria seem to be uncommon, despite India being endemic for malaria. There were no reported infections due to *P carinii* in our series, although worldwide data suggest an incidence varying between 2 and 7%.[25] Early initiation of Septran prophylaxis may have helped in this observation. Catheter-related infections are less common (7.8%) compared with the available data where the incidence varies from 12 to 40%.[26] This may be related to the aggressive catheter care practised by our nursing staff for all transplant recipients.

This study demonstrates that it is possible to perform BMT in the developing world with infection rates comparable to the western world. Despite the poor quality of the environment, contaminated water and poor sanitation as seen in many developing countries, the overall infection rates are not higher, suggesting that there may be enough immune recovery to prevent infections unless there is GVHD. Institution and adherence to a well-planned infection control strategy for the transplant units and an appropriate strategy for the prevention and management of sepsis may also have contributed to this decrease.

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