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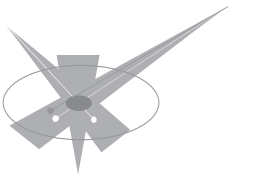

Review Paper

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Strategies for prevention of infectious complications in children after HSCT in relation to type of transplantation and GVHD occurrence

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Infectious complications are a major cause of morbidity and mortality in paediatric and adult patients undergoing haematopoietic stem cell transplantation (HSCT).

Aim Analysis of strategies for prevention of infectious complications in children after HSCT in relation to the type of transplantation and GVHD occurrence.

Materials/Methods A review of PubMed references based on evidence-based recommendations rated by the strength of the recommendation and the quality of the supporting evidence. The risk of infection was divided into: low for autologous HSCT, moderate for MSD-HSCT without GVHD, and high for unrelated, mismatched, haploidentical HSCT, cord blood HSCT, patients with moderate-to-severe GVHD, undergoing immunosuppressive treatment, CMV infection, *ex vivo* T-cell depletion or CD34 selection and *in vivo* T-cell depletion.

Results Prophylaxis strategy includes general infection control in hospital environment and pharmacological approach, related to antibacterial, antifungal and antiviral agents. Most studies were done on adult patients only, while some included both paediatric and adults patients. However, no differences in prophylaxis strategy and efficacy between age groups were reported in these studies. Recommendations for use of specific drugs in prophylaxis in transplantation period and recommendations for vaccination are presented in this paper.

Conclusions With changing practices, transplant teams are encouraged to review local patterns of infections and associated complications and communicate regularly with infection control committees for guidance on the evolution of isolation needs for the immunosuppressed patient before and after HSCT.

Key words **prophylaxis • infection • haematopoietic stem cell transplantation • strategy • vaccination**

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Background

Infectious complications are a major cause of morbidity and mortality in paediatric and adult patients undergoing haematopoietic stem cell transplantation (HSCT). The incidence and the severity code of infections depend on the function of the host's immune system. This function is strongly correlated with the application of immunosuppressive therapy and the time of immune reconstitution after HSCT. The risk of infection is higher in patients after allogeneic than autologous transplantation, and in patients with GVHD than without it. Patients with GVHD have severe immunological deficiencies due to the disease and the therapy itself. The risk of infection is higher in patients with delayed immune reconstitution, especially after haploidentical and cord blood transplantation (Table 1). Host defences compromised by HSCT that make patients vulnerable to infections can be divided into an early (before day +30), intermediate (days 30–100) and a late phase (after day +100). Each phase is related to increased risk of specific complications and specific infections that occur at variable frequency, but each of them carries relative life-threatening potential [1].

Table 1. Infections encountered after engraftment in intermediate and late phase of immunological recovery [2,3].

Infection	Relative frequency		
	Auto-HSCT	Allogeneic HSCT without GVHD	Allogeneic HSCT with GVHD
Intermediate phase			
Staphylococci	+	++	++
Fungi	+	++	+++
Gram-negative bacilli	–	–	+
CMV	+	++	+++
Late phase			
Encapsulated bacteria	–	–	++
Fungi	–	–	+

Aim

Review and analysis of strategies and recommendations for prevention of infectious complications in children after HSCT in relation to the type of transplantation and GVHD occurrence.

Methods of Data Collection

References were retrieved using the online database of the National Library of Medicine (PubMed; *http://www.ncbi.nlm.nih.gov/PubMed*) up to October 2006 (with emphasis on the latest randomized clinical trial reports). Terms used included: haematopoietic stem cell transplantation, infection, prophylaxis, strategy, guidelines, randomized clinical trials (RCT), meta-analysis, children, vaccination. The retrieved references were supplemented by references from the author's own database. The presented strategy is based on evidence-based recommendations (Table 2) rated by the strength of the recommendation and the quality of the supporting evidence [1].

Results

Determination of the risk for infection in specific patient populations is accomplished by evaluating various risk factors (exposure, state of immunosuppression and organ damage). For practical purposes, risk groups of infection after HSCT with respect to the type of transplantation can be divided into: (A) Low risk: autologous HSCT; (B) Moderate risk: MSD-HSCT with no GVHD (myeloablative, low-toxicity, reduced-intensity conditioning); (C) High risk: unrelated, mismatched, haploidentical HSCT (including cord blood HSCT), patients with moderate-to-severe GVHD, undergoing treatment with immunosuppressive agents (e.g. corticosteroids), CMV infection, *ex vivo* T-cell depletion or CD34

Table 2. Evidence-based rating system used to determine strength and quality of supporting evidence for recommendations of HSCT guidelines.

Category definition to determine strength of recommendation	Category definition to determine quality of supporting evidence
A. Should always be offered	I. Evidence from at least 1 properly randomized, controlled trial.
B. Should generally be offered	II. Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 centre), or from multiple time-series or dramatic results from uncontrolled experiments.
C. Optional	
D. Should generally not be offered	
E. Should never be offered	III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

selection of the allograft, *in vivo* T-cell depletion with ATG, anti-CD52 or fludarabine [2–4]. Multivariate analysis identified the use of steroids as the most significant variable associated with infectious episodes. Peripheral blood HSCT was associated with more infections in the post-engraftment period [5].

A. General infection control in hospital environment

Sources of infectious agents both in hospitals and in houses include mainly: air, dust, construction area, ventilation system, potted plants, flowers, cereals, nuts, spices, carpets and water with secondary aerosolization.

Intensive infection control measures that include isolation of patients within protective hospital environments have become a standard practice during allogeneic stem cell transplantation. There are no studies indicating the role and range of environment control with respect to autologous HSCT. The foremost principle of infection prophylaxis is minimization of the possibility that encounters with the health care team and exposure to the hospital environment place patients at greater risk for acquired infection.

General recommendations for the prevention of opportunistic infections in HSCT recipients include a wide range of interventions related to the management of: ventilation systems, BMT unit construction and cleaning, isolation and barrier precautions, interactions with health-care workers and visitors, skin and oral care, infection surveillance, and the prevention of specific nosocomial and seasonal infections. Isolation procedure is essential for all allogeneic HSCT patients who must enter the system aimed at reducing exposure to contagious agents, which includes: (a) Preventing dust accumulation by cleaning all surfaces, isolating patient care wards from outside air (recommendation AII), maintaining positive room pressure and providing patients with masks when moving into unprotected areas (BIII); (b) Stay in rooms with greater than 12 air exchanges per hour with high-efficiency particulate air (HEPA) filters (AII) capable of removing particles >0.3 μm in diameter; (c) Investigating potential outbreaks; (d) Avoiding patient exposure to tap water during severe immunosuppression, using sponge baths instead of showers and cleaning the showering facility prior to use. Measures to reduce hospital-acquired candidal infections in these patients rely on hand washing (AIII), an important, simple and inexpensive infection control strategy [6]. These practices should also be implemented both before and after patients' discharge, with stress on avoiding risk of environmental exposure and decontamination of food (CIII).

B. Pharmacological preventive strategies

Antibacterial primary prophylaxis

During the neutropenic period, the risk of infection is comparable regardless of HSCT type; thus antibacterial prophylaxis should be adjusted to the length of neutropenia and mucosal injury. Mucositis is usually lower in RIC and low-toxicity conditioning, so risk of infection is decreased in these HSCTs. The advantage of use of cotrimoxazol and quinolones in antibacterial prophylaxis in neutropenia after allo-HSCT in RCT and meta-analyses has been documented (AI) [7,8]. Widely used prophylaxes include quinolones, which decrease the risk of G-infection, but not mortality [9,10]. After both allo- and auto-HSCT, prophylaxis with oral penicillin derivatives is compulsory (AI) against encapsulated G+ bacteria (Table 3) [11].

Antifungal prophylaxis

Antifungal prophylaxis should be based on risk stratification. High-risk group patients obviously

Table 3. Recommendations for antimicrobial prophylaxis.

Prophylaxis	Indication	First and second recommendation	Beginning	End
Antibacterial	All patients	Ciprofloxacin (AI) Ofloxacin, Levofloxacin [11]	Conditioning	Engraftment
Pneumocystis jiroveci	All patients	Cotrimoxazole (AII) Pentamidine [12–14]	Conditioning/ Engraftment	End of IST or GVHD (>6 months)
Yeasts	All patients	Fluconazol (AI) Itraconazole [15,16]	Conditioning, I: Day +1	Day +75
Moulds	Secondary prophylaxis [AIII]	Posaconazole, Voriconazole, Itraconazole, Micafungin [4,17–21]	Conditioning, I: Day +1	At the earliest of engraftment
CMV	High-risk patients	Ganciclovir (AI) Foscarnet, Cidofovir [22,23]	Engraftment	Day +100
HSV	IgG positive patients	Acyclovir (AI) Valacyclovir [24–26]	Day +1	Day +30
VZV	Secondary prophylaxis	Acyclovir Valacyclovir [27]	Day +1	End of IST or GVHD
Toxoplasmosis	Secondary prophylaxis	Cotrimoxazole Clindamycine or pyrimethamine+LV [28]	Conditioning	End of IST
Vaccinations	All patients (AIII)		6-12 months	

IST – immunosuppressive therapy.

should be given antifungal prophylaxis. There is no recommendation for antifungal prophylaxis in all patients in the low-risk group. The most controversial is the moderate group, which is a heterogeneous group. It is believed that those patients should be offered antifungal prophylaxis or frequent HRCT and laboratory screening.

Transplantation strategies that reduce the duration and degree of mucosal injury, the duration of myeloid, macrophage and Th1-type immunodeficiency, the severity of GVHD, and the need for corticosteroids, parenteral nutrition or intravenous catheters, would all contribute to a decrease in invasive fungal infections. Candida spp. is a mucocutaneous commensural organism and violating the integrity of these surfaces is directly related to the risk for infection. Outbreaks of candidal infections have also been associated with transmission via the skin and nails of healthcare workers. In contrast, the incidence of aspergillus has been shown to be related to environmental exposures, which may have occurred prior to the diagnosed infection [3]. Central to the prevention of aspergillosis is the avoidance of inhalation of spores. In the outpatient setting, there are no proven methods to decrease risk of colonization. Avoidance of contact with soil and plants, gardening, or maintenance of compost piles would be prudent (AII). The optimal duration of this prohibition is not clear [6,29].

Administration of fluconazole 2×200 mg until day +75 (both in children and adults, Table 3) decreases the risk of infection and mortality with Candida albicans [30]. Prophylaxis against moulds is accepted with relevant active agents only as secondary prophylaxis. There is a lack of RCT, but it seems that posaconazole, voriconazole, amphotericine and ecchinocandines are of important value [20,31]. The value of itaconazole is diminished by limited oral availability and more adverse effects [32,33]. The duration of anti-mould prophylaxis remains to be established, as median time to invasive aspergillosis far exceeds day +100 [34]; thus immunological recovery at 1 year after HSCT in patients without GVHD might be recommended as the end of prophylaxis.

Antiviral primary prophylaxis

CMV: The preventive strategies for CMV disease include the use of appropriate blood products, and use of antiviral agents either as chemoprophylaxis or pre-emptive therapy (AI). There are two general approaches to prevention of CMV disease, using either gancyclovir or foscarnet: (a) treatment of all at-risk patients for the defined period of risk as pre-emptive therapy, and (b) treatment

Table 4. Recommendations for vaccinations after stem cell transplantation [42,43].

	Type of vaccine	Beginning of vaccination	Doses	Indications	Recommendations
Viral					
Influenza	Inactivated	4–6	1	Every year	AII [44]
Polio	Inactivated	6–12	3	Yes	BII [45]
Hepatitis B*	Inactivated	6–12	3	Yes	BII [46]
Hepatitis A	Inactivated	6–12	3	Optional	CIII [42]
MMR	Alive	24	1	Individually	BII / CII [47]
Varicella	Alive	24	1?	Optional	CIII [48, 49]
Yellow fever	Alive	24 (or before)	1	Optional	CIII
Bacterial					
H. influenzae B*	Conjugated	6	3	Yes	BII [50, 51]
N. meningitidis A i C	Polysaccharide	6–12	1	Optional	CII [52]
N. meningitidis C	Conjugated	6	1	Optional	CIII [42]
Tetanus*	Toxoid	6–12	3	Yes	BII [53]
Diptheria	Toxoid	6–12	3	Yes	BII [42]
Bordetella pertusis	Acellular	6–12	3	Optional	CIII [42]
S. pneumoniae	Polysaccharide	12	1	Yes	BII [49, 54]
S. pneumoniae *	Conjugated	?	3	Yes	AII [55-57]
Tuberculosis	Alive	No	0	No	EII [58]

* recommended donor vaccination.

of early blood-borne CMV infection prior to onset of disease. Pre-emptive therapy is the most common and effective prophylactic strategy in patients with CMV reactivation. Intravenous ganciclovir prophylaxis is an effective strategy for the prevention of CMV disease and could be used in subgroups of allogeneic HSCT patients at high risk for CMV disease (AI) [22,23,35]. Oral valganciclovir could be a useful alternative to intravenous ganciclovir [36,37]. In randomized studies both acyclovir and valacyclovir were shown to reduce the risk of CMV infection, but not CMV disease [38,39]. However, their use must be combined with CMV monitoring and preemptive therapy (AI). Intravenous immunoglobulin (IGIV) for the prevention of CMV infection or disease is not recommended (DII) [40]. New concepts in CMV prophylaxis in a selected group of patients include immunotherapy with donor T lymphocytes sensitized to CMV antigens, but this is still an experimental approach.

Other herpes viruses: Prophylaxis against Herpes simplex (HSV) with acyclovir should be introduced in seropositive patients only, in –1 to +30 days (Table 3). Acyclovir effectively and safely prevents VZV disease during the first year after haematopoietic cell transplantation. Periods of prophylaxis longer than 12 months may be beneficial for those haematopoietic cell transplant recipients on continued immune suppression. Acyclovir significantly reduced VZV infections at 1 year after transplantation [41]. For other herpes viruses there are no standard pharmacological recommendations, as reviewed by Kruger et al. [19]. Prospective studies are needed to further examine management strategies for these viruses.

C. Vaccination strategy

Vaccination is a potentially important strategy for reducing the risk for vaccine-preventable infections after SCT. The EBMT recommendations for vaccination of HSCT recipients published in Bone Marrow Transplantation in 1995 and in 2005 [42] updated with current knowledge are presented in Table 4.

There are new data indicating the benefit of donor vaccination before HSCT. This is of proven value for prophylaxis of infections with viral hepatitis B [59,60], *Haemophilus influenzae* [50,51], *Streptococcus pneumoniae* with conjugated vaccine [55,56] and tetanus [61]. In all cases, early recipient vaccination post-HSCT is recommended.

Discussion

Most studies were done on adult patients only, while some included both paediatric and adult patients; however, no differences in prophylaxis strategy or efficacy between age groups were reported in these studies.

Local conditions, microbiological characteristic and patient situation should decide the specific pharmacological prophylaxis. This concerns first of all antifungal prevention, but may play a key role also in antibacterial and antiviral prophylaxis. Hand washing is of utmost importance to avoid transmission of infectious agents from one patient to another and from staff to patients. Avoidance of any exposure to infection and decontamination of food are always very important practices. Bacterial surveillance cultures have been found to be useful in detecting antibiotic-resistant bacteria [62].

Apart from general control and pharmacological strategy, adjunctive measures like growth factors, IGIV supplementation and granulocyte transfusions might have an important role in infection prophylaxis. Controlled trials of administrations of haematopoietic growth factor G-CSF have failed to show improved outcome in either HSCT [63] or non-HSCT neutropenic patients, other than shortening of neutropenia duration and antibiotic utilization. Keratinocyte growth factors have abilities to enhance mucosal stem cell growth and decrease local injury [64]. IGIV is regarded not to show benefit, both in autologous HSCT [65] and in MSD-HSCT patients [5]. Modest, but significant, benefit of G-CSF-mobilized HLA-matched prophylactic granulocyte transfusions, expressed by reduction of febrile days and intravenous antibiotic usage, was demonstrated in neutropenic allogeneic HSCT recipients, but it is still controversial [66].

Conclusions

With changing practices, transplant teams are encouraged to review local patterns of infections and associated complications and communicate regularly with infection control committees for guidance on the evolution of isolation needs for the immunosuppressed patient before and after HSCT.

References:

1. Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients: recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation. MMWR Morb Mortal Wkly Rep, 2000; 49(RR-10): 1–128. Available from *http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm.* Accessed October 30, 2006
2. O'Brien SN, Blijlevens NM, Mahfouz TH, Anaissie EJ: Infections in patients with hematological cancer: recent developments. Hematol Am Soc Hematol Educ Program, 2003; 438–72
3. Brown JMY: Fungal infections after hematopoietic cell transplantation. In: Blume KG, Forman SJ, Appelbaum FR (eds.): Thomas' hematopoietic cell transplantation. Malden, Blackwell Publishing, 2004; 683–700
4. Strasfeld L, Weinstock DM: Antifungal prophylaxis among allogeneic hematopoietic stem cell transplant recipients: current issues and new agents. Expert Rev Anti Infect Ther, 2006; 4: 457–68
5. Nucci M, Andrade F, Vigorito A et al: Infectious complications in patients randomized to receive allogeneic bone marrow or peripheral blood transplantation. Transpl Infect Dis, 2003; 5: 167–73
6. Dykewicz CA: Hospital infection control in hematopoietic stem cell transplant recipients. Emerg Infect Dis, 2001; 7: 263–7
7. Van de Wetering MD, de Witte MA, Kremer LC et al: Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: a systematic review of randomised controlled trials. Eur J Cancer, 2005; 41: 1372–82
8. Van de Wetering MD, van Woensel JB, Kremer LC, Caron HN: Prophylactic antibiotics for preventing early Gram-positive central venous catheter infections in oncology patients, a Cochrane systematic review. Cancer Treat Rev, 2005; 31: 186–96
9. Lew MA, Kehoe K, Ritz J et al: Ciprofloxacin versus trimethoprim/sulfamethoxazole for prophylaxis of bacterial infections in bone marrow transplant recipients: a randomized, controlled trial. J Clin Oncol, 1995; 13: 239–50
10. Engels EA, Lau J, Barza M: Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. J Clin Oncol, 1998; 16: 1179–87
11. Cruciani M, Malena M, Bosco O et al: Reappraisal with meta-analysis of the addition of Gram-positive prophylaxis to fluoroquinolone in neutropenic patients. J Clin Oncol, 2003; 21: 4127–37

12. Maltezou HC, Petropoulos D, Choroszy M et al: Dapsone for *Pneumocystis carinii prophylaxis* in children undergoing bone marrow transplantation. Bone Marrow Transplant, 1997; 20: 879–81
13. Souza JP, Boeckh M, Gooley TA et al: High rates of *Pneumocystis carinii pneumonia* in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. Clin Infect Dis, 1999; 29: 1467–71
14. Link H, Vohringer HF, Wingen F et al: Pentamidine aerosol for prophylaxis of *Pneumocystis carinii pneumonia* after BMT. Bone Marrow Transplant, 1993; 11: 403–6
15. Goodman JL, Winston DJ, Greenfield RA et al: A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med, 1992;326: 845–51
16. Marr KA, Seidel K, Slavin MA et al: Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood, 2000; 96: 2055–61
17. Offner F, Cordonnier C, Ljungman P et al: Impact of previous aspergillosis on the outcome of bone marrow transplantation. Clin Infect Dis, 1998;26: 1098–103
18. Hoover M, Morgan ER, Kletzel M: Prior fungal infection is not a contraindication to bone marrow transplant in patients with acute leukemia. Med Pediatr Oncol, 1997; 28: 268–73
19. Kruger WH, Bohlius J, Cornely OA et al: Antimicrobial prophylaxis in allogeneic bone marrow transplantation. Guidelines of the infectious diseases working party (AGIHO) of the german society of haematology and oncology. Ann Oncol, 2005; 16: 1381–90
20. Van Burik JA, Ratanatharathorn V, Stepan DE et al: Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis, 2004; 39: 1407–16
21. Cordonnier C, Maury S, Pautas C et al: Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. Bone Marrow Transplant, 2004; 33: 943–8
22. Reusser P, Einsele H, Lee J et al: Randomized multicenter trial of foscarnet versus ganciclovir for preemptive therapy of cytomegalovirus infection after allogeneic stem cell transplantation. Blood, 2002; 99: 1159–64
23. Ljungman P, Deliliers GL, Platzbecker U et al: Cidofovir for cytomegalovirus infection and disease in allogeneic stem cell transplant recipients. The Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Blood, 2001; 97: 388–92
24. Saral R, Burns WH, Laskin OL et al: Acyclovir prophylaxis of herpes-simplex-virus infections. N Engl J Med, 1981; 305: 63–7
25. Gluckman E, Lotsberg J, Devergie A et al: Prophylaxis of herpes infections after bone-marrow transplantation by oral acyclovir. Lancet, 1983; 2: 706–8
26. Ljungman P, Wilczek H, Gahrton G et al: Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens *in vitro*. Bone Marrow Transplant, 1986; 1: 185–92
27. Selby PJ, Powles RL, Easton D et al: The prophylactic role of intravenous and long-term oral acyclovir after allogeneic bone marrow transplantation. Br J Cancer, 1989; 59: 434–8
28. Slavin MA, Meyers JD, Remington JS, Hackman RC: Toxoplasma gondii infection in marrow transplant recipients: a 20 year experience. Bone Marrow Transplant, 1994; 13: 549–57
29. Oren I, Haddad N, Finkelstein R, Rowe JM: Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. Am J Hematol, 2001; 66: 257–62
30. Slavin MA, Osborne B, Adams R et al: Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. J Infect Dis, 1995; 171: 1545–52
31. Ullmann AJ, Cornely OA, Burchardt A et al: Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection. Antimicrob Agents Chemother, 2006; 50: 658–66
32. Vardakas KZ, Michalopoulos A, Falagas ME: Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. Br J Haematol, 2005; 131: 22–8
33. Oren I, Rowe JM, Sprecher H et al: A prospective randomized trial of itraconazole vs fluconazole for the prevention of fungal infections in patients with acute leukemia and hematopoietic stem cell transplant recipients. Bone Marrow Transplant, 2006; 38: 127–34
34. Grow WB, Moreb JS, Roque D et al: Late onset of invasive aspergillus infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant, 2002; 29: 15–9
35. Winston DJ, Ho WG, Bartoni K et al: Ganciclovir prophylaxis of cytomegalovirus infection and disease in allogeneic bone marrow transplant recipi-

ents. Results of a placebo-controlled, double-blind trial. Ann Intern Med, 1993; 118: 179–84

36. Winston DJ, Baden LR, Gabriel DA et al: Pharmacokinetics of ganciclovir after oral valganciclovir versus intravenous ganciclovir in allogeneic stem cell transplant patients with graft-versus-host disease of the gastrointestinal tract. Biol Blood Marrow Transplant, 2006; 12: 635–40
37. Einsele H, Reusser P, Bornhauser M et al: Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. Blood, 2006; 107: 3002–8
38. Prentice HG, Gluckman E, Powles RL et al: Impact of long-term acyclovir on cytomegalovirus infection and survival after allogeneic bone marrow transplantation. European Acyclovir for CMV Prophylaxis Study Group. Lancet, 1994; 343: 749–53
39. Ljungman P, de La Camara R, Milpied N et al: Randomized study of valacyclovir as prophylaxis against cytomegalovirus reactivation in recipients of allogeneic bone marrow transplants. Blood, 2002; 99: 3050–6
40. Ljungman P, Reusser P, de la Camara R et al: Management of CMV infections: recommendations from the infectious diseases working party of the EBMT. Bone Marrow Transplant, 2004; 33: 1075–81
41. Boeckh M, Kim HW, Flowers ME et al: Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation – a randomized double-blind placebo-controlled study. Blood, 2006; 107: 1800–5
42. Ljungman P, Engelhard D, de la Camara R et al: Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant, 2005; 35: 737–46
43. Machado CM: Reimmunization after bone marrow transplantation-current recommendations and perspectives. Braz J Med Biol Res, 2004; 37: 151–8
44. Engelhard D, Nagler A, Hardan I et al: Antibody response to a two-dose regimen of influenza vaccine in allogeneic T cell-depleted and autologous BMT recipients. Bone Marrow Transplant, 1993; 11: 1–5
45. Parkkali T, Stenvik M, Ruutu T et al: Randomized comparison of early and late vaccination with inactivated poliovirus vaccine after allogeneic BMT. Bone Marrow Transplant, 1997; 20: 663–8
46. Locasciulli A, Alberti A, Bandini G et al: Allogeneic bone marrow transplantation from HBsAg+ donors: a multicenter study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood, 1995; 86: 3236–40
47. Ljungman P, Fridell E, Lonnqvist B et al: Efficacy and safety of vaccination of marrow transplant recipients with a live attenuated measles, mumps, and rubella vaccine. J Infect Dis, 1989; 159: 610–5
48. Sauerbrei A, Prager J, Hengst U et al: Varicella vaccination in children after bone marrow transplantation. Bone Marrow Transplant, 1997; 20: 381–3
49. Hata A, Asanuma H, Rinki M et al: Use of an inactivated varicella vaccine in recipients of hematopoietic-cell transplants. N Engl J Med, 2002; 347: 26–34
50. Molrine DC, Guinan EC, Antin JH et al: Haemophilus influenzae type b (HIB)-conjugate immunization before bone marrow harvest in autologous bone marrow transplantation. Bone Marrow Transplant, 1996; 17: 1149–55
51. Molrine DC, Guinan EC, Antin JH et al: Donor immunization with Haemophilus influenzae type b (HIB)-conjugate vaccine in allogeneic bone marrow transplantation. Blood, 1996; 87: 3012–8
52. Parkkali T, Kayhty H, Lehtonen H et al: Tetravalent meningococcal polysaccharide vaccine is immunogenic in adult allogeneic BMT recipients. Bone Marrow Transplant, 2001; 27: 79–84
53. Parkkali T, Olander RM, Ruutu T et al: A randomized comparison between early and late vaccination with tetanus toxoid vaccine after allogeneic BMT. Bone Marrow Transplant, 1997; 19: 933–8
54. Avanzini MA, Carra AM, Maccario R et al: Antibody response to pneumococcal vaccine in children receiving bone marrow transplantation. J Clin Immunol, 1995; 15: 137–44
55. Molrine DC: Recommendations for immunizations in stem cell transplantation. Pediatr Transplant, 2003; 7(Suppl.3): 76–85
56. Molrine DC, Antin JH, Guinan EC et al: Donor immunization with pneumococcal conjugate vaccine and early protective antibody responses following allogeneic hematopoietic cell transplantation. Blood, 2003; 101: 831–6
57. Antin JH, Guinan EC, Avigan D et al: Protective antibody responses to pneumococcal conjugate vaccine after autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant, 2005; 11: 213–22
58. De la Camara R, Martino R, Granados E et al: Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Spanish Group on Infectious Complications in Hematopoietic Transplantation. Bone Marrow Transplant, 2000; 26: 291–8
59. Ilan Y, Nagler A, Adler R et al: Ablation of persistent hepatitis B by bone marrow transplantation from a hepatitis B-immune donor. Gastroenterology, 1993; 104: 1818–21
60. Wimperis JZ, Brenner MK, Prentice HG et al: Transfer of a functioning humoral immune system

in transplantation of T-lymphocyte-depleted bone marrow. Lancet, 1986; 1: 339–43

61. Storek J, Dawson MA, Lim LC et al: Efficacy of donor vaccination before hematopoietic cell transplantation and recipient vaccination both before and early after transplantation. Bone Marrow Transplant, 2004; 33: 337–46

62. Wingard JR, Dick J, Charache P, Saral R: Antibiotic-resistant bacteria in surveillance stool cultures of patients with prolonged neutropenia. Antimicrob Agents Chemother, 1986; 30: 435–9

63. Mitchell PL, Morland B, Stevens MC et al: Granulocyte colony-stimulating factor in established febrile neutropenia: a randomized study of pediatric patients. J Clin Oncol, 1997; 15: 1163–70

64. Spielberger R, Stiff P, Bensinger W et al: Palifermin for oral mucositis after intensive therapy for hematologic cancers. N Engl J Med, 2004; 351: 2590–8

65. Wolff SN, Fay JW, Herzig RH et al: High-dose weekly intravenous immunoglobulin to prevent infections in patients undergoing autologous bone marrow transplantation or severe myelosuppressive therapy. A study of the American Bone Marrow Transplant Group. Ann Intern Med, 1993; 118: 937–42

66. Oza A, Hallemeier C, Goodnough L et al: Granulocyte-colony-stimulating factor-mobilized prophylactic granulocyte transfusions given after allogeneic peripheral blood progenitor cell transplantation result in a modest reduction of febrile days and intravenous antibiotic usage. Transfusion, 2006; 46: 14–23