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Analysis of early infectious complications in pediatric patients undergoing bone marrow transplantation

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Abstract The purpose of the present study was to analyze the characteristics of infectious complications occurring during the first 100 days after bone marrow transplantation (BMT) in a cohort of 123 pediatric patients with hematological malignancies ($n=73$), solid tumors ($n=32$) and nonmalignant disorders ($n=18$). Fifty-eight patients received allogeneic grafts, and 65 patients an autologous transplant. Fever developed in 107 (87%) children; 82% of infectious complications occurred during the neutropenic period. Documented infection developed in 33 (31%) patients, while 74 (69%) patients had possible infection (i.e. fever of unknown origin). The incidence of bacteremia was 21%, and gram-positive cocci were the predominant pathogens; non-bacteremic microbiologically documented infection developed in 6% of patients; clinically evident infection developed in 4% of subjects. The incidence of primary febrile episodes was not significantly different between autologous and allogeneic BMT (86% vs 88%); nor did the median number of days to the onset of fever (5 days in both groups) or the median duration of fever (5 days in both groups) differ. In contrast, the frequency of secondary febrile episodes was significantly higher ($P=0.0001$) in allogeneic BMT recipients (40%) than in autologous recipients (15%). The mortality rate due to infections was 2/36 (5%) for matched sibling donor BMT, and 1/13 (8%) for matched unrelated donor BMT. No deaths occurred in the 65 patients who were autografted. Invasive fungal infections accounted for 2 of the 3 infectious deaths. In conclusion, the majority of children undergoing BMT experienced at least one infectious episode; allogeneic BMT recipients were at high risk of developing secondary febrile episodes, but the overall mortality rate due to infection in the first 100 days after transplantation was low.

Key words Infectious complications · Bone marrow transplantation in children · Bacteremia

Introduction

Although the results of bone marrow transplantation (BMT) have been encouraging, infectious complications still result in significant morbidity and mortality and remain major obstacles to further improvement of survival rates [3, 28].

Infections following BMT are determined in part by the sequential events that occur in the process of marrow ablation, hematopoietic engraftment and immunologic recovery. The type of infections and their severity

are related to the patient's underlying disease, the method of marrow ablation and the speed and completeness of marrow recovery [19].

Early and late infectious complications after autologous and allogeneic BMT are well documented [6, 7, 9, 13, 16]. Approximately 35–100% of adult patients receiving BMT become infected, with an infectious mortality rate ranging from 5% to 33% [6, 9, 14, 15, 30, 31]. In contrast, there have been few published reports dealing exclusively with children undergoing BMT [2, 17, 23, 25].

The present study aims to analyze the characteristics of all febrile episodes occurring during the first 100 days after BMT in a cohort of 123 pediatric patients who were grafted at a single institution over a 6-year period.

Patients and methods

Patients

One hundred twenty-eight consecutive children received their first hematopoietic precursor cell transplantation at the Department of Pediatrics, University of Turin, during the period from October 1989 (the start of our BMT program) to August 1996.

Three patients who received an haplo-identical transplant and two patients who were grafted while febrile were excluded from the analysis. Thus, the study group consisted of 123 patients who were examined for evidence of infection during the first 100 days posttransplant.

Fifty-nine percent of transplantations were performed in children with hematological malignancies, 26% in children with solid tumor and 15% in children with nonmalignant disorder. Table 1 summarizes the patient characteristics.

Table 1 Patients' characteristics (*BM* bone marrow, *PBPC* peripheral blood precursor cells, *CBSC* cord blood stem cells, *CMV* cytomegalovirus, *TBI* total body irradiation, *TAI* thoraco-abdominal irradiation, *CSA* cyclosporin, *MTX* methotrexate, *ATG* antithymocyte globulin)

	Autologous transplantation	Allogeneic transplantation
No. of patients	65	58
Median age in years (range)	8 (2–20)	7.5 (2–20)
Sex: male/female	40/25	37/21
Underlying disease		
Malignancy		
Acute leukemia	30	35
Lymphoma	2	3
Hodgkin's disease	1	0
Chronic myelogenous leukemia	0	1
Myelodysplastic syndrome	0	1
Solid tumor	32	0
Nonmalignant disorders		
Thalassemia	0	10
Blackfan-Diamond anemia	0	1
Severe aplastic anemia	0	1
Fanconi anemia	0	2
Lysosomal storage diseases	0	4
Donor relationship		
HLA-identical sibling transplants	NA	36
Non-identical family transplants	NA	9
Matched unrelated donor transplants	NA	13
Source of transplant		
Bone marrow	59	54
PBPC	6	3
CBSC	NA	1
Serological status before transplant		
Recipient CMV positive	43	40
Donor CMV positive	NA	35
Preparative regimen		
Chemotherapy	44	29
Chemotherapy + TBI	21	27
Chemotherapy + TAI	0	2
Median no. (range) of nucleated cells infused $\times 10^8$/kg	1.70 (0.40–13.4)	3.55 (0.60–15.5)
GVHD prophylaxis		
CSA	NA	24
CSA+MTX	NA	21
CSA-MTX+ATG	NA	12
Ex vivo T cell depletion	NA	1

Transplantation procedure

Only primary transplants were included in the present analysis. Grafts were from genotypically HLA-matched siblings for 36 patients, a partially matched related donor for 9 patients (2 siblings, 7 parents) and an unrelated volunteer donor for 13 patients; 65 patients underwent an autologous transplantation.

All patients were prepared for transplantation according to protocols appropriate to their underlying disease and the type of transplant. In 48 of the 123 transplants (21 autologous, 13 allogeneic, 5 mismatched and 9 unrelated marrow transplants) the conditioning regimen included total-body irradiation (TBI).

Peripheral blood progenitor cells (PBPCs) for allogeneic transplantation were collected through aphereses after G-CSF mobilization in 3 donors.

Tissue typing for all patients and unrelated donors included serotyping for HLA-A,-B,-DR and DQ antigens. HLA-D region compatibility was also defined by DRB1 typing using sequence-specific oligonucleotide probe hybridization.

In 4 autologous recipients marrow was purged ex vivo by means of 4-hydroperoxycyclophosphamide prior to cryopreservation. In 1 patient receiving BMT mismatched for one antigen, bone marrow was treated ex vivo before infusion with vincristine and methylprednisolone.

Microbiological evaluation

Pretransplant evaluation included a complete medical history, particularly focusing on previous major infections and a careful physical examination for signs and symptoms of infection. Surveillance cultures of oropharynx, nose, urine and stool were obtained before the transplant and weekly thereafter. Cytomegalovirus (CMV), herpes simplex virus (HSV) and Epstein-Barr virus (EBV) serology and CMV antigenemia/viremia were analyzed before the transplant and weekly thereafter until day 100 after the transplant.

At the development of fever at least three blood cultures were taken, one from a peripheral vein and the others from the indwelling central venous catheter (CVC), as well as cultures from any clinically relevant site. The initial screening also included determination of creatinine and transaminase levels, C-reactive protein (CRP) and a complete blood cell count including differential leukocyte count.

Diagnostic definitions

Neutropenia was defined by an absolute neutrophil count of less than 0.5×10^9 cells/l.

Fever was defined as an axillary temperature of 38–38.5 °C on two separate occasions 2 h apart or more than 38.5 °C on one occasion and not related to transfusion of blood products. Febrile episodes were categorized as primary or secondary: the primary episode was the first one developing after transplantation, while secondary febrile episodes were those occurring after at least 72 h of defervescence from a previous episode.

According to EORTC criteria [4], infections were subclassified as Microbiologically Documented With Bacteremia when pathogenic microorganisms were recovered from the blood, as Microbiologically Documented Without Bacteremia when pathogenic microorganisms were recovered from any affected site except blood (i.e. urine, stool, oropharynx), and as Clinically Documented when signs and/or symptoms of infection at anatomic sites were present but pathogens were not detected. Patients who developed fever but lacked clinical or microbiological evidence of infection or other obvious causes were classified as having fever of unknown origin (FUO).

CMV disease was defined as positive antigenemia and/or recovery of virus from a visceral site or by bronchoscopy with lavage (BAL) in patients with associated signs and symptoms consistent with CMV infection [20].

Patients who had a relapse of their malignancy following transplant were, from then on, no longer considered to be at risk for infectious complications.

Supportive measures

All patients had central venous access with single-lumen ($n=24$) or double-lumen ($n=99$) catheters inserted before conditioning. Patients were nursed in reverse isolation in positive pressure or in a laminar air flow room. All patients were scheduled to receive a low microbial diet without food sterilization procedures.

A gut decontamination regimen with oral nonabsorbable antibiotics was started on day 1 after transplant in 53 patients; 29 patients were given prophylactic fluoroquinolone antibiotics treatment; and 5 patients received nonabsorbable and absorbable antibiotics. Thirty-six children did not receive any gut decontamination regimen because of an inability to take oral medications. Fifty-five patients received either fluconazole ($n=11$) or amphotericin B i.v.($n=12$), oral itraconazole ($n=25$) or nystatin ($n=7$) as prophylaxis against fungal infections.

In order to shorten the period of neutropenia following the transplant, 92 patients received hematopoietic growth factors: 65 patients received G-CSF, 20 patients GM-CSF, and 7 patients G-CSF and GM-CSF; 31 patients did not receive any hematopoietic growth factor.

All patients were given cotrimoxazole or pentamidine after the graft for prophylaxis against *Pneumocystis carinii* infection.

Patients who were CMV seropositive were treated prophylactically with intravenous acyclovir at a dose of 500 mg/m^2 every 8 h from day –5 until day +30 or discharge, whichever was earlier. From September 1992 allogeneic recipients who were CMV positive received prophylactic ganciclovir as described elsewhere [1]. Acyclovir (250 mg/m^2 every 8 h) was also given, using the same route and schedule as previously described, to patients seropositive for herpes simplex virus but seronegative for CMV.

Immunoglobulin preparations were administered at a dose of 500 mg/kg weekly from 1 week before until day 90 after transplant and then monthly until day 180 (in 42 autologous transplant recipients) or day 360 (in 51 allogeneic transplant recipients).

Blood component therapy was used to maintain the hemoglobin level >9 g/dl and platelets $>20 \times 10^9$/l; all cellular products were filtered, leukocyte-depleted and routinely irradiated with 25 cGy, but were not screened for CMV.

Statistical methods

Between-group comparisons were performed and the Chi-square test of significance applied. When required, Bonferroni's correction and Fisher's exact test were used. A result was declared significant at the 5% level, and the confidence interval was computed.

Results

Fever developed in 107 (87%) of the 123 patients, 16 patients (9 autologous;7 allogeneic) remaining free of infection and fever periods during the entire observation period. Table 2 summarizes the characteristics of

Table 2 Characteristics of infections complications (*MDI* microbiologically documented infection, *CDI* clinically documented infection, *FUO* fever of unknown origin)

	Primary	Secondary
No. of febrile episodes/all patients	107/123 (87%)	38/123 (31%)
Autologous BMT	56/65 (86%)	10/65 (15%)
Allogeneic BMT	51/58 (88%)	23/58[a] (40%)
First day with fever, median (range)		
All patients	5 (0–62)	22.5 (6–84)
Autologous BMT	5 (0–14)	17 (9–34)
Allogeneic BMT	5 (1–62)	22 (6–84)
Median (range) duration of fever (days)		
All patients	5 (1–41)	3 (1–38)
Autologous BMT	5 (1–13)	2 (1–9)
Allogeneic BMT	5 (1–41)	4 (1–38)
Diagnosis		
MDI with bacteremia	23 (21%)	2 (5%)
MDI without bacteremia	6 (6%)	5 (13%)
CDI	4 (4%)	1 (2%)
FUO	74 (69%)	30 (80%)

[a] 29 patients had 1 secondary febrile episode, 3 patients had 2, and 1 patient had 3 secondary febrile episodes

infectious complications that developed during the first 100 days after transplant.

Profound granulocytopenia occurred in all patients. The absolute neutrophil count (ANC) remained below 0.5×10^9/l for a median of 14 days (range 7–59 days) and below 0.1×10^9/l for a median of 8 days (range 0–35 days). ANC remained below 0.5×10^9/l for a similar period of time in autologous (median 15 days, range 7–59 days) and in allogeneic transplants (median 14 days, range 7–30 days); severe granulocytopenia (ANC $< 0.1 \times 10^9$/l) lasted 8 days in both autologous (range 0–35 days) and allogeneic (range 2–17 days) grafts.

Eighty-two percent of infectious complications occurred during the neutropenic period, with 76% of patients having the first febrile episode within 7 days after the graft. Seven patients had the first febrile episode occurring after recovery from neutropenia.

The incidence of primary febrile episodes, the median number of days to the onset the first febrile episode and the median duration of fever did not significantly differ between the autologous and the allogeneic BMT group (Table 2). In contrast, the frequency of secondary febrile episodes was higher in allogeneic BMT recipients (23 patients, 40%) than in autologous BMT recipients (10 patients, 15%), and the difference was statistically significant ($P = 0.0001$). When autologous and allogeneic BMT recipients were stratified by the type of underlying disease, no remarkable differences in rates of infection or in time to onset or duration of the first febrile episode were noted, except for a shorter duration of fever among patients allografted for non-malignant disorders ($P = 0.21$); the same figures apply to secondary febrile episodes.

In the allogeneic BMT group there was no significant difference between those receiving an HLA-identical sibling transplant and those receiving BMT from an unrelated donor or an HLA-nonidentical related donor with respect to the incidence of primary febrile episodes, the median number of days to the onset of the first febrile episode or the median duration of fever (data not shown). Recipients of BMT from unrelated donors had a higher incidence of secondary febrile episodes (69%) than recipients of an HLA-identical sibling BMT (41%) or HLA-mismatched related donor BMT (44%), but this difference was not statistically significant ($P = 0.227$).

When the rates of infectious complications were stratified according to the year of transplantation (group A: 1989–1991; group B: 1992–1993; group C: 1994–1995), no statistically significant differences were noted among the three groups (group A 83%; group B 82%; group C 95%, $P = 0.1$)

The percentage of documentation was similar in primary and in secondary episodes (31% vs 20%; $P = 0.33$). The incidence of microbiologically or clinically documented infections was higher with unrelated donor allografts (43%) than with autografts (32%), sibling allografts (20%) and partially matched related transplants (15%), although the difference was not statistically significant ($P = 0.28$).

Twenty-eight (78%) of the 36 identified organisms were bacteria, 7 (19%) were fungi and 1 (3%) was a virus (Table 3).

Microbiologically confirmed bacterial infection developed in 34 (27%) patients. The most common bacterial infection was bacteremia, occurring in 25 patients (20%). Two of these had catheter-related infections according to the criteria described elsewhere [18].

Table 3 Features of documented infections (*MDI* microbiologically documented infection)

	Primary	Secondary	Total
MDI with bacteremia			
Gram positive bacteria	16	2	18
Coagulase negative staphylococci	6	1	7
Viridans streptococci	8	–	8
Corynebacterium group JK	1	–	1
Staphylococcus aureus	–	1	1
Propionibacterium acnes	1	–	1
Gram negative bacteria	7	0	7
Pseudomonas aeruginosa	2	–	2
Pseudomonas paucimibilis	1	–	1
Escherichia coli	2	–	2
Fusibacterium nucleatum	1	–	1
Klebsiella pneumoniae	1	–	1
MDI without bacteremia			
Localized bacterial infections (gram negative)	2	1	3
Fungal infections			
Mucocutaneous (*Candida*)	4	1	5
Invasive (*Aspergillus, Cryptococcus*)	–	2	2
Viral infections			
Rotavirus	–	1	1
Clinically documented infections			
Cutaneous infections	2		2
Pulmonary infiltrates	2	1	3

We did not observe any significant difference in the incidence of bacteremias between autologous (21%) and allogeneic (19%) transplants ($P=0.849$). When the 22 patients who received an unrelated donor transplant or a mismatched parental donor transplant were excluded from the analysis, the incidence of bacteremia in the allogeneic transplant group dropped to 13%.

Features of documented infections are shown in Table 3. Nonbacteremic microbiologically documented infections included 4 cases of urinary tract infection, 3 cases of mucocutaneous infection and 2 cases of enteritis; 1 patient had pneumonia and 1 had meningitis.

We did not observe any case of CMV disease in our cohort of BMT recipients.

The global incidence of infectious episodes was 1.4 episodes/100 risk days.

Overall survival on day 100 was 78%. Sixteen patients died before 100 days after BMT, and in 14 cases autopsy was performed.

Infection was found to be a primary or associated cause of death in 3 of 16 (12%) patients who died during the observation period. Nine patients died of transplant-related complications (3 of GVHD, 2 of hepatic failure, 2 of ARDS, 1 of multi-organ failure, 1 of heart insufficiency), and 4 patients died of recurrent malignancy.

The mortality rate due to infections was 2/36 (5%) for matched sibling donor BMT, and 1/13 (8%) for matched unrelated donor BMT. No deaths occurred in the 65 patients who were autografted. The median

number of days after transplant when death occurred was 57 (range 6–89 days).

Invasive fungal infections accounted for 2 of the 3 infectious deaths (1*Aspergillus*, 1*Cryptococcus* infection); both patients received antifungal prophylaxis (itraconazole and fluconazole respectively).

Discussion

Infection is almost invariably a complication of bone marrow transplantation. Only a few studies have examined the overall incidence and spectrum of infectious complications associated with BMT [6, 9, 15], whereas several reports have described the specific incidence of CMV [29], Varicella-zoster virus [21], pneumonia [12, 27] or fungal infections [8] in this setting. In addition, the vast majority of these series are made up of adults, and few studies report data on children [2, 17, 23, 25].

In our experience, infections were documented at a very high frequency in children receiving BMT: roughly 90% of the patients experienced at least one infectious episode, although the median duration of fever was 5 days only. Granulocytopenia following BMT had a remarkable impact on the occurrence of infections: more than two-thirds of patients developed fever during the period of neutropenia. Recently, the use of hematopoietic growth factors has resulted in a shortening of the periods of neutropenia following BMT, and theoretically this might also reduce infective complica-

tions. Our results indicated that patients had an early onset of fever, with 76% of subjects having the first febrile episode by day 7 after BMT, when the impact of hematopoietic growth factors on marrow recovery might yet not be apparent. Overall, these results share similarities with those reported from other studies [2, 10, 25].

The majority of febrile episodes were of undetermined origin. The incidence of FUO was particularly high in our series compared with the results reported by others: whilst 69% of our patients developed FUO, this pattern of infection occurred in about 35–40% of patients included in other studies [2, 9, 25]. Possible reasons behind this unexpected high incidence of possible infections may be (1) the presence of fever of very short duration (1–2 days) in one-third of cases attributed to FUO which might be related to noninfective causes (e.g. medications), or (2) the occurrence of FUO in allogeneic BMT recipients (50% of FUO) who developed acute GVHD, which is primarily mediated by cytokine dysregulation and therefore represents a major risk factor for fever.

Several reports have demonstrated that approximately 20% of granulocytopenic cancer patients have a documented bacteremia [25]. This is confirmed by our analysis, since bacteremia occurred in as many as 21% of our patients. The distribution of isolates did not differ from that of other series of BMT recipients, as gram-positive organisms have been found to be predominant in recent years [5, 10, 11, 25]. Many factors have been advocated to explain this high incidence of gram-positive bacteremias, including the increasing use of indwelling venous devices [24], the use of prophylactic antibiotics against gram-negative bacteria [22], and the use of more aggressive preparative regimens leading to severe mucosal damage and invasion by all saprophytes harbored in the oral cavity [26]. The concomitance of these three factors was present in half of the patients in our study group. Prophylactic regimens aimed at achieving selective or nonselective decontamination are widely used by the transplant teams. Because sample sizes in this study were small, owing to the different protocols utilized, we were unable to produce statistically relevant data on the efficacy of prophylactic gut decontamination.

Allogeneic BMT for the treatment of nonhematological disorders was associated with a decreased incidence of infectious complications and a shorter duration of fever. It should be remembered that patients with hematological malignancies received multiple chemotherapeutic and radiotherapeutic courses prior to BMT, which may in turn have predisposed these children to more severe peri-transplant infections.

The pattern of first febrile episode in autologous recipients did not differ substantially from that of patients who received allogeneic BMT: the rate of infectious complications and the onset of fever were similar, as was the median duration of fever, although these results may have been influenced by the small number of patients included in the analysis. In contrast, there were noticeable differences regarding secondary febrile episodes. Overall, one-third of patients had secondary episodes; patients receiving allogeneic BMT, especially unrelated marrow donor recipients, had a significantly higher proportion of secondary episodes than did autografted patients (40% vs 15%; $P = 0.0001$), irrespective of the duration of neutropenia. The extent of recovery of the host's new immune system, the presence of GVHD and its effects on immune recovery and mucosal barriers, and the use of immunosuppressive agents for prophylaxis and treatment of GVHD are the major determinants of infection in the postengraftment period of BMT. It is conceivable that these mechanisms may also be implicated in our series, since two thirds of the patients who had a secondary episode developed severe acute GVHD requiring immunosuppressive therapies, including steroids and antithymocyte globulin (ATG).

In the first 100 days after BMT the mortality due to infections was only 2% and reflected the low transplant-related mortality observed in our series (10%). These data compare favorably with those reported in the allogeneic BMT setting (17%) [2], although it should be pointed out that the small number of patients included in the present analysis may have influenced significantly the low mortality rate from infection.

In summary, our data indicate that the vast majority of children who received BMT experienced febrile episodes. Only one-third of all episodes involved documented infections, whereas the remainder could not be definitely attributed to infections. Bacteremia was documented in 20% of primary episodes, and gram-positive bacteria were the leading pathogens involved. Allogeneic BMT recipients were at high risk of developing secondary febrile episodes as result of host defense defects associated with the procedure. The overall infectious disease mortality was very low in our series (2%) despite a large number of febrile episodes and fungal infections causing 2 of 3 deaths. The diagnosis and the treatment of fungal infections in BMT recipients remain a major issue for the clinician, as confirmed by our experience.

References

1. Atkinson K, Downs K, Golenia M, Biggs J, Marshall G, Dodds A (1991) Prophylactic use of ganciclovir in allogeneic bone marrow transplantation: absence of clinical cytomegalovirus infection. Br J Haematol 79:57–62

2. Dell'Orto M, Rovelli A, Barzaghi A, et al (1997) Febrile complications in the first 100 days after bone marrow transplantation in children: a single center's experience. Pediatr Hematol Oncol 14:335–347

3. Engelhard D, Marks MI, Good RA (1986) Infections in bone marrow transplant recipients. J Pediatr 108:335–345

4. EORTC Antimicrobial Therapy Project Group (1978) Three antibiotic regimens for the treatment of infection in febrile granulocytopenic patients with cancer. J Infect Dis 137:14–29

5. EORTC – International antimicrobial cooperative group (1990) Gram-positive bacteraemia in granulocytopenic cancer patients. Eur J Cancer 26:569–574

6. Gilbert C, Meisenberg B, Vredenbergh J, et al (1994) Sequential prophylactic oral and empiric once-daily parenteral antibiotics for neutropenia and fever after high-dose chemotherapy and autologous bone marrow support. J Clin Oncol 12:1005–1011

7. Hoyle C, Goldman JM (1994) Life-threatening infections occurring more than 3 months after BMT. Bone Marrow Transplant 14:247–252

8. Jantunen E, Ruutu T, Niskanen L, et al (1997) Incidence and risk factors for invasive fungal infections an allogeneic bone marrow transplant recipients. Bone Marrow Transplant 19:801–808

9. Kirk JL, Greenfield RA, Slease RB, Epstein RB (1988) Analysis of early infectious complications after autologous bone marrow transplantation. Cancer 62:2445–2450

10. Kolbe K, Domkin D, Drigs HG, Bhakdi S, Huber C, Aulitzky WE (1997) Infectious complications during neutropenia subsequent to peripheral blood stem cell transplantation. Bone Marrow Transplant 19:143–147

11. Lim JH, McMillan AK, Chpra R, et al (1991) Transplant related septicemia in patients undergoing autologous bone marrow transplantation for lymphoma and acute leukemia. Leuk Lymphoma 5:127–132

12. Lossos IS, Breyer R, Or R, et al (1995) Bacterial pneumonia in recipients of bone marrow transplantation. Transplantation 60:672–678

13. Meyers JD (1986) Infection in bone marrow transplant recipients. Am J Med 81:27–38

14. Meyers J, Petersen FB, Counts W, Reed EC, Skerret SJ, Bowden RA, Sullivan K, Buckner CD (1987) Bacterial, fungal, and protozoan infection after marrow transplantation. In: Baum SJ, Santos GW, Takaku F (eds) Recent advances and future directions in bone marrow transplantation. Springer, Berlin Heidelberg New York, pp 171–176

15. Mossad SB, Longworth DL, Goormastic M, Serkey JM, Keys TF, Bolwell BJ (1996) Early infectious complications in autologous bone marrow transplantation: a review of 219 patients. Bone Marrow Transplant 18:265–271

16. Ochs L, Shu XO, Miller J, et al (1995) Late infections after allogeneic bone marrow transplantation: comparison of incidence in related and unrelated donor transplant recipients. Blood 86:3979–3986

17. Ogden AK, Steuber CP, Mahoney DH, Fernbach DJ (1990) Bone marrow transplantation in childhood leukemia using reverse isolation techniques. Med Pediatr Oncol 18:1–5

18. Raad II, Bodey GP (1992) Infectious complications of indwelling vascular catheters. Clin Infect Dis 15:197–210

19. Sable CA, Donowitz GR (1994) Infections in bone marrow transplant recipients. Clin Infect Dis 18:273–284

20. Saltzman RL, Quirk MR, Jordan MC (1990) Disseminated cytomegalovirus infection. J Clin Invest: 81:75–81

21. Schuchter LM, Wingard JR, Piantadosi S et al (1989) Herpes zoster infection after autologous bone marrow transplantation. Blood 74:1424–1427

22. Shaes DM, Binezewski B, Rice BL (1993) Emerging antimicrobial resistance and the immunocompromised host. Clin Infect Dis 17 [Suppl 2]:s527–s536

23. Skinner J, Finlay JL, Sondel PM, Trigg ME (1986) Infectious complications in pediatric patients undergoing transplantations with T lymphocyte-depleted bone marrow. Pediatr Infect Dis 5:319–324

24. Uderzo C, D'angelo P, Rizzari C, et al (1992) Central venous catheter-related complications after bone marrow transplantation in children with hematological malignancies. Bone Marrow Transplant 9:113–117

25. Viscoli C, Castagnola E, Moroni C, Boni L, Dallorso S, Garaventa A, Lanino E, Dini G (1991) Early infectious complications in children undergoing BMT. Bone Marrow Transplant 6 [Suppl 1]:42–47

26. Wade JC, Schimpff SC, Newman KA, et al (1982) *Staphylococcus epidermidis*: an increasing cause of infection in patients with granulopenia. Ann Intern Med 97:503–508

27. Weiner RS, Bortin MM, Gale R et al (1986) Interstitial pneumonitis after bone marrow transplantation. Assessment of risk factors. Ann Intern Med 104:168–175

28. Wingard JR (1990) Advances in the management of infections complications after bone marrow transplantation. Bone Marrow Transplant 6:371–383

29. Wingard JR, Chen DY, Burns WH et al (1988) Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood 71:1432–1437

30. Winston DJ, Ho WG, Champlin RE, Gale RP (1984) Infectious complications of bone marrow transplantation. Exp Hematol 12:205–215

31. Young LS (1984) An overview of infection in bone marrow transplant recipients. Clin Haematol 13:661–678