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PREFACE

Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective

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Introduction

This report, cosponsored by Center for International Blood & Marrow Transplant Research (CIBMTR), National Marrow Donor Program (NMDP), European Group for Blood and Marrow Transplantation (EBMT), American Society for Blood and Marrow Transplantation (ASBMT), Canadian Blood and Marrow Transplant Group (CBMTG), Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), Association of Medical Microbiology and Infectious Disease (AMMI), Centers for Disease Control (CDC) and the Health Resources and Services Administration, represents an update of the guidelines published in 2000 for preventing infections among hematopoietic cell transplant (HCT) recipients.[1] An international group of experts in infectious diseases, hematopoietic cell transplantation and public health worked together to compile this document with four goals in mind: (1) to summarize the current available data in the field; (2) to provide evidence-based recommendations regarding the prevention of infectious complications among HCT patients; (3) to serve as a reference for health-care providers worldwide who care for HCT recipients; and (4) to serve as a reference for HCT recipients and their nonmedical caregivers. In updating these guidelines, the committee sought to summarize the currently available data and present them as concisely as possible in an evidence-based manner.

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Significant changes in the field of HCT since the publication of the original guidelines necessitated this update. These changes include new antimicrobial agents, broader use of reduced-intensity conditioning (RIC), the increasing age of HCT recipients and more frequent use of alternative donor stem cell sources such as haploidentical donors and umbilical cord blood. Furthermore, as with any field of medicine, published studies continue to add to the evidence regarding supportive medical care. Despite—or perhaps because of—these changes, infections still occur with increased frequency or severity among HCT recipients as a patient population.

In presenting these guidelines, the committee does not intend to dictate standards of practice. Although considerable effort has gone into ensuring that the guidelines have a global perspective on the basis of currently available medical evidence, adherence to a particular recommendation may be inconsistent with national or regional guidelines, the availability of specific procedures or medications or local epidemiological conditions. Individual clinicians may follow practice patterns that, although deviating from these recommendations, are nevertheless effective and sound.

Using these guidelines

For the purpose of this report, HCT is defined as transplantation of any blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (that is, allogeneic or autologous) or cell source (that is, BM, peripheral blood or umbilical cord blood). The definition of immune competence after transplant is loosely defined by the ability of the HCT recipient to receive live vaccine after recovering from transplant. Conventionally, this is thought to occur at $\sim$24 months after HCT in patients who are not

receiving immunosuppressive therapy and who do not have active GVHD.[1] For patients with ongoing GVHD or continued use of immunosuppressive therapy, it is recommended to consider the patient as immune deficient and still at risk for significant infectious complications.

Unless otherwise noted, the recommendations presented in this report address allogeneic and autologous, and pediatric and adult HCT recipients. These recommendations are intended for use by the recipients, their household and other close contacts, as well as by transplant and infectious diseases specialists, HCT center personnel and public health professionals. For most recommendations, prevention strategies are rated by the strength of the recommendation and the quality of evidence supporting the recommendation (Table 1). The principles of this rating system were developed by the IDSA and the US Public Health Service for use in guidelines for preventing opportunistic infections among HIV-infected persons.[2] This rating system allows assessments of the strength of recommendations.

Table 1 Evidence-based rating system used in the hematopoietic cell transplantation (HCT) guidelines[2]

Category	*Definition*
Strength of recommendation	
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered**
B	Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. **Should generally be offered.**
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (for example, drug toxicity, drug interactions) or cost of the chemoprophylaxis or alternative approaches. **Optional**.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered**.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered**.
Quality of evidence supporting the recommendation	
I	Evidence from at least one well-executed, randomized, controlled trial.
II	Evidence from at least one well-designed clinical trial without randomization; cohort or case–controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Executive summary

In the past decade, modifications in HCT management and supportive care have resulted in changes in recommendations for the prevention of infection in HCT patients. These changes are fuelled by new antimicrobial agents, increased knowledge of immune reconstitution and expanded conditioning regimens and patient populations eligible for HCT. Despite these advances, infection is reported as the primary cause of death in 8% of autologous HCT patients and in 17–20% of allogeneic HCT recipients.[3] The major changes in this document, including changes in recommendation ratings, are summarized here.

The organization of this document is similar to that of previous guidelines. Specifically, the prevention of exposure and disease among pediatric and adult autologous and allogeneic HCT recipients is discussed. The current recommendations consider myeloablative and reduced-intensity conditioning for allogeneic HCT to be similar, as data on infectious complications after reduced-intensity conditioning compared with myeloablative conditioning are sparse.[4–7] However, increased information regarding post transplant immune recovery highlighting differences between myeloablative and reduced-intensity HCT is included.

The sections of the document have been rearranged in an attempt to follow the time course of potential infectious risks for patients receiving HCT. After the background section, information on hematopoietic cell product safety is provided. The subsequent sections discuss prevention of infection by specific microorganisms. After organism-specific information, the sections then discuss the means of preventing nosocomial infections, as well as the 'dos' and don'ts' for patients after discharge post transplant. Finally, information on vaccinations is provided. This will hopefully allow the reader to follow the prevention practices needed from the time a donor is selected until the patient regains immune competence.

Several topics are new or expanded from the previous document (Table 2). These include information on multiple organisms that were previously not discussed but have seemingly become more clinically relevant in HCT patients over the past decade. Data and, where possible, recommendations are provided regarding the following organisms that were not included in the previous document: *Bordetella pertussis*; polyomaviruses, BK and JC; hepatitis A, B and C viruses; human herpesviruses 6, 7 and 8; human metapneumovirus; HIV; tuberculosis; nocardiosis; malaria; and leishmaniasis. In recognition of our global society, several organisms are discussed that may be limited to certain regions of the world. Included in that section are also those infections that may be ubiquitous but occur infrequently, such as *Pneumocystis jiroveci* and *Nocardia*.

Several other changes should be noted. For bacterial infections, these guidelines now recommend quinolone prophylaxis for patients with neutropenia expected to last for at least 7 days (BI). In addition, the recommendations for contact precautions (AIII), vaccination (BI) and prophylaxis for patients with GVHD (AIII) against *Streptococcus pneumoniae* have been strengthened. The subsection on central line-associated blood stream infections is now included in the bacterial section. The vaccination section has been dramatically expanded. Changes include the recommendations for pneumococcal conjugate vaccine (PCV) rather than for pneumococcal polysaccharide vaccine 23-valent (PPSV-23) for pneumococcal vaccination, starting some vaccinations earlier post transplant, as well as the addition of recommendations for

Table 2 Summary of changes compared with the guidelines published in 2000[1]

Major changes	*Starting page*
Updated background on immune recovery after HCT, including differences based on conditioning regimen and stem cell sources	457
Changes to the Bacterial section	
(1) Quinolone prophylaxis is recommended for patients with neutropenia expected to last $\geqslant$7 days (BI)	467
(2) Added recommendations regarding central line-associated bloodstream infections (CLABSI) (in addition to the section in Infection Prevention and Control)	468
(3) *Streptococcus pneumoniae*	468
(a) Contact precautions now an AIII (earlier BIII)	
(b) Antimicrobial prophylaxis in patients with GVHD now an AIII (earlier BIII)	
(c) Vaccination with PCV now a BI recommendation (earlier BIII)	
Changes to the Fungal section	
(1) Micafungin is an alternative for prevention of candidiasis during pre-engraftment (BI)	485
(2) Voriconazole and posaconazole may be used for prevention of candidiasis after engraftment (BI)	485
(3) Itraconazole oral solution as prevention of mold infections (BI—earlier, no data)	486
(4) Posaconazole for prevention of mold infections in patients with GVHD (BI)	486
PCR screening for *Toxoplama gondii* can be considered in high-risk patients when unable to tolerate prophylaxis (BII)	492
Changes in Vaccination Recommendations	
(1) Pneumococcal vaccine: use PCV vaccine and start 3–6 months after HCT	525
(2) Optional to use acellular pertussis vaccine in all patients	525
(3) Varicella vaccine (Varivax) is optional. Zostavax is contraindicated	526
(4) Vaccinations with inactivated vaccines may be started as early as 6 months after HCT (and earlier for PCV and influenza)	522
(5) Information regarding use of HPV vaccine	523
Sections added to the Infection Prevention and Control section	
(1) Recommendations regarding multiple drug-resistant Gram-negative bacilli	503
(2) Recommendations regarding adenovirus	505
(3) Recommendation regarding viral gastroenteritis	505
Section added to the Safe Living after Hematopoietic Cell Transplantation	
Recommendations regarding household contacts who receive live-attenuated vaccines	510
Appendix 1 (Dosing) changes	
(1) Alternative CMV prophylaxis/treatment: foscarnet now AI (earlier CIII) and added valganciclovir and cidofovir	529
(2) EBV prophylaxis/treatment with rituximab	530
(3) VZV: added alternatives to VZIG for exposure and new information on prophylaxis	530
(4) Influenza: added dosing information for oseltamivir and zanamivir	531
(5) RSV: added dosing information	531
(6) Split the fungal section into data for standard risk and high-risk patients	532
(7) Added dosing information for micafungin, posaconazole and voriconazole	532
(8) Alternative PCP prophylaxis: added atovaquone and changed aerosolized pentamidine to CII (earlier CIII)	532
New organisms	
Bordatella pertussis	470
Human metapneumovirus	477
Polyomaviruses, BK and JC	477
Hepatitis A	478
Hepatitis B	478
Hepatitis C	481
Human herpes virus 6 and 7	481
Human herpes virus 8	482
HIV	482
Mycobacterium tuberculosis	489
Nocardia	492
Leishmania	493
Malaria	494

Abbreviations: PCP = Pneumocystis pneumonia; PCV = pneumococcal conjugate vaccine; RSV = respiratory syncytial virus.

Varivax, human papillomavirus (HPV) vaccine and (the nonuse of) Zostavax vaccine. Two additional appendices have been added to provide information on desensitization to sulfa drugs and visitor-screening questionnaires. Finally, the dosing appendix has merged both adult and pediatric dosing and provides recommendations for several newer antimicrobial agents that were not previously available.

In summary, the changes and expansion to this document reflect the growing body of literature detailing infectious complications in HCT patients.