



## **Infections After Bone Marrow Transplantation in Children – A Retrospective Analysis**

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## **Abstract**

**Introduction:** Bone marrow transplantation and/or stem cell transplantation have become standard therapy offering potential cures to many hematologic malignancies and immunologic conditions. There are very few BMT centers in Pakistan thus, data is very rare from our settings. In a retrospective study rate of infections after bone marrow transplant was assessed within 100 days after bone marrow transplant in children.

**Methodology:** A cross sectional (retrospective) study was conducted at the Bone Marrow Transplant Unit in Children Hospital, PIMS, Islamabad in a period of 6 months after approval of synopsis. Medical record of a total of 95 patients transplanted between 2009 and 2016 was reviewed. All children both male and female who had undergone bone marrow transplant below 12 years were included. The study outcome was measured in terms of post-transplant infection in first 100 days after bone marrow transplant.

**Results:** The average age of patients was 7.1 years with male dominance with 64 (67.3%) cases. Post-transplant infection was found in 51 (53.6%) study cases. Blood culture and pus culture proven infection was seen in majority of the study cases. Of the total 95 cases, 52 (54.7%) were cured, in 17 (17.9%) cases BMT was rejected whereas 26 (27.4%) patients expired.

**Conclusion:** Post BMT infection was high in this study. Further studies should be done to see the causative factors of post bone marrow transplant in our local pediatric population.

**Keywords:** Post BMT Infection; Demographical; Clinical; Pathological; Factors.

## **Introduction**

Bone marrow transplantation and/or stem cell transplantation have become standard therapy offering potential cures to many hematologic malignancies and immunologic conditions in children. Historically critically ill patients with any blood disease or immunologic disorder did not have choice of such therapy. All of these cells develop from a type of basic cell found in the bone marrow, called a stem cell [1].

Bone marrow is a soft blood forming tissue that fills the cavities of bones and contains fat and immature and mature blood cells, including white blood cells, red blood cells, and platelets. A bone marrow transplant is a process to replace unhealthy bone marrow with healthy bone marrow. Bone marrow transplants can be used to treat patients with; life-threatening blood cancers like leukemia, other immune system or genetic diseases and hemoglobinopathies like beta thalassaemia major [2].

The donor source for a bone marrow transplant could be the patient (autologous), a sibling or unrelated person also known as HLA matched (allogeneic), an identical twin (syngeneic), or a genetical- lyunrelated matched bone marrow or umbilical cord blood [3].

Around 20 to 40% patients receiving bone marrow transplant would require ICU admission in the initial post transplantation phase [2]. The survival rates after admission to the ICU are dis- mal, particularly if mechanical ventilation is required for respiratory failure. Infection remains the major source of morbidity and mortality in patients who undergo BMT [4]. Children are at much higher risk of developing post-transplant infections. These include infections with bacteria, respiratory and enteric viruses, herpes simplex virus, candida and aspergillus fungi. Other pathogens include pneumocystis, toxoplasma, tuberculosis, pneumococcus, H. influenza and varicella zoster [5]. The mortality rates are as high as 60% which have been reported for infectious diseases [6].

According to the National Marrow Donor Program, of 462 patients in the United States who underwent an unrelated allogeneic BMT between December 1987 and November 1990, 66% had died by 1991, with infection as the most common primary cause of death [7]. In spite of the availability of bone marrow transplantation, the sufferings of the affected patients before and after the transplant remain worrisome for investigators. However, with optimal monitoring and evaluation of these cases and adequate management, the post-transplant complications can be curtailed. Evidence-based guidelines for the management of pediatric febrile neutropenia are beneficial from a pediatric-specific focus, such as consideration of outpatient management and oral antibacterial therapy [8].

Evidence on patients with bone marrow transplantation is limited, specially, with reference to interventions for the cure of infections [8,9]. There are very few BMT centers in Pakistan thus, data is very rare from our healthcare settings. We conducted a retrospective study to determine infections after bone marrow transplant conducted in children presenting to Bone Marrow Transplantation Clinic, Children Hospital, PIMS, Islamabad.

## Methodology

### Study definitions

**Bone Marrow Transplant:** Bone marrow transplant is a process to replace unhealthy bone marrow with healthy bone marrow.

**Infection:** A patient in the state of being infected which is known as a disease caused by germs that enter the body, fever of 38°C or above, recent blood products and/or any obvious focus; CRP and blood cultures suggestive of infection. The infection was observed till 100 days after BMT.

### Subject selection and study methods:

A retrospective cross-sectional study was conducted at the Bone Marrow Transplant Unit in the Children Hospital, PIMS, Islamabad in a period of 6 months. Medical record of a total of 95 patients who were transplanted between 2009 and 2016 was re-viewed to fill the pre-structured study proforma. All children both male and female who had undergone bone marrow transplant below the age of 12 years were included in the study.

The baseline data regarding the patients was recorded first. A thorough evaluation was performed of the medical records of all selected patients. The type of infection was assessed and the final outcome of these patients in terms of morbidity and mortality was also recorded.

### Statistical considerations

SPSS 17.0 was used to enter and analyze data. Descriptive analysis was done to measure frequency and percentages from categorical variables whereas mean and standard deviations from continuous numerical variables.

## Results

The average age of patients was 7.1 years ranging from 1.1 to 12 years. Male gender was dominant with 64 (67.3%) cases. Post-transplant infection was found in 51 (53.6%) study cases. Almost one third 29 (30.5%) mothers were illiterate, 30 (31.5%) had up to secondary level education whereas 36 (37.8%) had higher secondary to graduate level. Similarly, 15 (15.7%) fathers were illiterate in the study, 38 (40.0%) had up to secondary level education and 42 (44.2%) had higher secondary/graduate level education in this study. The majority of the study cases 83 (87.3%) were suffering from thalassaemia major disease for which BMT was done. Of the rest of patients, 10 (10.5%) had aplastic anemia whereas 2 (2.1%) patients had MDS. In all 95 (100.0%) study cases allogeneic HLA matched type of BMT was done (Table 1).

	No. of cases	% age
<b>Age (years)</b>		
≤ 5	29	30.5%
6-12	66	69.5%
<b>Gender</b>		
Male	64	67.3%
Female	31	32.7%
<b>Mothers education</b>		
Illiterate	29	30.5%
Up to secondary	30	31.5%
Higher secondary/graduate	36	37.8%
<b>Fathers education</b>		
Illiterate	15	15.7%
Up to secondary	38	40.0%
Higher secondary/graduate	42	44.2%
<b>Socioeconomic status</b>		
High	10	10.5%
Middle	31	32.5%
Poor	54	56.8%
<b>Disease for BMT</b>		
Thalassaemia major	83	87.3%
Aplastic anemia	10	10.6%
MDS	2	2.1%

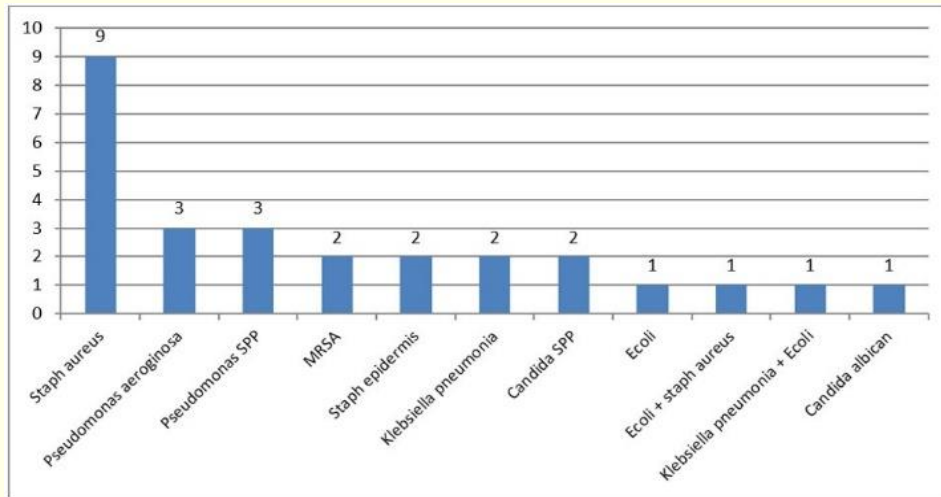
**Table 1:** Socio-demographic characteristics of study patients (n=95).

The findings of pathological investigations were assessed in the study. Of the total 95 study cases, 51 (53.4%) had positive CRP. PCR test found cytomegylovirus in 15 (15.8%) study cases. It was found out that 27 (28.4%) patients had positive blood culture. The most frequent bacterial pathogen found was staph aureaus in 9 (9.4%) study cases, pseudomonas aeruginosa was present in 3 (3.1%) and pseudomonas SPP also in 3 (3.1%) cases. Similarly, MRSA, staph epidermis, klebsiella pneumoniae and candida SPP were found in 2 (2.1%) patients each (Table 2).

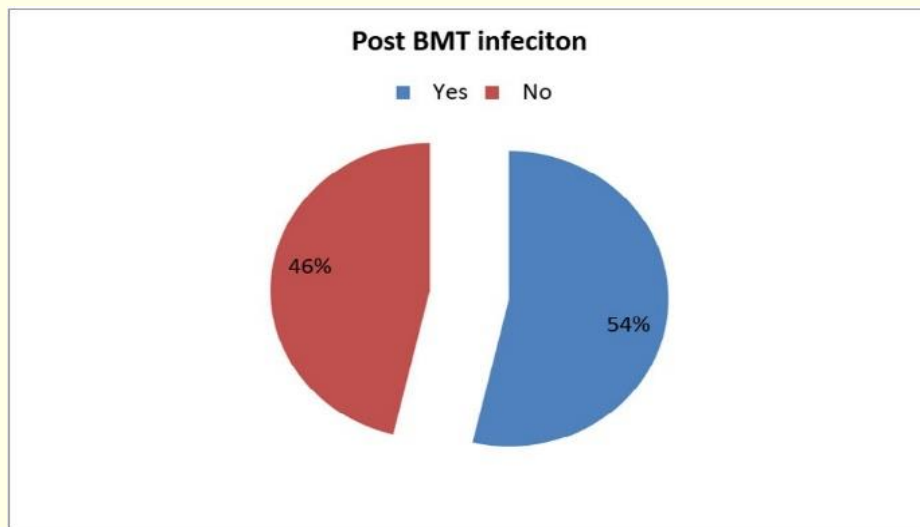
	No. of cases	% age
<b>CRP</b>		
Positive	51	53.6%
Negative	44	46.4%
<b>Blood culture</b>		
Positive	27	28.4%
Negative	68	71.6%
<b>Urine culture</b>		
Positive	3	3.1%
Negative	92	96.9%
<b>Pus culture</b>		
Positive	11	11.5%
Negative	84	88.5%
<b>PCR</b>		
Cytomegylovirus	15	15.8%

**Table 2:** Pathological investigations in the study patients (n=95).

Overall post-transplant infection within 100 days of transplantation was found in 51 (53.6%) study cases (Figure 1,2). The out- come of bone marrow transplant was assessed, and of the total 95 cases, 52 (54.7%) were cured, in 17 (17.9%) cases BMT was rejected whereas 26 (27.4%) patients expired (Table 3).



**Figure 1:** Findings of blood culture in the study (n=27).



**Figure 2:** Status of infection after bone marrow transplant in the study (n=95).

	No. of cases	% age
Cured	52	54.7%
Rejected BMT	17	17.9%
Expired	26	27.4%

**Table 3:** Outcome of the bone marrow transplant in the study (n=95).

## Discussion

The current study was based on children who were transplanted in the Bone Marrow Center, Children Hospital, PIMS, Islamabad with the aim to determine post-transplant infection in children. Mean age of patients was 7.1 years with male gender preponderance in this study (67.3%). A study by Ball LM from Holland also saw male dominance with (57.8%) proportion [10]. A previous study by Irfan M et al from Pakistan also witnessed a similar trend of male dominance [11]. Feng Z et al witnessed that almost (90.0%) of their study cases were males [12]. The above mentioned reports of male gender's preponderance are comparable with the current study results.

The overall rate of post BMT infection was 53.6% in this study and the most frequent pathogens were staphylococcus aureus followed by pseudomonas aeruginosa, pseudomonas SPP and others like staphylococcus epidermis, klebsiella pneumonia and candida SPP. A recent study by Mynarek M on infection and its risk factors after stem cell transplantation revealed that up to 40% patients developed infection in the initial post bone marrow transplant period and required intensive care.4 Another study by Wingard JR et al reported that 40% of post transplantation infections were due to gram negative bacteria including Pseudomonas, Enterobacter, Escherichia coli and Klebsiella [13]. Hachem AR revealed that fungal infections are overall responsible for post transplant infections in up to 20% cases with candida albicans as the main source [14]. These previous reports on infections according to different types are not closely comparable to our study findings.

In the present study of the total of 95 bone marrow transplants, (54.7%) were fully cured, (17.9%) experienced BMT rejection whereas (27.4%) died. Lawson et al witnessed disease-free survival of 81.0% cases [15]. A previous study reported that majority 66% of the patients transplanted died of infection as the most common primary cause [7]. A study from Taiwan witnessed 44% survival rate after transplant [12].



A previous study from Karachi Pakistan reported disease free survival of (58.0%), BMT rejection in (10.5%) cases and mortality in (31.0%) cases [11]. In post transplantation period, infections are a very lethal condition and cause huge mortality in majority of the affected cases.

There are numerous advantages of the current study. Firstly, there are very few studies on children with bone marrow trans-plant, this is one of the very few studies done locally and at national level as well. A significant sample of children's record who underwent BMT was reviewed. There were few limitations of the study which mainly lie in the observational design of the study as we gathered information retrospectively and the flaws and weak- nesses of this study design were there. But for record purpose the advantages of the study outnumber the limitations.

Many previous reports are quite comparable to the current study findings, except for Lawson's study which was conducted in the settings of a developed country and others discussed are from healthcare settings of developing countries. In this way it can be argued that experience of the bone marrow transplant profession-also and setting of the transplant centers as well as ethnic back- ground and geographical region also plays an important role in the overall success and disease-free survival of patients after bone marrow transplant.

## Conclusion

Post BMT infection was very high in this study. Apparently, low socioeconomic status and illiteracy seems in majority of the patients transplanted which may have immune-compromised status which many have a role in this high rate of infection. Furthermore, the factors responsible for these infections should be explored.

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