



# Preventing Opportunistic Infections After Hematopoietic Stem Cell Transplantation: The Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and Beyond

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This review presents evidence-based guidelines for the prevention of infection after blood and marrow transplantation. Recommendations apply to all myeloablative transplants regardless of recipient (adult or child), type (allogeneic or autologous) or source (peripheral blood, marrow or cord blood) of transplant.

In Section I, Dr. Dykewicz describes the methods used to rate the strength and quality of published evidence supporting these recommendations and details the two dozen scholarly societies and federal agencies involved in the genesis and review of the guidelines.

In Section II, Dr. Longworth presents recommendations for hospital infection control. Hand hygiene, room ventilation, health care worker and visitor policies are detailed along with guidelines for control of specific nosocomial and community-acquired pathogens.

In Section III, Dr. Boeckh details effective practices to prevent viral diseases. Leukocyte-

depleted blood is recommended for cytomegalovirus (CMV) seronegative allografts, while ganciclovir given as prophylaxis or preemptive therapy based on pp65 antigenemia or DNA assays is advised for individuals at risk for CMV. Guidelines for preventing varicella-zoster virus (VZV), herpes simplex virus (HSV) and community respiratory virus infections are also presented.

In Section IV, Drs. Baden and Rubin review means to prevent invasive fungal infections. Hospital design and policy can reduce exposure to air contaminated with fungal spores and fluconazole prophylaxis at 400 mg/day reduces invasive yeast infection.

In Section V, Dr. Sepkowitz details effective clinical practices to reduce or prevent bacterial or protozoal disease after transplantation. In Section VI, Dr. Sullivan reviews vaccine-preventable infections and guidelines for active and passive immunizations for stem cell transplant recipients, family members and health care workers.

## I. DEVELOPMENT OF EVIDENCE-BASED GUIDELINES FOR PREVENTING OPPORTUNISTIC INFECTIONS AMONG HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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The development of “Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients” represents several years of collaborative efforts of the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), the American Society for Blood and Marrow Transplantation (ASBMT), and two dozen other scholarly societies and federal agencies.<sup>1</sup> The following describes the goals and process of guideline develop-

ment and methods for evaluating the supporting evidence.

In 1992, the Institute of Medicine (IOM) issued a report entitled “Emerging Infections: Microbial Threats to Health in the United States.”<sup>2</sup> In this document, IOM recommended that CDC lead a global effort to detect and control emerging infectious disease threats. In response to this recommendation, the National Center for Infectious Diseases (NCID) of CDC published “Addressing Emerging Infectious Disease Threats: A Prevention Strategy for the United States.”<sup>3</sup> Goal III of this report stated that the development and implementation of guide-

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lines for the prevention of opportunistic infections (OIs) in immunosuppressed persons was a high priority for NCID. In 1995, the “USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus,” or HIV OI guidelines, were first published.<sup>4</sup> Revised editions appeared in 1997 and 1999.<sup>5,6</sup> Following these publications, NCID subsequently proposed that CDC expand its OI prevention activities to include non-HIV-infected immunocompromised persons. In 1996, CDC performed an informal survey of hematology, oncology and infectious disease specialists at major stem cell transplant centers to determine the need for developing evidence-based guidelines for prevention of OIs in hematopoietic stem cell transplant (HSCT) recipients. Almost unanimously, the persons surveyed said that such guidelines should be formulated.

Dr. Clare Dykewicz at CDC was asked to develop the guidelines, and external consultants were selected equally from the infectious disease and transplant communities. CDC contacted IDSA and the ASBMT, and the International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry of North America (IBMTR/ABMTR) to request assistance in selecting consultants. IDSA selected Drs. Robert Rubin and Kent Sepkowitz to be its representatives on the working group. ASBMT nominated Dr. Keith Sullivan to be its representative and the IBMTR/ABMTR chose Dr. Philip Rowlings. The Hospital Infections Program at CDC/NCID selected an expert in hospital infection control, Dr. David Longworth, to join the working group. Dr. David Emanuel was invited to join the working group because of his pediatric transplant expertise. Other members of the working group included two other leaders in infectious disease and transplantation, Drs. Raleigh Bowden and John Wingard. In addition, representatives from NCID and CDC’s National Immunization Program volunteered to participate in working group activities.

For the purpose of these guidelines, OIs were defined as infections that occur with increased frequency or severity in HSCT recipients. HSCT was defined as any transplantation of hematopoietic cells, regardless of type (allogeneic vs. autologous) or source (bone marrow, peripheral blood, or placental/umbilical cord blood). The goals of the guidelines were to 1) summarize current data regarding the risk of OIs in HSCT recipients; 2) produce an evidence-based statement of recommended strategies for the prevention of OIs; and 3) decrease the prevalence, morbidity, and mortality of OIs in HSCT recipients. The target audience for the guidelines included HSCT unit and clinic staff, transplant and infectious disease physicians, adult and pediatric HSCT recipients, and their households and close contacts.

Nine sections were created for the evidenced-based

guidelines. Each non-CDC working group member led at least one section. The background and introduction were followed by sections on the prevention of viral, bacterial, fungal, protozoal, and helminth infections. The disease-specific chapters sections address prevention of exposure and disease for pediatric and adult, autologous, and allogeneic HSCT recipients. The hospital infection control sections review room ventilation, isolation and barrier precautions, and prevention of nosocomial infections and infections acquired from construction, visitors, plants, and playrooms. The strategies for safe living section addresses avoiding environmental exposures, safe sex, pet safety, water and other beverage safety, and travel safety. The immunization section details immunization of HSCT recipients, their household contacts, and health care workers, travel immunizations, and passive immunization with immune globulin products. The safety chapter contains recommendations on preventing the transmission of infections to HSCT recipients from donated cells.

Each recommendation is followed by a rating of both the strength of the recommendation and the quality of evidence supporting the recommendation. The rating system used follows the system developed by IDSA and the USPHS for the HIV OI guidelines.<sup>7</sup> As shown in **Table 1**, an “A” rating means that this measure should always be implemented, “B” is a measure that should generally be implemented, “C” is optional, and “D” and “E” ratings refer to measures that should not be implemented, with increasing degrees of contraindication. Roman numerals are used to denote the quality and type of supporting evidence for a recommendation. A “I” rating means there is supporting evidence from at least one properly randomized, controlled trial. A “II” rating means there is supporting evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series or there are dramatic results from uncontrolled experiments. A “III” rating means there is supporting evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

The first draft of the guidelines was presented at a meeting at CDC on March 19 and 20, 1997. Representatives from ASBMT and IBMTR/ABMTR attended, as well as representatives from the university and community hospital-affiliated infectious disease programs and HSCT groups. These included the Eastern Oncology Collaborative Group, Pediatric Oncology Group, Southwest Oncology Group, Children’s Cancer Group, Response Oncology, Inc., the American Academy of Pediatrics (AAP), the American College of Physicians, and the CDC Advisory Committee on Immunization Prac-

**Table 1. Evidence-based rating system used in the Hematopoietic Stem Cell Transplantation (HSCT) Guidelines.**

**Strength of the recommendation**

**Category Definition**

- 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, (e.g., 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**

**Category Definition**

- I** Evidence from at least one properly randomized, controlled trial.
- II** Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series or dramatic results from uncontrolled experiments.
- III** Evidence from opinions of respected authorities based on clinical experience, descriptive

tices (ACIP). CDC also invited representatives from governmental agencies such as the National Institutes of Health (NIH), the Health Resources and Services Administration, the Health Care Financing Administration (HCFA) and the Food and Drug Administration (FDA). Overall, nearly 40 persons from outside CDC attended the Atlanta meeting. Meeting participants were asked to review and critique the draft HSCT guidelines and to make suggestions for revisions.

Following the meeting, the guidelines were revised extensively. In addition to comments received from meeting participants, CDC solicited comments from disease-specific experts on each section of the guidelines. For example, the sections on “Hospital Infection Control” and “Strategies for Safe Living After HSCT” were reviewed by the Hospital Infection Control Advisory Committee and the Society for Healthcare Epidemiology of America with additional input from Andrew Streifel and Dr. Jan Patterson. Dr. Richard Whitley was selected by the AAP Committee on Infectious Diseases to review the pediatric content of the guidelines. Dr. Thomas Walsh of NIH provided comments on the fungal section of the

guidelines. The safety section was revised by Dr. Liana Harvath of FDA and Dr. Donna Przepiorcka of International Society of Hematotherapy and Graft Engineering (ISHAGE), with input from the National Marrow Donor Program and the American Association of Blood Banks. The CDC/NCID Zoonoses Working Group wrote the recommendations for prevention of pet-associated infections in the section on “Strategies for Safe Living After HSCT.”

An additional working group was formed to address immunizations for HSCT recipients. Dr. Keith Sullivan chaired this immunization working group (IWG); other members were Drs. Albert Donnenberg, Donna Ambrosino, and Deborah Molrine. The need for development of such recommendations along with recent literature indicating that immunizations were underutilized in transplant recipients,<sup>8</sup> was presented by the IWG to the ACIP in June 1997. ACIP decided that it was “critically important” to become involved in the process of developing an immunization schedule for HSCT recipients in collaboration with the AAP and IWG.

Consequently, a meeting was held at CDC on October 6 and 7, 1997, to develop an immunization schedule for HSCT recipients. Participants included representatives from ACIP, AAP, ASBMT, and IWG, along with representatives from CDC and the FDA. The group developed an interim immunization schedule for HSCT recipients that is to be used until further data are available and an ACIP statement on immunizations for HSCT recipients can be prepared.

To review the entire draft guidelines, the HSCT guidelines working group also requested input from other USPHS agencies. Specifically, we solicited comments and review from the National Institute for Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, the FDA, and HCFA. AAP endorsement was requested and obtained for the pediatric content of the guidelines, including the immunization schedules. The “Hematopoietic Stem Cell Safety” section was endorsed by ISHAGE. CDC requested that IDSA and ASBMT cosponsor the guidelines, which precipitated further review of the draft guidelines by these two organizations. The Council of State and Territorial Epidemiologists also asked to review the draft guidelines, and AAP representatives reviewed all recommended pediatric drug doses. Finally, all disease-specific experts at CDC were requested to review relevant sections of the guidelines and verify accuracy.

On September 15, 1999, CDC released a copy of the revised draft guidelines on the CDC internet website soliciting both public review and comment from transplant practitioners as well as the participants in the March 1997 meeting. CDC received public comments from North and South America, Europe, the Middle East, and

Asia. All public comments were reviewed and, whenever possible, suggestions were incorporated into the document. The guidelines were published in *Morbidity and Mortality Weekly Report* and in *Biology of Blood and Marrow Transplantation*.<sup>1</sup> They are also available on the web at [www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4910a1.htm). The following sections review and update the literature supporting these practice guidelines.

## II. HOSPITAL INFECTION CONTROL AND PREVENTION OF NOSOCOMIAL INFECTIONS AMONG HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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The CDC, the IDSA, and the ASBMT have recently published guidelines for preventing opportunistic infections among HSCT recipients.<sup>1,2</sup> These evidence-based guidelines provide 211 recommendations specific for hospital infection control issues in allogeneic and autologous HSCT and focus on room ventilation; construction, renovation and building cleaning; isolation and barrier precautions; hand hygiene; equipment management; issues involving health care workers (HCW) and visitors to HSCT centers; patient skin and oral care; prevention of bacterial intravascular catheter-related infections; infection control surveillance; and prevention and control of specific nosocomial infections, including *Legionella* species, methicillin-resistant *Staphylococcus aureus*, staphylococci with reduced susceptibility to vancomycin, vancomycin-resistant enterococci (VRE), *Clostridium difficile*, tuberculosis and community-acquired respiratory viruses (CRVs).

Recommendations are graded by strength and quality of evidence supporting them. Among the 211 infection control guidelines, 171 are level III (supported by expert opinion, consensus committee or descriptive studies), 33 are level II (supported by at least one well-designed nonrandomized clinical trial, case-control or cohort study, multiple time-series studies, or dramatic results from uncontrolled studies), but only 7 are level I (supported by data from at least one randomized controlled trial) as shown in **Table 2**. Among the 59 A-level (strongly recommended) guidelines, 41 are AIII, while among the 103 B-level (generally recommended) guidelines, 89 are BIII. In most instances, these level III guidelines reflect expert opinion or consensus committee recommendations. The relative paucity of evidence from well designed clinical trials in this field highlights the need for future studies to better define optimal infection

control practices in HSCT recipients.

This review emphasizes 19 recommendations that are strongly recommended (A) or never recommended (E) for which supporting evidence is available at levels I or II. While other aspects of the guidelines and this chapter discuss BI recommendations, no BI recommendations are found in the infection control section of the guidelines. These 19 AI-II and EII guidelines are summarized in **Table 3**. Because of the clinical importance of infection control in this patient population and the controversy in certain areas, this review also discusses recommendations of lesser strength in selected areas of particular relevance to practitioners and HSCT centers.

### Room Ventilation

Staff in HSCT centers should prevent access of birds to hospital air intake ducts (AII), as studies have linked such exposures to the subsequent development of invasive pulmonary respiratory tract infections in HSCT recipients.<sup>3,4</sup>

Although well designed clinical trials have not validated this approach, it is recommended that all allogeneic recipients be placed in rooms with > 12 air exchanges per hour and point-of-use HEPA filters that are capable of removing particles  $\geq 0.3$   $\mu\text{m}$  in diameter<sup>5</sup> (AIII). The utility of HEPA filtration has not been established in autologous transplant recipients, but the guidelines suggest consideration of its use in high risk autologous recipients with prolonged neutropenia who are at risk of invasive aspergillosis (CIII). Although data from the early 1980s suggested the benefit of laminar air flow (LAF) rooms in allogeneic transplant recipients with aplastic anemia who received grafts from HLA-identical siblings,<sup>6</sup> more recent studies suggest no survival benefit from routine LAF use in all HSCT recipients.<sup>7</sup>

**Table 2. Number of recommendations stratified by strength and quality of supporting evidence in infection control.**

Recommendation level*	Number
AI	6
AII	12
AIII	41
BII	14
BIII	89
CII	2
CIII	19
DI	1
DII	4
DIII	22
EII	1

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\* Definitions of levels are provided in Section I by Dr. Dykewicz.

**Table 3. Infection control guidelines with level AI, All, and EII strength and quality of supporting evidence.**

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**AI Recommendations**

1. All persons should wash their hands before entering and after leaving the rooms of HSCT recipients and candidates undergoing conditioning therapy, or before any direct contact with patients regardless of whether they were soiled from the patient, environment or objects.
2. All health care workers with diseases transmissible by air, droplet, and direct contact (e.g. varicella zoster virus, infectious gastroenteritis, herpes simplex lesions of lips or fingers and upper respiratory tract infections) should be restricted from patient contact and temporarily reassigned to other duties.
3. When a case of laboratory confirmed legionellosis is identified in a person who was in the inpatient HSCT center during all or part of the 2-10 days before illness onset, or if two or more cases of laboratory-confirmed Legionnaire's disease occur among patients who had visited an outpatient HSCT center, hospital personnel in consultation with the hospital infection control team should perform a thorough epidemiologic and environmental investigation or determine the likely environmental source(s) of *Legionella* species (e.g. showers, tap water faucets, cooling towers and hot water tanks).
4. To control VRE exposure, strict adherence to standard infection control measures is necessary, as outlined in the text.
5. All HCWs who anticipate contact with a *Clostridium difficile*-infected patient or the patient's environment or possessions should put on gloves before entering the patient's room and before handling the patient's secretions and excretions.
6. HSCT candidates with a recently positive tuberculin skin test or a history of a positive skin test and no prior preventive therapy should be administered a chest radiograph and evaluated for active TB.

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**All Recommendations**

1. HCST centers should prevent birds from gaining access to hospital air-intake ducts.
2. Appropriate gloves should be used by all persons when handling potentially contaminated biological materials.
3. Work exclusion policies should be designed to encourage HCWs to report their illnesses or exposures.
4. Visitors who might have communicable infectious diseases (e.g. upper respiratory tract infections, flu-like illnesses, recent exposure to communicable diseases, an active shingles rash whether covered or not, a VZV-like rash within 6 weeks of receiving a live attenuated varicella vaccine, or a history of receiving an oral polio vaccine within the previous 3-6 weeks) should not be allowed in the HSCT center or have direct contact with HSCT recipients or candidates undergoing conditioning therapy.
5. If *Legionella* species are detected in the water supplying an HSCT center, the water supply should be decontaminated and eradication of *Legionella* should be verified.
6. HSCT centers should follow basic infection control practices for control of MRSA infection and colonization, including hand washing between patients and use of barrier precautions, including wearing gloves whenever entering the MRSA-infected or MRSA-colonized patient's room.
7. HSCT personnel should institute prudent use of all antibiotics, particularly vancomycin, to prevent the emergence of staphylococci with reduced susceptibility to vancomycin.
8. Use of intravenous vancomycin is associated with the emergence of VRE; vancomycin and all other antibiotics, particularly antianaerobic agents, should be used judiciously.
9. All patients with *Clostridium difficile* disease should be placed under contact precautions for the duration of the illness.
10. When caring for an HCST recipient or candidate undergoing conditioning therapy with upper or lower respiratory tract infection, HCWs and visitors should change gloves and wash hands in circumstances outlined in the text.
11. Visitors and HCWs with infectious conjunctivitis should be restricted from direct patient contact until the drainage resolves and the ophthalmology consultant concurs that the infection and inflammation have resolved to avoid possible transmission of adenovirus to HSCT recipients.
12. For patients with suspected or proven pulmonary or laryngeal TB, HSCT personnel should follow guidelines regarding the control of TB in health care facilities.

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**EII Recommendations**

- Bacillus of Calmette and Guerin (BCG) vaccination is contraindicated among HSCT candidates and recipients because of its potential to cause disseminated or fatal disease among immunocompromised persons.

Abbreviations: HSCT, hematopoietic stem cell transplantation; TB, tuberculosis; VRE, vancomycin-resistant enterococci; HCWs, health care workers; VZV, varicella-zoster virus; MRSA, methicillin-resistant *Staphylococcus aurea*

Survival of patients with aplastic anemia patients undergoing HSCT has improved in recent years, and no follow-up studies have been performed to evaluate the utility of LAF use in this population. The use of LAF rooms, even if available, is therefore deemed optional (CII).

### **Construction, Renovation, and Building Cleaning**

This portion of the guidelines contains no AI, AII, or E level recommendations. There are five AIII level guidelines. To minimize the risk of nosocomial aspergillosis, individuals responsible for HSCT construction or renovation are advised to consult published recommendations regarding environmental controls during construction.<sup>8</sup> In addition, when construction or renovation is anticipated, staff in HSCT centers should intensify aspergillosis-control measures (AIII), as outlined in a series of BIII recommendations. HSCT recipients, health care workers and visitors should avoid construction and renovation areas to the extent possible (AIII). N95 respirators have been proposed for HSCT recipients during transport near construction or renovation areas (CIII), but fit-testing and training are necessary for maximal benefit; standard surgical masks afford little protection against inhalation of fungal spores and are not recommended (DIII).

Newly constructed areas should be cleaned before patients are permitted to enter them (AIII)<sup>8</sup> as outlined in several BIII guidelines. HSCT patients should not be exposed to activities such as vacuuming of floors or carpets, which are apt to result in the aerosolization of *Aspergillus* spores (AIII).<sup>8</sup>

### **Isolation and Barrier Precautions**

This section of the guidelines contains no AI, AII, or E recommendations. Members of HSCT centers are advised to follow published guidelines for hospital isolation practices, including guidelines for the prevention of nosocomial infections (AIII).<sup>3,9,10</sup> The utility of specific isolation and barrier precautions in the prevention of nosocomial infections in HSCT recipients has not been studied, however, and these recommendations are extrapolated from other settings.

### **Hand Hygiene**

The importance of good handwashing practices in the care of HSCT patients cannot be over-emphasized. All persons, especially HCWs, are advised to wash hands before entering and after leaving the rooms of HSCT patients and of those receiving conditioning therapy. In addition, handwashing should be performed before and after direct contact with patients irrespective of whether soiling from the patient or from objects in the environment occurs (AI).<sup>11</sup> Handwashing produces a reduction in the carriage of potential pathogens on the hands and

has been shown to reduce morbidity and mortality from nosocomial infections in numerous studies.<sup>11</sup> Handwashing may be performed with an antimicrobial soap and water, or with hygienic hand rubs (AIII).

Gloves should be worn by all persons when handling potentially infected biologic material (AII). Gloves should be changed between patients or prior to touching a clean area when soiled (AIII). Items worn on the hands by HCWs such as rings, artificial nails, and adhesive bandages should be avoided, as they may serve as a nidus for pathogenic microorganisms (BII).

### **Equipment**

This section contains no AI-II or E level recommendations. HSCT centers are advised to adhere to established guidelines for the sterilization, disinfection and maintenance of devices and equipment utilizing only EPA-registered agents (AIII).<sup>3,12-14</sup>

### **Health Care Workers**

All HCWs with diseases transmissible by direct contact, droplet or airborne transmission should be restricted from direct patient contact and temporarily reassigned to other tasks (AI) and should follow published guidelines regarding the duration of work restriction (BIII).<sup>15</sup> These include individuals with illnesses such as varicella zoster virus (VZV) infection, infectious gastroenteritis, herpes simplex infections involving the fingers or lips, and upper respiratory tract infections. Staff at HSCT centers should formulate work exclusion policies to ensure that HCWs report illnesses or potential exposures to communicable pathogens (AII). HSCT institutions should have a written policy regarding HCW immunizations that meets guidelines recommended by the CDC, the Advisory Committee on Immunization Practices, and the Healthcare Infection Control Practices Advisory Committee (BIII).<sup>16</sup>

### **Visitors to Transplant Centers**

Visitors with potentially communicable illnesses should be barred from the HSCT center and should not have direct contact with HSCT recipients or with candidates receiving preparative therapy (AII). Such illnesses include upper respiratory tract infection, flu-like illnesses, varicella zoster infection, a VZV-like rash developing within 6 weeks of a live attenuated VZV vaccine, or a history of receiving oral polio vaccine within the preceding 6 weeks. All visitors to HSCT centers should be capable of practicing recommended handwashing guidelines irrespective of age (AIII). HSCT centers should have written policies regarding screening of visitors for potentially communicable diseases (BII).

## Patient Skin and Oral Care

This section of the guidelines contains no AI, AII or E guidelines. Six AIII level recommendations are offered. Education regarding dental hygiene is recommended for HSCT recipients and their caregivers concerning the importance of good dental hygiene following transplantation, so as to minimize the likelihood of oral and dental infection (AIII). In addition, all HSCT candidates should be evaluated for dental disease (AIII) and likely sources of infection should be eliminated (AIII).<sup>17</sup> Ten to 14 days should elapse between completion of dental therapy and initiation of a preparative regimen (AIII). Oral hygiene should be maintained in HSCT recipients or candidates receiving conditioning therapy who have oral mucositis through the use of 4-6 oral rinses per day with normal saline, sterile water or sodium bicarbonate solutions.<sup>18</sup>

Following urination or defecation, female HSCT recipients should wipe the perineum from front to back to prevent urethral contamination and subsequent urinary tract infection (AIII).

## Prevention of Intravascular

### Catheter-Related Bacterial Infections

This section of the guidelines contains no AI-II or E level recommendations. HSCT centers should follow published guidelines for preventing intravascular device-related infections (AIII).<sup>19</sup>

## Control of Specific Nosocomial and Community-Acquired Pathogens

### *Legionella species*

Legionellosis should be considered in the differential diagnosis of pneumonia in HSCT recipients (AIII). The incubation period for Legionnaires' disease (LD) is 2-10 days. Therefore, patients with laboratory-confirmed LD who are continuously hospitalized for  $\geq 10$  days prior to symptom onset have definite nosocomial legionellosis. Those with proven LD who have been in hospital 2-9 days prior to illness onset have possible nosocomial acquisition. If LD is confirmed in a patient hospitalized on the HSCT unit for all or part of the 2-10 days before illness onset, or if 2 or more cases of proven LD occur in patients visiting an outpatient HSCT clinic, a thorough epidemiologic and environmental investigation should be conducted in conjunction with the infection control team to determine the environmental source(s) of the outbreak (AI).<sup>20</sup> This should include assessment of cooling towers, hot water tanks, showers and tap water faucets. Once identified, the environmental source should be removed or decontaminated (AIII). If *Legionella* species are found in the HSCT center water supply, it should be decontaminated (AII) and patients should

not take showers (DIII) but should receive sponge baths utilizing *Legionella*-free water (BIII). In addition, water from faucets contaminated with *Legionella* species should not be used in the HSCT unit so as to prevent the creation of infectious aerosols (CIII). Only sterile water should be used for rinsing nebulation devices and other respiratory care equipment after cleaning, and for filling reservoirs of these devices (BII).<sup>3</sup>

### *Methicillin-resistant staphylococci*

Personnel at HSCT centers should adhere to standard infection control practices in order to optimize the control of methicillin-resistant *Staphylococcus aureus* (MRSA) (AII).<sup>9</sup> These practices include handwashing between patient encounters, use of appropriate barrier precautions, and wearing gloves when entering the room of an MRSA-infected or colonized patient. Intravascular devices infected or colonized with MRSA should be removed (AIII).

### *Staphylococci with reduced susceptibility to vancomycin*

At present, staphylococci with reduced susceptibility to vancomycin are fortunately rare.<sup>21</sup> HSCT centers should have laboratory facilities capable of identifying and performing antimicrobial susceptibility testing on all staphylococci (AIII). In addition, routine surveillance should be performed for staphylococci with reduced susceptibility to vancomycin (AIII), defined as a vancomycin minimal inhibitory concentration (MIC)  $\geq 4$   $\mu\text{g}/\text{mL}$  for *Staphylococcus aureus* and  $\geq 8$   $\mu\text{g}/\text{mL}$  for coagulase negative staphylococci. If such isolates are identified and confirmed, the laboratory should contact hospital infection control personnel, the HSCT center, the patient's physician, the local or state health department, and the CDC's Hospital Infection Program so that a prompt epidemiologic investigation may be performed (AIII). Hospitalized patients who are infected or colonized with these organisms should be cohorted (AIII). Prudent antibiotic use by HSCT centers, especially of vancomycin, is essential to prevent the emergence of resistant staphylococci and is recommended (AII). In addition, intravascular devices colonized or infected with staphylococci with reduced susceptibility to vancomycin should be removed (AIII).

### *Vancomycin resistant enterococci*

The emergence of VRE is associated with the use of vancomycin and antianaerobic agents, and these drugs should be used judiciously (AII).<sup>22</sup> To limit exposure of HSCT recipients and patients receiving conditioning therapy to VRE, adherence to standard infection control measures is recommended as summarized in the following guidelines (AI). These measures include compliance with handwashing guidelines outlined above and the

cohorting of VRE-colonized or infected patients. In addition, patient rooms and equipment should be disinfected with an FDA- or EPA-registered disinfectant, including surfaces of the hospital environment such as walls, floors, bed frames, doors and bathrooms. In pediatric areas, a nontoxic disinfectant should be used (BIII). Patients with VRE should be placed under contact precautions until cultures are negative and antibiotics are discontinued (BIII). Gloves should be worn in the room of VRE-infected or colonized patients and discarded prior to leaving the room.

#### *Clostridium difficile*

Patients with *Clostridium difficile* disease should be placed under contact precautions for the duration of their illness.<sup>9</sup> Gloves should be worn by HCWs who anticipate contact with HSCT patients who are colonized or infected with *C. difficile* or with their possessions or environment; gloves should be put on before entering the patient's room (AI). Standard published guidelines for the prevention and control of *C. difficile* infection should be followed, including the judicious use of antibiotics (AIII).<sup>23</sup> The prophylactic use of lyophilized *Saccharomyces boulardii* to prevent diarrhea among HSCT recipients receiving antibiotics is contraindicated, as it has no salutary effect and has been associated with the development of *S. boulardii* fungemia (DII).<sup>24</sup>

#### *Community-acquired respiratory virus infections*

Community-acquired respiratory viruses (CRVs) may produce significant morbidity and mortality in HSCT recipients,<sup>25</sup> and may produce nosocomial infection if introduced into the HSCT center. Measures to prevent the introduction and spread of CRVs on the HSCT unit are therefore recommended. When caring for a patient at the HSCT center with upper or lower respiratory tract infection, HCWs and visitors should change gloves and wash hands after contact with a patient, after handling respiratory secretions or objects contaminated with respiratory secretions, and between contact with a contaminated body site and the respiratory tract of or respiratory device used on the same patient (AII). This practice is important because most CRVs are transmitted by contact, especially from hand to nose and eye.

Appropriate infection control measures to prevent nosocomial pneumonia among HSCT patients should be followed, especially during outbreaks of community or nosocomial CRVs (AIII).<sup>3</sup> It is crucial to identify and place under contact precautions HSCT recipients with respiratory syncytial virus (RSV) infection so as to prevent nosocomial transmission (AIII). To minimize the risk of CRV spread on the HSCT unit, HCWs and visitors with symptoms of upper respiratory infection should be restricted from contact with HSCT patients and indi-

viduals undergoing conditioning therapy (AIII). Because of the risk of adenovirus transmission to HSCT recipients, HCWs and visitors with infectious conjunctivitis should be prohibited from contact with patients until ocular drainage resolves and an ophthalmologist agrees that inflammation and infection have subsided (AII). Finally, when suctioning patients with upper or lower respiratory tract infections, HCWs should wear surgical masks, eye protection and gowns to avoid splashes with the patient's secretions. In addition, protective clothing should be donned when entering the patient's room, removed and discarded prior to leaving, and always changed between patient rooms (AIII).

#### *Tuberculosis*

Because HSCT recipients may reactivate tuberculosis in the face of immunosuppression, candidates for HSCT should be screened by history and chart review for a history of prior exposure to tuberculosis (AIII). A tuberculin skin test utilizing 5 tuberculin units of either the Tubersol or Aplisol formulations may be administered by the Mantoux method, but may be unreliable because of the patient's baseline immunosuppression. For immunocompromised individuals, a positive skin test is defined as  $\geq 5$  mm of induration.<sup>26</sup> Individuals with a recently positive skin test or a previously positive skin test and no prior preventive therapy should have a chest radiograph and an evaluation for active tuberculosis (AI).

Staff at HSCT centers should follow published guidelines concerning the control of tuberculosis in health care facilities, which include the institution of airborne precautions and the use of negative pressure rooms for patients with suspected or confirmed laryngeal or pulmonary tuberculosis (AII).<sup>9,27</sup> With such patients, HCWs should wear N95 respirators, even in isolation rooms, when exposed to potentially infected patients (AIII). For maximal efficacy of N95 respirators, HCWs should be fit-tested and trained in their use (AIII).

Immunization with the Bacillus of Calmette and Guerin (BCG) vaccine is contraindicated in HSCT candidates and recipients because of its potential to produce disseminated and fatal infection in immunocompromised hosts (EII).<sup>28</sup>

#### **Infection Control Surveillance**

This section of the guidelines contains no A or E level recommendations. HSCT centers are advised to refrain from performing routine bacterial or fungal surveillance cultures of asymptomatic HSCT recipients (DII)<sup>29</sup> or, in the absence of clusters of infections, of the environment or of equipment or devices used for pulmonary function testing, delivery of inhalation anesthesia, or respiratory care (DIII). In addition, in the absence of an outbreak of nosocomial fungal infection, personnel at HSCT cen-



ters should not perform routine fungal surveillance cultures of devices or dust in patient rooms (DIII).

### Author's Update and Future Directions

Several studies of relevance to infection control practices on HSCT units have been published in the past year. Weinstock et al reported an outbreak of nosocomial influenza A in January 1998 occurring on a 30 bed HSCT unit, and described enhanced interventions implemented to terminate the outbreak and to prevent nosocomial influenza the following season.<sup>30</sup> These interventions included strict isolation of patients with influenza, reverse isolation of all other patients on the HSCT unit during the outbreak, more rapid laboratory turnaround of diagnostic tests for influenza, restriction of visitors, cohorting of HCWs assigned to the HSCT unit, universal rimantadine prophylaxis of all patients and HCWs on the unit during the outbreak, and an enhanced influenza vaccine campaign for HCWs the following season.

Mayfield et al evaluated the role of environmental disinfectants in reducing the incidence of nosocomial *Clostridium difficile*-associated diarrhea (CDAD).<sup>31</sup> In a before and after intervention study, the incidence rate of CDAD among HSCT patients fell from 8.6 to 3.3 cases per 1000 patient days when the environmental disinfectant was switched from quaternary ammonium to 1:10 hypochlorite solutions in the rooms of patients with CDAD. When quaternary ammonium solution was re-instituted, the CDAD rate among HSCT recipients again increased to 8.1 cases per 1000 patient days.

Laura et al performed a randomized multicenter study in HSCT patients comparing two different time interval protocols for central venous catheter (CVC) dressing changes.<sup>32</sup> Three hundred ninety-nine patients with tunneled (230, Group A) or non-tunneled (169, Group B) CVCs were randomized to receive dressing changes with transparent impermeable polyurethane dressings. Patients in Group A had dressings changed at 5 versus 10 days, compared with 2 versus 5 days in Group B. There was no significant increase in local infections in those individuals randomized to longer dressing change intervals, and longer intervals were associated with lower costs and less patient discomfort.

The relative paucity of level AI, AII, BI, and E level recommendations in the infection control guidelines is striking. Among the AI and AII recommendations, most are more global and generic recommendations, derived from and applicable to other clinical settings. More evidence-based studies are necessary to define optimal infection control practices in these high-risk patients undergoing hematopoietic cell transplantation.

### III. PREVENTION OF VIRAL INFECTIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Michael Boeckh, MD\*

Viral infections are common and potentially fatal complications after HSCT. A key aspect of prevention of viral infections is risk assessment based on viral and host factors as well as the time patterns of infections after transplant. This time pattern has changed over the past two decades due to the introduction of standard viral prevention strategies. Several important changes in transplantation techniques have occurred over the past decade, such as use of different sources of stem cells (i.e. peripheral blood or cord blood instead of marrow), graft manipulation (e.g. CD34 selection or T cell depletion), and the use of novel and less toxic conditioning regimens (i.e. non-myeloablative or regimens with reduced toxicity). All these factors may affect the posttransplant risk and thus the prevention regimens. For some of the more recent changes, little information is available on their impact of infectious risk following transplantation. Ultimately, the choice of the prevention strategy is determined by the host immune status as well as the efficacy, toxicity, feasibility, cost and ratio of treated versus untreated individuals (i.e. 'number needed to treat') of the intervention.

All evidence ratings in the paragraphs "preventing exposure" and "preventing disease and disease recurrence" are identical with those in the published guidelines.<sup>1</sup> Ratings in the paragraph "update since publication of the guidelines" are assigned by the author of this chapter and have not been authorized by CDC or any of the underwriting organizations. If not otherwise noted, recommendations apply for both adult and pediatric HSCT candidates and recipients (although dosing may be different in children). For specific dosing information, the reader is referred to the original guidelines.<sup>1</sup> This chapter only addresses infection prophylaxis in recipients of myeloablative conditioning regimens. Infection prophylaxis in non-myeloablative conditioning regimens is subject of ongoing studies.

### Cytomegalovirus Infection

#### Preventing exposure

Determination of cytomegalovirus (CMV) IgG serostatus is recommended in all transplant candidates and their

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prospective donors (AIII) (Table 4). Seronegative HSCT recipients should receive seronegative or leukocyte-depleted blood products (AI). Seronegative autograft recipients are susceptible for primary CMV infection via blood products. Thus, seronegative or leukocyte-depleted blood products may be used to prevent transfusion-transmitted CMV infection (CIII). Seronegative candidates and HSCT recipients who are sexually active and not in long-term monogamous relationships should use latex condoms during sexual contacts (AII). Handling or changing diapers or wiping oral secretions from toddlers also represents a potential risk for CMV transmission to seronegative individuals and should therefore be avoided (AII).

#### Preventing disease or disease recurrence

One of two strategies should be used to prevent CMV disease in allogeneic HSCT recipients between engraftment and day 100 after transplant (AI) (Table 4). The first strategy is to give ganciclovir prophylaxis from engraftment until day 100.<sup>2</sup> An alternative strategy is to use virologic surveillance and administer ganciclovir for early evidence of subclinical CMV infection.<sup>3,4</sup> Tests used for this purpose include CMV blood cultures, the pp65 antigenemia assay, and DNA detection methods.<sup>5</sup> Due to lower sensitivity, blood culture methods are generally not recommended. Limited data exist on other detection methods such as detection of pp67 mRNA and DNA by the hybrid capture method<sup>6</sup> and no comparative study has been reported for preemptive therapy using these assays. Centers without access to highly sensitive CMV detection methods should use prophylaxis (BII). In seronegative recipients with a positive donor, the incidence of CMV infection is only 15-20% when seronegative or leukocyte-reduced blood products are given. Thus, pre-

emptive therapy with ganciclovir rather than prophylaxis is preferred in these patients (BII). Preemptive therapy is started on the basis of any positive antigenemia assay or two positive DNA PCR test results (BII). Ganciclovir is continued for a minimum of 3 weeks with one week of induction dosing or until day 100, whichever is longer (AI). Other regimens use 2 weeks of induction dosing and maintenance until PCR negativity<sup>7</sup> (BIII).

Ganciclovir recipients should have absolute neutrophil counts (ANC) checked at least twice a week during the first 100 days after transplant (BIII). Management of ganciclovir-related neutropenia (ANC < 1000/mm<sup>3</sup>) includes discontinuations of ganciclovir (CIII) and/or use of G-CSF (CIII). Neutropenic patients with ongoing CMV detection in blood should be treated with foscarnet (CIII).

Late CMV disease is an emerging problem in HSCT recipients given ganciclovir prophylaxis or preemptive therapy.<sup>2,8,9</sup> Risk factors for late CMV disease include chronic graft-versus-host disease (GVHD), low CD4 counts (< 50/mm<sup>3</sup>), and CMV infection before day 100. If there is continued evidence of CMV in blood by day 100, ganciclovir should be continued until CMV is no longer detectable (AI). CMV surveillance should be continued until one year after transplant in these high-risk HSCT recipients. Ganciclovir should be administered for antigenemia, viremia, or PCR test positivity (e.g. 3 weeks or until CMV is no longer detectable) (BIII).

High-dose acyclovir given until day 30 or until engraftment has limited efficacy in preventing CMV disease, especially when antigenemia-guided preemptive therapy is given;<sup>10</sup> however, survival was improved in one randomized trial with extended use of high-dose acyclovir.<sup>10</sup> High-dose acyclovir given until day 30 does not seem to be effective in preventing CMV infection

**Table 4. Summary of major recommendations for prevention of cytomegalovirus (CMV).**

Type of Prevention	Rating
<b>Prevention of Exposure</b>	
Testing of recipient and donor IgG serostatus	AIII
Provision of seronegative or leukocyte-depleted blood to seronegative allograft recipients	AI
Counseling of seronegative recipient on transmission mode of CMV	All
Use of latex condoms during sexual contacts in sexually active seronegative recipients not in long-term monogamous relationships	All
Avoiding diaper changes and contact with oral secretions from toddlers or seronegative recipients	All
<b>Preventing Disease and Disease Recurrence</b>	
Ganciclovir prophylaxis or preemptive therapy based on pp65 antigenemia or DNA detection between engraftment and day 100 for patients at high risk for CMV disease	AI
Preferential use of preemptive therapy based on pp65 antigenemia or DNA detection between engraftment and day 100 in seronegative recipients with a seropositive donor	BII
CMV surveillance and preemptive therapy in CMV seropositive recipients of CD34 selected autologous transplants	BII
Use of IVIG or CMV-Ig for prevention of CMV infection and disease	DI
Use of high-dose acyclovir for prevention of CMV infection and disease in seropositive autograft recipients	DI

and disease in seropositive autograft recipients and is therefore not recommended (DII). Intravenous immunoglobulin is not recommended for prevention of CMV disease (DI).

Autologous transplant recipients generally have a lower risk of CMV disease than allograft recipients. However, among recipients of CD34-selected autografts the risk may be similar to that seen after allografting.<sup>11</sup> Therefore, CMV prevention strategies in CD34-selected autologous transplant recipients should be similar to those applied in allogeneic transplant recipients (BII). In recipients of unmodified autologous transplants, CMV surveillance and preemptive therapy is recommended in patients with hematologic malignancies or in those who have recently received fludarabine (CIII). Quantitative rather than qualitative CMV detection methods are preferred in autograft recipients (BII). In seropositive nonmodified autograft recipients a treatment course of 3 weeks is recommended if antigenemia levels of > 5 cells per slide are detected (BII).

#### *Author's update since publication of guidelines.*

New information indicates that the in vivo replication time of CMV is short and influenced by the host immune status.<sup>12</sup> This information can be used to optimize the duration of induction dosing. For example, viral load may continue to rise despite start of ganciclovir in transplant recipients, especially in those receiving high-dose corticosteroids or anti-thymocyte globulin (ATG).<sup>13,14</sup> In such a situation, induction dosing should be continued until a decline of viral load is documented by quantitative detection methods such as DNA PCR or the pp65 antigenemia assay. Conversely, in HSCT recipients with immediate decline of viral load, shorter induction courses may be possible. Increases of CMV loads early during preemptive therapy (first 4 weeks) are only very rarely due to antiviral resistance in ganciclovir-naïve transplant recipients.<sup>13</sup> However, genotypic ganciclovir resistance has been described early after transplant in T cell depleted pediatric HSCT recipients.<sup>15</sup>

More information is now available on the optimal duration of ganciclovir preemptive therapy. In an uncontrolled series of 84 patients there was no early rebound CMV disease after discontinuation of ganciclovir following a short course of ganciclovir with 2 weeks of induction and subsequent maintenance treatment until polymerase chain reaction (PCR)-negativity.<sup>7</sup> Thus, discontinuation of ganciclovir based on negative PCR testing is an alternative to treatment until day 100.

Continuation of surveillance and preemptive therapy as well as long-term secondary prophylaxis have been reported in uncontrolled trials.<sup>16,17</sup> A randomized trial is ongoing to assess the relative benefits of these two strategies for prevention of late CMV disease.

Foscarnet has been shown to be as effective as ganciclovir for preemptive therapy in a prospective randomized study. Cidofovir has been associated with moderate renal toxicity similar to that reported for foscarnet in a retrospective analysis of the clinical experience of European centers;<sup>18</sup> however, no recommendations about its use can be made at this time. Only limited data exist on oral ganciclovir in allogeneic HSCT recipients.<sup>19,20</sup> To date, no data exist on valganciclovir in HSCT. High-dose valacyclovir (8 g per day) moderately reduced the incidence of CMV infection (and therefore the need for preemptive therapy) compared to high-dose acyclovir in a randomized placebo-controlled double-blind study<sup>21</sup> and showed similar efficacy as ganciclovir when given prophylactically in another randomized trial. The incidence of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome was not increased compared to acyclovir.<sup>21</sup> A CMV-specific monoclonal antibody (MSL-109) has not been effective in preventing CMV infection.<sup>22</sup>

The type of posttransplant immunosuppression seems to determine, and in some cases limit, the efficacy of preemptive treatment strategy. One non-randomized study showed a high CMV disease rate in cohort of allogeneic HSCT patients who received high-dose steroid prophylaxis, mycophenolate mofetil, and ATG with preemptive PCR-guided therapy based on two consecutive positive results two weeks apart and discontinuation based on negative PCR.<sup>23</sup> Thus, earlier intervention, more frequent monitoring or ganciclovir prophylaxis may be required in patients who are heavily immunosuppressed.

Analysis of the impact of pretransplant CMV serostatus on survival indicates that seronegative recipients of a seropositive donor have a higher mortality than seronegative recipients of a seronegative donor.<sup>24</sup> Thus, a CMV seronegative donor should be used if possible.

## **Epstein-Barr Virus Infection**

### *Preventing exposure*

Serologic testing is generally not recommended; however, it may be useful in recipients of T cell depleted or pediatric HSCT. Known Epstein-Barr virus (EBV) seronegative transplant candidates should be advised of behavior that could decrease the likelihood of EBV transmission (AII), including safe hygiene practices (e.g. handwashing [BIII]), and should avoid contact with potentially infected respiratory secretions (AII).

### *Preventing disease and disease recurrence*

Data are emerging that donor-derived EBV-specific cytotoxic T lymphocytes (CTL) can be used effectively for prophylaxis in high-risk patients, i.e. T cell depleted transplant recipients. The strategy has potential but has not been rated by CDC.

### Author's update since publication of guidelines

Posttransplant surveillance with quantitative PCR for EBV DNA and preemptive therapy with rituximab, an anti-CD 20 monoclonal antibody, have been reported to be effective in reducing viral load in a small number of high-risk patients for EBV posttransplant lymphoproliferative disease.<sup>25</sup> However, additional studies are needed and no firm recommendations can be made at this time. Additional data have been presented on prophylactic use of donor derived EBV-specific T cells.<sup>26</sup> Although this strategy is complex it may be considered in high-risk patients.

## Herpes Simplex Virus

### Preventing exposure

Determination of herpes simplex virus (HSV) IgG serostatus is recommended in all transplant candidates (AIII) (Table 5). Testing of donor serostatus is currently not routine in most centers since HSV transmission by marrow or stem cell products has not been documented. HSV seronegative recipients should be informed about the mode of transmission of HSV and be advised of behavior that will decrease the likelihood of exposure, e.g. avoiding potentially infectious secretions such as cervical secretions and saliva (AII).

### Preventing disease or and disease recurrence.

Acyclovir prophylaxis is recommended for all HSV seropositive allograft recipients (AI) (Table 5). Most centers administer acyclovir from the onset of conditioning until engraftment and resolution of mucositis (BIII). This may occur before day 30 after transplant, which is the time period that was used in the original randomized studies of acyclovir prophylaxis. Routine extension of HSV prophylaxis beyond day 30 is not recommended in the absence of randomized trials (DIII); however, patients with frequent recurrences might benefit from extended suppressive therapy (CIII). Although the original studies were performed with intravenous (IV)

acyclovir, oral administration is often used in individuals who can take oral medication; however, adequate dosing seems important.<sup>27</sup> Patients receiving ganciclovir (CIII), foscarnet, or cidofovir for CMV prevention or treatment do not require concomitant acyclovir prophylaxis due to the in vitro activity of these compounds against HSV. Routine acyclovir prophylaxis in HSV seronegative recipients is not indicated (D III), even if the donor is seropositive.

Valacyclovir has been used instead of oral acyclovir for prevention of HSV in HSCT (CIII). There are no data on the use of famciclovir for HSV prophylaxis in HSCT recipients; however, the drug has in vitro activity as well. Foscarnet should not be used for routine HSV prophylaxis due to substantial renal toxicity (DIII).

## Varicella-Zoster Virus

### Preventing exposure

Determination of VZV IgG serostatus is recommended in all transplant candidates (AIII) (Table 6). Testing of donor serostatus is currently not routinely conducted by most centers since VZV transmission by marrow or stem cell products has not been documented. VZV is highly contagious and vaccination of family members, household contacts, and prospective visitors who are known seronegative for VZV or have no history of VZV infection should be performed (AII). This is usually done at the time of first contact with the transplant center to allow for sufficient time to complete the vaccination (ideally > 4 weeks prior to start of conditioning) (BIII). Seronegative transplant candidates and recipients should be informed about VZV transmission and advised of strategies on how to avoid exposure (AII). Transplant recipients and candidates should also avoid vaccine recipients who experience a rash after vaccination (BIII). Such rash may occur between 5 and 35 day after vaccination (median 22 days).<sup>1</sup>

All patients with VZV disease should be placed under airborne and contact isolation (AII). Isolation should

**Table 5. Summary of major recommendations for prevention of herpes simplex virus (HSV).**

Type of Prevention	Rating
<b>Prevention of Exposure</b>	
Testing of recipient IgG serostatus	AIII
Counseling of seronegative recipient on transmission mode of HSV	All
Use of latex condoms during sexual contacts in sexually active seronegative recipients not in long-term monogamous relationships	All
Counseling of seronegative recipient of behavior that will decrease HSV transmission	All
Contact isolation for persons with disseminated, severe, or severe mucocutaneous HSV disease	AI
<b>Prevention of Disease or Disease Recurrence</b>	
Acyclovir prophylaxis in seropositive allograft recipients	AI
Duration of acyclovir prophylaxis: start of conditioning until engraftment or resolution of mucositis	BII

**Table 6. Summary of major recommendations for prevention of varicella-zoster virus infection.**

Type of Prevention	Rating
<b>Prevention of Exposure</b>	
Testing of recipient IgG serostatus	AIII
Counseling about the seriousness of VZV infection in HSCT and strategies to prevent exposure	AII
Vaccination of family members and close household contacts who are seronegative or have no history of VZV	AIII
Respiratory and contact isolation of HSCT recipients with VZV	All
<b>Preventing Disease or Disease Recurrence</b>	
VZIG within 96 hours for VZV seronegative recipients following an exposure with wild-type VZV	All

Abbreviations: HSCT, hematopoietic stem cell transplantation; VZV, varicella-zoster virus; VZIG, varicella-zoster immunoglobulin

be continued until all lesions have crusted. Airborne precautions should be instituted 10 days after an exposure of a susceptible transplant recipient to VZV and continued until 21 days after the last exposure or 28 days post-exposure if the patient received varicella-zoster immunoglobulin (VZIG) (AI). Note that individuals infected with VZV can be contagious before the rash appears.

#### *Preventing disease or and disease recurrence*

VZIG should be administered to a seronegative recipient at risk for complications of VZV (i.e. < 24 months after transplant, or ≥ 24 months if on immunosuppressive therapy and/or having chronic GVHD) as soon as possible after exposure (< 96 hours) (AII) (Table 6). Seronegative recipients or candidates undergoing conditioning therapy should also receive VZIG if they are exposed to a VZV vaccinee having a varicella-like rash (BIII); these recommendations may be extended to seropositive recipients (CIII). If a second exposure occurs less than 21 days after a dose of VZIG in a susceptible individual (see above), a second dose of VZIG should be administered.

Any HSCT recipient or candidate undergoing conditioning therapy who experiences a VZV-like rash should be started immediately on preemptive intravenous acyclovir until ≥ 2 days after all lesions are crusted (BIII). Virologic confirmation may be useful in situations where the appearance of the rash is atypical. A rash following exposure to a VZV vaccinee should be treated similarly (BII). Long-term acyclovir prophylaxis for 6 months to prevent VZV infection is generally not recommended (DIII); however, such prophylaxis could be considered in HSCT recipients with severe, long-term immunodeficiency (CIII) (see below).

VZV vaccine use is contraindicated for individuals < 24 months after HSCT (EIII). Use of VZV vaccine among HSCT recipients is restricted to research protocols for individuals > 24 months after HSCT who are presumed immunocompetent (i.e., off immunosuppressive therapy and free of chronic GVHD).

#### *Author's update since publication of guidelines*

Long-term suppressive prophylaxis with acyclovir with doses higher (800 mg twice daily) and of longer duration (one year) than previously reported appears to be successful in preventing VZV reactivation.<sup>28</sup> Valacyclovir (500 mg twice daily for prophylaxis, 1000 mg three times daily for recipients with stable non-disseminated disease) is being increasingly used due to its higher bioavailability. Initial concerns of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome which had been observed in HIV-infected individuals, have not been observed in two large randomized trials at much higher doses than those used for VZV.<sup>21,29</sup>

Whether seropositive transplant recipients can be reinfected with a second strain of virus is poorly defined. However, this may occur in the context of severe immunosuppression such T cell depletion, high-dose steroid therapy, or use of ATG. Thus, exposure should also be avoided in highly immunosuppressed seropositive recipients, and postexposure prophylaxis with VZIG or acyclovir<sup>30</sup> or valacyclovir (1000 mg three times daily) given from day 2-22 of exposure may be considered.

As VZV vaccination is more commonly used in the general population, an increased frequency of previously vaccinated transplant candidates can be expected. The risk of reactivation of vaccine strains after transplantation is currently unknown. Also, whether transplant recipients who have been vaccinated prior to transplant are more susceptible to infections with wild-type VZV than those who have been naturally infected with VZV is unknown. Because the vaccine is not 100% protective even in immunocompetent individuals,<sup>27</sup> an exposure to wild-type VZV in a HSCT recipient is likely to carry a high risk and should be treated similar to exposures in seronegative HSCT recipients or candidates, especially when intense immunosuppression is administered (e.g. T cell depletion, high-dose corticosteroids, or ATG).

**Table 7. Summary of major recommendations for prevention of community respiratory virus infection.**

Type of Prevention	Rating
<b>Prevention of Exposure</b>	
Targeted surveillance system for respiratory viruses (virologic evaluation of HSCT candidates and recipients with upper respiratory symptoms)	AIII
Contact isolation of HSCT recipients and recipients with respiratory symptoms	AIII
<b>Prevention of Disease or Disease Recurrence</b>	
Influenza vaccination of HSCT recipients is not recommended < 6 months after transplant	AI

Abbreviations: HSCT, hematopoietic stem cell transplantation

## Respiratory Virus infections

### *Preventing exposure*

Respiratory viruses (respiratory syncytial virus [RSV], parainfluenza viruses, influenza viruses, adenovirus) are highly contagious. Strict infection control practices are advised (AIII). A targeted surveillance system that evaluates HSCT recipients with upper respiratory symptoms for the presence of respiratory viruses should be in place (AIII). Isolation should be instituted in all symptomatic patients, even before virologic confirmation (AIII) (Table 7).

Influenza vaccination is strongly advised for all staff members, family members and close household contacts during each influenza season before HSCT and at least 24 months after HSCT (AI). During a nosocomial influenza A outbreak situation of strains that are not covered by the vaccine health care workers, family members, and close household contact should be offered chemoprophylaxis with amantidine or rimantidine (for influenza A) (BIII) or with neuraminidase inhibitors (zanamavir, oseltamavir) if amantidine/rimantidine is not tolerated, the outbreak strain is resistant to these agents, or the outbreak is due to influenza B (BI). Neuraminidase inhibitors have not been evaluated in children.

### *Preventing disease or diseases recurrence*

Respiratory secretions of HSCT candidates and recipients with upper respiratory symptoms should be evaluated for the presence of respiratory viruses (BIII). Several strategies have been proposed to prevent progression from upper to lower tract RSV infection, including aerosolized ribavirin alone and combination with RSV-specific antibodies or palivizumab, an RSV-specific monoclonal antibody. Controlled clinical trials are currently underway to establish the efficacy of these strategies, thus, no firm recommendations can be made. Intravenous ribavirin is not recommended for preemptive therapy (DIII).

Amantidine or rimantidine chemoprophylaxis is recommended in influenza A outbreak situations for all HSCT recipients < 6 months after transplant (BIII). Af-

ter 6 months, vaccination should be resumed (BIII). Chemoprophylaxis for all HSCT recipients < 24 months or > 24 months if treated for chronic GVHD has also been recommended during outbreak situations due to the poor immunologic response to the vaccine. However, no formal recommendation regarding such prophylaxis can be made because of lack of data. Influenza vaccinations during the first 6 months after transplant are unlikely to be effective (DII).

### *Author's update since publication of guidelines*

Neuraminidase inhibitors are now available for treatment and prevention of influenza infection in immunocompetent subjects. However, no formal evaluation has been performed in immunocompromised patients. Thus, no recommendations can be made. Palivizumab, a RSV-specific monoclonal antibody, has been licensed for prevention in high-risk immunocompetent children; however, no prevention studies have been performed in HSCT recipients. A study of palivizumab for treatment of RSV infection showed no significant toxicity.<sup>31</sup> Some centers use palivizumab for prophylaxis in pediatric (age < 2 years) HSCT recipients and candidates throughout the respiratory virus season. Whether rhinovirus is a significant pathogen in HSCT recipients remains controversial.<sup>32,33</sup>

## IV. PREVENTION OF FUNGAL INFECTION IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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A primary goal in the practice of transplant medicine is the prevention of infection. This is particularly true when

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one considers fungal infections in HSCT recipients. Fungal infection in this patient population is difficult to diagnose and treat, and, not surprisingly, is associated with a prohibitively high mortality. Factors contributing to this mortality include the following:<sup>1</sup>

1. Diagnosis is difficult, as conventional microbiologic approaches are both insensitive and often nonspecific. Invasive sampling of tissues is often necessary for diagnosis, or, alternatively, an empiric therapeutic approach is employed.
2. Because of the impaired inflammatory response present during the neutropenic phase preengraftment and during the treatment of GVHD postengraftment, clinical signs and symptoms of invasive fungal infection can be greatly blunted until disease is relatively far advanced. As a result, the microbial burden is usually far greater at the time of diagnosis than in nonimmunocompromised patients, a potentially important prognostic factor in determining the outcome of therapy.
3. Outcome is directly related to how early the therapy is instituted, with the previously listed two factors making early diagnosis difficult.
4. Currently licensed antifungal therapies are not ideal, having limited spectra of activity (e.g., fluconazole), a propensity for selecting resistance (e.g., flucytosine), or a particular ability to induce systemic (e.g., infusion toxicity resulting in a cytokine release syndrome with amphotericin) or organ toxicity (e.g., renal toxicity from amphotericin and hepatic toxicity from certain azoles).
5. The treatment of invasive fungal infection needs to be more prolonged than that needed in the management of invasive bacterial infection.

Fungal infections of major concern can be divided into three general categories: invasive infection due to *Candida* and *Aspergillus* species, which account for > 90% of the fungal infections occurring in this patient population; infection due to the geographically restricted systemic mycoses (e.g., *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*); and invasive infection due to the so-called “newly emerging fungi” (e.g., *Fusarium*, *Paecilomyces*, the zygomycetes, and such dematiaceous fungi as *Scedosporium*, *Scopulariopsis*, and *Dactylaria*).<sup>2-9</sup>

### **Risk Factors in the Pathogenesis of Fungal Infection in the HSCT Patient**

The occurrence of invasive fungal infection in the HSCT patient is largely determined by the interaction of three factors: the presence of technical/anatomic abnormalities that compromise or attenuate the functioning of the primary mucocutaneous barrier to infection; excessive

environmental exposures to potential fungal pathogens; and the net state of immunosuppression. The major technical/anatomic abnormalities that occur in the HSCT patient are those that arise from the placement of a central venous catheter for blood sampling and fluid administration and post-chemotherapy mucositis—both of which providing a portal of entry for *Candida* isolates. In addition, serious injury to the skin (e.g., water immersion injury, dermal or subcutaneous injury due to extravasation of noxious chemicals into soft tissues because of malfunction of vascular access devices) will commonly become secondarily infected by *Candida*, *Aspergillus*, and even zygomycetes species. Invasion of the skin and blood vessels can then occur, followed by secondary dissemination from the cutaneous portal of entry. The creation of devitalized tissue, the occurrence of undrained fluid collections, and the development of significant tissue injury (especially of the lungs) increases the risk of secondary fungal invasion.<sup>1,10</sup>

In the hospital setting, two epidemiologic patterns of exposure are observed: domiciliary and nondomiciliary. The term domiciliary refers to exposures occurring where the patient resides in the hospital. There is often clustering of cases in time and space. Although such exposures are usually due to a contaminated air supply, with molds such as *Aspergillus* being the major concern, person-to-person spread (usually on the hands of medical personnel) of *Candida* species, often azole resistant strains, can also occur.<sup>11</sup> Nondomiciliary exposures can occur anywhere within the hospital as the patient travels for an essential procedure (the operating room, the radiology or endoscopy suite, or the halls of the hospital where construction is taking place). Nondomiciliary exposures are probably more common than domiciliary, but are often more difficult to define because of the lack of clustering of cases. Indeed, the leading clue to the presence of such an environmental problem is the occurrence of a case of invasive fungal infection at a point in time when the net state of immunosuppression should not be great enough for such an infection to occur without a particularly intense exposure.<sup>1,4,10,12</sup>

Particularly notable contributors to the net state of immunosuppression for the HSCT recipient include neutropenia, GVHD and its treatment, and immunomodulating viral infection. In addition, such metabolic factors as protein-calorie malnutrition, uremia, and, perhaps, hyperglycemia contribute to the net state of immunosuppression. The patient receiving an allograft is far more immunosuppressed than the autologous HSCT recipient since the duration of neutropenia is greater and GVHD has a sustained effect in the allogeneic recipient. Reflecting this difference, the incidence of invasive fungal infection is far higher among the allogeneic population.

Not unexpectedly, preventative strategies that are shown to be effective in the allogeneic HSCT recipient can be assumed to be effective in the autologous recipient; unfortunately, the converse is not necessarily true.<sup>1</sup>

### **Prevention of Fungal Infection in the HSCT Recipient**

As delineated in two recent publications,<sup>13,14</sup> there is a dearth of well designed, randomized, concurrently controlled clinical trials, not because of a lack of will on the part of investigators, but rather because of the inherent challenges in approaching fungal infection in this patient population: confounding factors (e.g., duration of neutropenia and other markers of the severity of the underlying disease) can obscure the efficacy of one or another antifungal regimen. In addition, the underlying disease for which the HSCT has been performed can be the cause of mortality, rather than failure of the antifungal program (other endpoints such as fever can also be problematic). The diagnosis of invasive fungal infection remains a problematic endpoint as well. Thus, the evidence relies less on randomized clinical trials and more on comparative studies that employ historical controls and careful clinical observation. Studies carried out by Benson<sup>15</sup> and Sacks<sup>16</sup> and their colleagues are reassuring in demonstrating that in other therapeutic areas, studies that employed historical controls yielded comparable results to those obtained in concurrently controlled clinical trials in at least 75% of instances.

### **Prevention of Exposure to Potentially Invasive Fungal Species**

Aerosols containing excessive numbers of the geographically restricted systemic mycoses, as well as such molds as *Aspergillus* species, constitute a significant risk. It is generally recommended that HSCT recipients be educated to avoid circumstances in which aerosols of fungal spores might be encountered (BIII): areas of high dust exposure, urban renewal and other construction projects, chicken coops, bat caves, avocational (e.g., gardening) and vocational activities that require digging up soil, marijuana smoking, and the preparation and handling of foods that contain molds (e.g., blue cheese). Similarly, HSCT recipients should avoid exposures to naturopathic medicines, which can be contaminated with molds (CIII).<sup>11,17-21</sup>

Although invasive candidal infection in the HSCT patient is almost always of endogenous origin, the endogenous candidal flora is modified within the hospital. A particular issue is the person-to-person transfer of *Candida* species (which are frequently azole-resistant) from the hands of medical personnel. Appropriate hand-washing procedures by medical is strongly recommended to prevent the introduction of more difficult to treat *Cand*

*ida* species into the “endogenous” flora (AIII).<sup>1,11,22</sup>

Of even greater importance are exposures to air contaminated with fungal spores, which result in invasive infection with such molds as *Aspergillus* species and such newly emerging species as *Fusarium* and the Mucorales. The portals of entry of these infections are the lungs and nasal sinuses. Special effort is required to protect HSCT recipients from contact with air containing excessive fungal spore counts (BII).<sup>1,11,17,18</sup>

1. High efficiency (> 90%) particulate air (HEPA) filtration in patient rooms.
2. Controlled air pressures, such that the air pressure in patients' rooms, are positive in relation to the corridor, and that air flows from the rooms into the corridors.
3. Correctly sealed rooms, including correctly sealed windows and electrical outlets.
4. High rates of room air exchange (i.e., > 12 air changes/hour).
5. The construction of effective barriers between patient care and renovation or construction areas (e.g., sealed plastic) that prevent dust from entering patient care areas and that are impermeable to *Aspergillus* species.
6. Careful attention to travel routes within the hospital to avoid areas of renovation and construction. Ideally, patients leaving their rooms should be wearing highly effective masks as a further barrier to the inhalation of fungal spores.

Although HEPA filters and air pressure systems are essential and effective cleaning procedures to minimize fungal spores are important, routine surveillance cultures of the air or of the patient are not recommended (DIII).<sup>11</sup>

### **Minimization of Deficits in Host Defenses Against Invasive Fungal Infection**

The first principle of practice is the eradication of all treatable infection prior to transplant. In patients with hematologic malignancies, it is not uncommon that previous attempts to induce remission with cytotoxic chemotherapy were complicated by invasive fungal infections due to *Candida* species or molds, especially *Aspergillus*. Such patients are still candidates for HSCT provided certain requirements are fulfilled (BIII): the patient has had a complete response clinically, microbiologically, and radiologically to effective antifungal chemotherapy; the patient can be continued on such therapy at least until engraftment occurs post-HSCT; and any residual anatomic abnormality (e.g., an infarcted area of lung due to invasive *Aspergillus* infection) or devitalized tissue has been considered for surgical resection (CIII).<sup>1,11,23-25</sup>



The first host defense deficit usually encountered by HSCT recipients is neutropenia secondary to the preparative regimen. Growth factors (e.g., GM-CSF and G-CSF) reduce the duration of neutropenia, although there is currently no evidence that this shortened effect has translated into a lower incidence of invasive fungal infection. Therefore, these agents cannot be recommended for the routine prevention of invasive fungal infection (DIII).<sup>1,11,26</sup>

CMV infection is an important cause of morbidity and mortality with both direct and indirect effects. The direct infectious disease effects of CMV in this population include life-threatening pneumonia and a systemic multisystem disease. CMV infection also contributes to the net state of immunosuppression, with an increased susceptibility to both yeast and mold infection being noted during active CMV disease. Accordingly, control of CMV replication is recommended, not only for its direct benefits but also to decrease the incidence of invasive fungal infection (BIII).<sup>1,4,11</sup>

Effective control of GVHD can reduce occurrence of invasive fungal infection.<sup>1,4,11,27</sup> A major lesson from the solid organ transplant experience is the need for so-called steroid sparing therapy; that is, the use of additional drugs such as cyclosporine +/- mycophenolate permit a decrease in prednisone dose and lower the risk of opportunistic infection, including that caused by fungi.<sup>10</sup> In addition, the correction of metabolic abnormalities such as protein-calorie malnutrition, uremia, and hyperglycemia should decrease the net state of immunosuppression and the subsequent risk of invasive fungal disease.<sup>10</sup>

### Antifungal Therapy in the Prevention of Invasive Fungal Infection

There are three different modes in which antifungal drugs can be administered to prevent invasive fungal infection: a **prophylactic** mode, an **empiric** mode, and a **pre-emptive** mode.<sup>28</sup> In HSCT recipients the administration of topical (non-absorbable) antifungal agents (e.g., clotrimazole, nystatin, amphotericin B) orally or to the skin can be shown to decrease the colonizing fungal burden, particularly with yeasts, when applied to specific skin sites or the gastrointestinal tract. In addition, mucosal manifestations of superficial yeast infection (e.g., oral thrush, pharyngeal, and esophageal candidiasis) are probably decreased by topical therapy (CIII). However, such topical therapy does not reduce the incidence of either invasive candidiasis or invasive mold infection in HSCT patients and cannot be recommended for these purposes (DII).<sup>1,11</sup>

### Prophylaxis of Invasive Yeast Infection in HSCT Recipients

The efficacy of oral fluconazole, a well absorbed triazole antifungal agent with particular efficacy against *C. albicans* and *C. tropicalis*, appears to be dose dependent. At a dose of 100-200 mg/day orally, fluconazole has variable effects in the prevention of invasive candidal infection. Indeed, this regimen has been associated with the emergence of infection due to such invasive species of *Candida* as *C. krusei* and *C. glabrata*, which are fluconazole resistant. Therefore, this regimen is not recommended for the prevention of invasive yeast infection (nor, since molds are universally resistant to fluconazole, for invasive mold infection) in HSCT recipients (DII). In contrast, at a dose of 400 mg/day there are convincing data that fluconazole administered orally or intravenously, beginning at the time of HSCT and continuing until at least the time of engraftment, provides clinically important protection against invasive yeast infection (AII). When breakthrough candidal infection does occur despite such a regimen, it should be assumed that the isolate is fluconazole resistant. The increasing incidence of *C. krusei*, *C. glabrata*, and other non-*albicans* strains is in large part related to the widespread use of fluconazole prophylaxis. Overall, however, the incidence of invasive candidiasis appears to be significantly decreased by fluconazole prophylaxis (at a dose of 400 mg/day) in allogeneic HSCT recipients.<sup>1,11,29,30</sup>

In general, the risk of invasive yeast infection in recipients of autologous HSCT is low enough not to require fluconazole prophylaxis (DIII). However, certain autograft patients are at higher risk and do merit prophylaxis employed for allogeneic recipients (BIII): autologous patients with underlying hematologic malignancies who will have prolonged neutropenia and mucosal damage from intense conditioning regimens; and those who have been receiving fludarabine or 2-CDA before the transplant.<sup>11</sup>

### Antifungal Prophylaxis of Invasive Mold Infection

No regimen has been shown to be clearly effective in the prevention of invasive mold infection, whether the species of mold be *Aspergillus* or one of the newly emerging molds such as *Fusarium*; hence, the importance of the previously described environmental protection strategies. Regimens studied thus far include moderate dose (0.5 mg/kg/day) amphotericin B, low dose amphotericin B (0.1-0.25 mg/kg/day), intranasal amphotericin B spray, lipid formulations of amphotericin B, aerosolized amphotericin B, and itraconazole. Similarly, there is no convincing evidence that these strategies prevent the newly emerging molds (DIII).<sup>1,11</sup>

As mentioned above, increasing success is being

achieved in patients with previous invasive *Aspergillus* infection, which has been brought under control with an amphotericin preparation. HSCT, both allogeneic and autologous, has been successfully carried out in these individuals under the cover of antifungal prophylaxis, usually with an amphotericin preparation.<sup>1,11,23-25</sup>

### Antifungal Prophylaxis of the Geographically Restricted Systemic Mycoses

Although case reports or small series of HSCT patients infected with one of the endemic mycoses (particularly coccidioidomycosis and histoplasmosis) have been reported, this has not been a significant clinical problem. Indeed, prophylactic antifungal therapy against the endemic mycoses is not recommended (DIII).<sup>7-9,11</sup>

### Empiric Therapy of Fungal Infection

The importance of neutropenia, particularly profound (absolute neutrophil count < 100/mm<sup>3</sup>) and prolonged (> 7 days) in the pathogenesis of invasive fungal infection has long been recognized. Because of the previously discussed difficulty in establishing the diagnosis of invasive fungal infection and the need for early initiation of therapy, empiric therapy of the febrile, neutropenic HSCT has become the standard of care. Such empiric therapy is defined as the initiation of systemic antifungal therapy to neutropenic patients who remain febrile after four days of empiric broad spectrum antibacterial therapy, and whose clinical and laboratory evaluation (including multiple blood cultures) remain negative. Amphotericin B was established over the past two decades as the therapy of choice for this purpose, with a significantly lower incidence of invasive fungal infection observed among patients receiving amphotericin B.<sup>31-35</sup> More recently, liposomal amphotericin B has been shown to have equal efficacy to conventional amphotericin B, with significantly less infusion related toxicity (fever and chills) and dose related nephrotoxicity, but with significantly greater cost (BI).<sup>36,37</sup> Perhaps of greatest interest is the report of a multicenter, randomized trial in which standard liposomal amphotericin therapy at a dose of 3 mg/kg/day was compared to voriconazole at a dose of 3 mg/kg twice daily intravenously (or 200 mg orally) following two loading doses of 6 mg/kg 12 hours apart in a standard febrile neutropenia protocol. Voriconazole, a new broad-spectrum triazole agent available in oral and intravenous formulations, was equal or superior (fewer breakthrough cases of invasive fungal infection) to liposomal amphotericin. The major side effect from the voriconazole was transient visual disturbances, whereas febrile reactions and nephrotoxicity were significantly more common among the recipients of liposomal amphotericin.<sup>38</sup> Thus, empiric therapy of the febrile, neutropenic HSCT patient has been accepted

as standard care. Amphotericin B, liposomal amphotericin B, and voriconazole have comparable efficacy. However, voriconazole appears to have less toxicity and the added convenience of an oral formulation.

### Preemptive Therapy of Fungal Infection

Preemptive therapy is defined as the administration of an antimicrobial regimen to a patient population felt to be at high risk of life threatening infection before the onset of clinically recognizable disease.<sup>28</sup> In the case of invasive fungal infection in the HSCT patient, three opportunities for preemptive therapy have been defined:

1. Colonization of the respiratory tract with *Aspergillus* species as demonstrated by positive cultures of respiratory secretions (sputum or bronchoalveolar lavage specimen) carries a > 50% risk of subsequent or concurrent invasive disease and is an indication for the initiation of preemptive therapy to eradicate such colonization.<sup>1,4</sup> In contrast, colonization with *Candida* species does not correlate with the risk of invasive disease and is not an indication for antifungal therapy. There are currently two problems with this approach: the absence of such early colonization in a significant percentage of patients with invasive pulmonary aspergillosis and the lack of clear-cut information as to which is the best regimen for accomplishing preemptive therapy—amphotericin B, liposomal amphotericin, or voriconazole. Itraconazole appears to be less desirable for this task given less reliable pharmacokinetics and penetration into respiratory secretions.<sup>39</sup>
2. Protocol high resolution computerized tomographic scans of the lungs at regular intervals in HSCT patients during periods of high risk for invasive aspergillosis can result in earlier diagnosis of disease, and the opportunity for preemptive therapy. A particular morphology of the lung lesion, the so-called “halo sign,” is particularly suggestive of invasive aspergillosis (although *Aspergillus* infection is the most common cause of a halo sign, such other opportunistic infections as nocardiosis, mucormycosis, and others can also cause a halo sign). Antifungal therapy with an amphotericin preparation or one of the newer drugs (see below) is indicated in this circumstance.<sup>1,40</sup>
3. Detection of fungal antigens (e.g., *Aspergillus* galactomannan) or fungal metabolites (e.g., arabinitol) could give early evidence of invasive infection at a time when therapy would be most effective. Of particular interest are PCR based assays that will detect both yeast and mold infection. Linkage of such results to optimized antifungal strategies appears to be the wave of the future once these assays achieve adequate sensitivity and specificity.<sup>1,41-44</sup>

**Table 8. Summary of major recommendations for prevention of invasive fungal infection.**

Type of Prevention	Rating
Handwashing is recommended to prevent spread of exogenous <i>Candida</i> species	AIII
Fungal surveillance cultures are not indicated in asymptomatic patients	DII
Topical antifungal agents are not recommended for prevention of invasive candidiasis or invasive mold infection	DII
Fluconazole (400 mg/day) is recommended to prevent invasive yeast	AII
Patients are to avoid hospital construction or renovation areas	AIII

### New Antifungal Drugs in the Prevention of Invasive Fungal Infection

The licensure of the lipid associated amphotericin preparations has provided drugs with efficacy comparable to conventional amphotericin, but with considerably less toxicity, although cost issues remain of concern.<sup>1,11</sup> Also of great interest are two drugs that are in the late stages of clinical development. One of these, caspofungin acetate, the first of the echinocandins to be released for human use, has been approved for the salvage therapy of invasive aspergillosis. However, the preclinical data demonstrating broad-spectrum activity against yeasts and molds, and its potential utility in combination with other antifungal agents, suggest further benefits of this new agent.<sup>45,46</sup> Particularly appealing is its side effect profile, both in terms of infusion related and organ specific toxicity. A potential disadvantage is its availability only in a parenteral formulation.<sup>47</sup>

Voriconazole, a triazole with fungicidal activity against *Aspergillus* species and potent fungistatic activity against a wide variety of yeasts and molds, including several of the newly emerging fungi resistant to presently available agents, appears especially well suited to the management and prevention of fungal infection in the HSCT patient.<sup>46,48,49</sup> Particularly noteworthy is a large randomized study of invasive aspergillosis in immunocompromised patients, a large percentage of whom were HSCT recipients. In this study, voriconazole was significantly more efficacious than amphotericin, with significantly less toxicity.<sup>50</sup> **Table 8** provides a summary of major recommendations for prevention of fungal infection after hematopoietic cell transplantation.

### Summary and Conclusions

The prevention of invasive fungal infection in the HSCT recipient remains an important goal of transplant medicine. Accomplishing this task has been made difficult by the lack of sensitivity of diagnostic techniques and the lack of an ideal antifungal agent. Three different strategies have emerged to accomplish the task of antifungal prevention: prophylactic, empiric, and preemptive. Prophylactic fluconazole at a dose of 400 mg/day has been shown to decrease both the rate of invasive yeast infection and mortality. Thus far, no prophylactic strategy has

been shown to decrease the incidence of invasive mold infection, and the emphasis is on environmental protection. Empiric therapy in the febrile neutropenic patient has been established as a standard of care, with amphotericin B, lipid associated amphotericin, and voriconazole appearing to offer comparable efficacy. Preemptive therapy based on microbiologic markers, particularly non-culture based microbiologic assays, appears to be an approach for the future.

### V. PREVENTION OF BACTERIAL AND PROTOZOAL INFECTIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

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#### Bacterial Infections

Bacterial infections may complicate HSCT at any time but pose a particular risk during the neutropenia produced by cytoreduction. The main sources of infection include central venous catheters, mouth flora, and gut flora via bacterial translocation. As with all patient care, attention to proper handwashing is strongly recommended to minimize risk of a bacterial infection (AIII) (**Table 9**).<sup>1</sup>

In general, many decisions regarding use of prophylactic agents for bacterial infections must weigh the potential immediate benefit (prevention of infection) against the longer-term consequence (development of antibiotic resistance). Because of the potential severity of antibiotic-resistant infections, particularly among HSCT recipients, every effort should be made to use preventative antibacterials with restraint. The widespread development of VRE in most US hospitals is a recent reminder of how devastating drug-resistant bacteria may be.

#### Neutropenia

The neutropenia from cytoreduction results in risk for predictable organisms from bowel and mouth flora. Gut

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**Table 9. Summary of major recommendations for prevention of bacterial infections.**

Organism	Intervention	Strength of Recommendation	Comment
All bacteria	Handwashing	A III	Single most important intervention
Encapsulated	IVIg	D II	Unless profoundly hypogammaglobulinemic
<i>H. influenzae</i>	Vaccinate contacts	A II	
	Vaccinate HSCT recipient at 12, 14, 24 months	B II	
<i>S. viridans</i>	See dentist prior to HSCT	A III	Resolve dental problems before HSCT

Abbreviations: IVIG, intravenous immunoglobulin; HSCT, hematopoietic stem cell transplant

flora decontamination is not recommended (DIII) prior to HSCT given the lack of clear efficacy and its potential for fostering development of resistant organisms.<sup>2-5</sup> Because of limited data, no recommendation can be made regarding routine use of antibiotics for bacterial prophylaxis in afebrile and asymptomatic neutropenic patients. In particular, vancomycin should not be used in this setting (DIII), since overuse of this drug may encourage development of VRE.<sup>6</sup> Routine use of growth factors may shorten neutropenia but does not appear to change the rate of serious bacterial infection and so is not recommended to prevent bacterial infections.<sup>7</sup>

#### Central venous catheters

Guidelines for care of central venous catheters recently have been promulgated to reduce infectious and other complications.<sup>8,9</sup> Handwashing is recommended prior to changing dressings or manipulation at the site. Use of silver or antibiotic-impregnated catheters may result in lower rates of infection although no studies have been performed on indwelling or implantable devices in HSCT.<sup>8,9</sup> Similarly, chlorhexidine-impregnated gauze dressings may reduce infection rates, although no studies of this approach have been completed in HSCT.<sup>9</sup> Antibiotic ointments at the exit site are not recommended.<sup>8</sup> Catheters should be removed as soon as is practical; for patients with transfusion requirements, however, the central venous catheter may be required for months.

#### Chronic graft-versus-host disease

Patients with chronic GVHD are at risk for invasive infection from encapsulated organisms, particularly *S. pneumoniae*, although infection with *Haemophilus influenzae* and *Neisseria meningitidis* may also occur. Appropriate prophylactic antibiotics directed at these pathogens should be selected based on local resistance patterns. These should be used until resolution of chronic GVHD. Intravenous immunoglobulin (IVIg) is not recommended (DII), unless the patient is among the 20-25% of HSCT recipients with unrelated marrow grafts who experience severe hypogammaglobulinemia in the first 100 days post-HSCT (CIII).<sup>10,11</sup>

### Specific organisms

#### *Streptococcus pneumoniae*

*S. pneumoniae* infection is a particular risk for HSCT recipients with chronic GVHD or those with profound hypogammaglobulinemia.<sup>12,13</sup> Three distinct strategies can help prevent invasive *S. pneumoniae* infection in specific groups:

1. In patients with chronic GVHD, antibiotic prophylaxis is recommended for as long as GVHD therapy is administered (BIII).<sup>12,13</sup> Penicillin is the drug of choice in communities where *S. pneumoniae* remains likely to be penicillin-susceptible.<sup>13</sup> Trimethoprim-sulfamethoxazole, if given daily for pneumocystis prophylaxis, is adequate to prevent *S. pneumoniae* as well. However, no data were found to support its use for preventing *S. pneumoniae* disease.
2. Vaccination with the currently available 23-valent vaccine may be of benefit to any HSCT patient and should be administered 12 and 24 months post transplant (BIII).<sup>14</sup> The role of the new conjugate 7-valent vaccine has not been determined for HSCT recipients.
3. Among those profound hypogammaglobulinemia, use of IVIG may be effective (CIII).<sup>10,11</sup>

#### *Streptococcus viridans*

Mucositis may facilitate translocation of *S. viridans* from the mouth into the blood. A full dental evaluation should therefore be conducted for all patients prior to initiating HSCT conditioning (AIII).

Routine use of prophylaxis directed at *S. viridans* is not recommended (DIII) as such a strategy has not been shown to be effective and may promote the emergence of antibiotic-resistant organisms. At certain institutions, frequent cases of overwhelming shock due to *S. viridans* have been described.<sup>15</sup> In such a circumstance, prophylaxis might be considered (CIII). Selection of the best agent for prophylaxis should be made based on the hospital antibiotic susceptibility profile.

### *Haemophilus influenzae*

Pediatric household contacts of HSCT recipients should be current with *H. influenzae* type B (Hib) vaccine (AII). Exposure to infected household contacts and persons in the house who themselves had been exposed to an active case of invasive *H. influenzae* should be minimized.

Hib conjugate vaccine should be administered to all HSCT recipients at 12, 14, and 24 months post-HSCT (BII) because HSCT recipients have low levels of *H. influenzae* capsular antibody post-transplant.<sup>16</sup> This approach is particularly important among persons with chronic GVHD, whose risk for invasive *H. influenzae* is increased.

### Protozoal Infections

#### *Pneumocystis carinii pneumonia (PCP)*

The potential risk of nosocomial PCP remains controversial. Although some hospitals place patients with proven PCP into contact precaution isolation, the value of this strategy has not been established. When possible, HSCT recipients should avoid contact with persons with PCP (CIII).

Prophylaxis against PCP should be given to all allogeneic recipients from the time of engraftment until 6 months after HSCT (AII) (**Table 10**). Prophylaxis should be extended for those with chronic GVHD or those receiving immunosuppressive therapy for other indications until resolution of the underlying problem (BII).<sup>17,18</sup> In some centers, prophylaxis is given for 1-2 weeks prior to transplant. However, because no studies have been performed on this approach, no recommendations can be made.

Trimethoprim-sulfamethoxazole is the preferred prophylactic agent (AII). For those unable to receive trimethoprim-sulfamethoxazole, alternative agents include dapson 100 mg daily;<sup>19</sup> atovaquone 1500 mg daily,<sup>20</sup> or aerosol pentamidine<sup>21</sup> (BIII). Although these second-line agents have not been formally compared, daily dapson appears the preferred agent. Dapson given three times weekly should not be used.<sup>22</sup> Leucovorin (folinic acid) is often administered with trimethoprim-sulfamethoxazole but no studies support the use of this costly medication.<sup>23</sup>

PCP among autologous transplant recipients is rare but does occur.<sup>17</sup> Patients for whom prophylaxis might

be considered are those who have received fludarabine or 2-CDA, those with underlying lymphoma or leukemia, or those receiving intense conditioning regimens or graft manipulation (BIII). No recommendation can be given for other patients. In determining the best approach for a given transplant center, the risk of an adverse event related to trimethoprim-sulfamethoxazole, such as fever and rash or myelosuppression, should be weighed against the potential benefit of preventing this rare but sometimes fatal pneumonia.

#### *Toxoplasma gondii*

All HSCT recipients should be advised regarding the risk of acquiring toxoplasmosis via ingestion of undercooked meat or through exposure to cat feces (BIII).

Toxoplasmosis is a substantial risk (8.5% incidence) for T-cell depleted graft recipients if the host is seropositive for *T. gondii* pre-transplant.<sup>24</sup> Importantly, however, cases of toxoplasmosis post-HSCT have been reported when both host and donor are seronegative for *T. gondii*, reflecting the limited sensitivity of the serologic test.<sup>24</sup> Disseminated toxoplasmosis does occur, although less commonly, in other transplant setting.<sup>25</sup>

Prophylaxis might be considered for those with a history of invasive toxoplasmosis, particularly chorioretinitis, and for *T. gondii* seropositive patients with acute GVHD, but data demonstrating efficacy are limited (CIII). Trimethoprim-sulfamethoxazole is recommended for prophylaxis (BII). For those in whom trimethoprim-sulfamethoxazole cannot be given, clindamycin-pyrimethamine or pyrimethamine/sulfadoxine (Fansidar)<sup>26</sup> should be effective (CIII). Duration of prophylaxis should parallel that of PCP prophylaxis (CIII). Secondary prophylaxis should be given for the duration of immunosuppression (BIII).

Autologous transplant recipients do not have discernible risk and should not receive prophylaxis (DIII) nor should they be screened for serologic evidence of previous infection (DIII).

#### *Strongyloides stercoralis*

HSCT recipients should avoid situations, such as exposure to potentially infected soil that might result in acquisition of *S. stercoralis* (AIII).

**Table 10. Summary of major recommendations for prevention of protozoal infections.**

Organism	Intervention	Strength of Recommendation	Comment
<i>P. carinii</i>	Prophylaxis from engraftment to 6m	All	Trimethoprim-sulfa is drug of choice
	Longer course if graft-versus-host disease or receiving immunosuppressives	BII	For duration of immune suppression
<i>S. stercoralis</i>	Take careful history	AIII	Focus on residence in endemic areas

A thorough travel and residence history should be obtained for all HSCT candidates (BIII).<sup>27</sup> Areas with risk for *S. stercoralis* include the Southeastern US, the tropics, the sub-tropics, and Europe. Any potential HSCT recipient with unexplained peripheral eosinophilia or those with travel or residence to endemic areas should be screened by serologic test for asymptomatic *S. stercoralis* (BIII). If the serologic screen is unavailable, examination of three stool specimens can be performed, although this approach is less sensitive (BIII).

Patients with a positive serology, unexplained eosinophilia despite a negative serology, or a compelling history, should receive prophylaxis. Ivermectin is the preferred drug; if it is unavailable, thiabendazole may be given (BIII). No recommendation can be made for secondary prophylaxis. All infected patients should have  $\geq 3$  negative stools after completion of treatment, prior to beginning HSCT (AIII).

#### *Trypanosoma cruzii*

*T. cruzii*, which causes Chagas' disease, can be transmitted by blood transfusion and possibly via HSCT. It may also be transmitted congenitally. Because the infection is difficult to treat, potential donors should be screened for IgG against *T. cruzii* if they were born in, received a blood transfusion in, or ever lived for  $\geq 6$  months in Chagas' disease endemic areas, such as parts of Mexico, Central and South America (BIII).<sup>28,29</sup> Persons with active diseases should not serve as donors (DIII).

### VI. VACCINE-PREVENTABLE INFECTIONS: GUIDELINES FOR ACTIVE AND PASSIVE IMMUNIZATIONS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION

Keith M. Sullivan, MD\*

For the vast majority of individuals, immunizations are safe, effective and inexpensive means to prevent infectious disease.<sup>1-3</sup> While it is difficult to overestimate the benefit of vaccines on world health, misconceptions and missed opportunities may abrogate this protective advantage.<sup>4-6</sup> This appears especially true among individuals undergoing myeloablative HSCT, where care by multiple providers, faulty assumptions regarding immunocompetence or persistence of protective immunity and lack of immunization schedules contribute to underutilization or variability in best practices.<sup>7-9</sup>

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### Immunization of the Immunocompromised Host

Myeloablative conditioning before HSCT impairs immune function, fosters opportunistic infection and dampens immunogenic responsiveness to vaccination.<sup>10,11</sup> With passage of time, most patients recover adequate immune function, although the tempo of recovery can be delayed by older age, T-cell depletion, GVHD, anti-thymocyte globulin or other immunosuppressive agents.<sup>12-15</sup> Persisting immunodeficiency contributes to serious late infections, especially with encapsulated organisms.<sup>16-18</sup> Since vaccine efficacy is lessened during the immunocompromised period but the tempo of immune recovery varies widely, it is understandable that standardized data on antibody response to vaccination following HSCT are limited. Moreover, since the number of HSCT patients enrolled in controlled vaccination trials has been small, published efficacy measuring the frequency of late infections has been scanty. Thus, guidelines of level II and III recommendations are based on either surrogate markers of protective antibody titers or clinical experience extrapolated from other patient groups.<sup>10,11,19</sup>

Antibody titers persisting from childhood immunizations decrease after HSCT to barely protective or unprotective levels. This decline has been shown in allogeneic and autologous recipients of blood and marrow grafts.<sup>20-24</sup> In general, HSCT recipients respond better to vaccinations if several are given at and after 1 year posttransplant.<sup>22,25-28</sup> Unfortunately, responses are poorer for unconjugated pneumococcal polysaccharide vaccine (PPV) and unconjugated *Haemophilus influenzae* type b (Hib) vaccine.<sup>25,26,29,30</sup> Booster immunizations result in anamnestic antibody responses, but this benefit may be lost in those with chronic GVHD.<sup>12,25,28</sup>

### Active Immunization for HSCT Recipients

As shown in **Table 11**, guidelines are provided for allogeneic and autologous recipients given myeloablative conditioning.<sup>31</sup>

*Diphtheria, tetanus and pertussis.* Vaccinations at 12, 14 and 24 months posttransplant are recommended for diphtheria and tetanus toxoid (BII) and pertussis in children < age 7 years (BIII).<sup>23,25,27,28</sup> Patients should be reimmunized for tetanus-diphtheria toxoids every 10 years.<sup>19</sup>

*Haemophilus influenzae type b.* Hib conjugate vaccine is given three times beginning one year after HSCT (BII).<sup>25,26,28</sup> This is recommended for patients of any age.<sup>19</sup>

*Hepatitis B.* Immunization with the recombinant vaccine is recommended for those who are otherwise susceptible: children < age 18 or adults with risk factors for hepatitis B (BIII).<sup>32,33</sup> Persons who fail to exhibit a response should receive a second 3-dose series.

*Pneumococcal.* The 23-valent PPV had been rec-

**Table 11. Major recommendations for vaccinations for hematopoietic stem cell transplant (HSCT) recipients, including both allogeneic and autologous recipients.**

For these guidelines, HSCT recipients are presumed immunocompetent at ≈ 24 months after HSCT if they are not on immunosuppressive therapy and do not have graft-versus-host-disease (GVHD).

Vaccine or toxoid	Time after HSCT			Rating
	12 months	14 months	24 months	
Inactivated vaccine or toxoid				
Diphtheria, tetanus, pertussis Children aged < 7 years	Diphtheria toxoid-tetanus Toxoid-pertussis vaccine (DTP) or diphtheria toxoid-tetanus toxoid (DT)	DTP	DTP or DT	BIII
Children aged ≥ 7 years	Tetanus-diphtheria toxoid (Td)	Td	Td	BII
<i>Haemophilus influenzae</i> type b (Hib) conjugate	Hib conjugate	Hib conjugate	Hib conjugate	BII
Hepatitis (HepB)	HepB	HepB	HepB	BIII
23-valent pneumococcal polysaccharide (PPV23)	PPV23	—	PPV23	BIII
Influenza	Lifelong, seasonal administration, beginning before HSCT and resuming at ≥ 6 months after HSCT			BII
Inactivated Polio (IPV)	IPV	IPV	IPV	BII
Life-attenuated vaccine				
Measles-mumps-rubella (MMR)	—	—	MMR	BIII
Varicella vaccine	Contraindicated for HSCT recipients			EIII
Rotavirus vaccine	Not recommended for any person in the United States			EII

ommended at 12 and 24 months after HSCT along with chemoprophylaxis in individuals with chronic GVHD (BIII).<sup>34</sup> Recently, a 7-valent conjugate vaccine has been licensed. No data are currently available in HSCT recipients, but one strategy could be to give one or more doses of the 7-valent conjugate vaccine with subsequent broader coverage with the 23-valent product.<sup>24</sup>

**Influenza.** Beginning before HSCT and resuming > 6 months after transplant, individuals should receive life-long seasonal immunization (BII).<sup>2,19,35</sup> Children < age 9 receiving vaccine for the first time require two doses. Those < 12 years old should receive only split-virus vaccines.<sup>1</sup> For optimal protection, immunization and chemoprophylaxis can be combined.

**Polio.** Inactivated polio vaccine is recommended following allo and auto transplant (BII).<sup>21,36</sup> More information is needed regarding optimal schedules of vaccination.

**Measles, mumps, rubella.** MMR is a live-attenuated viral product and is indicated only in immunocompetent recipients at least 24 months posttransplant who are not receiving immunosuppressive drugs and are free of GVHD (BIII).<sup>11,19,20,37</sup> No data are available for use before 24 months posttransplant.

**Varicella.** Insufficient data are available to recommend this vaccine (EIII).<sup>24</sup>

**Others.** Vaccinations for HSCT patients travelling to endemic areas are either contraindicated (live-attenuated vaccines) or not rated due to limited experience.<sup>31</sup>

### Active Immunization for Family Members and Healthcare Workers

As shown in **Table 12**, a number of recommendations apply to close contacts of the patient in order to prevent spread of infectious disease.<sup>31</sup> The published evidence supporting these recommendations is provided by the Centers for Disease Control and Prevention.<sup>3</sup>

### Passive Immunization for HSCT Recipients

**Table 13** presents major recommendations for passive immunization with immunoglobulin.<sup>31</sup> As shown elsewhere in this chapter, CMV immunoglobulin is not indicated (DI) but VZIG is recommended (AII).<sup>38</sup> Intramuscular immunoglobulin may be of benefit for those who travel to areas endemic for hepatitis A or were exposed to measles but not vaccinated after HSCT (BIII).<sup>39,40</sup> Intravenous immunoglobulin can be administered to patients with persisting hypogammaglobulinemia (Ig < 400 mg/dl) and recurrent bacterial infection (CIII).<sup>41-45</sup>

### Future Directions

Because most studies are not randomized and enroll relatively few patients, future recommendations will evolve based on more robust data on antibody titers and infection rates. Due to the small number of patients transplanted at each center, multi-center trials with detailed tracking of late infections are clearly needed. Studies are also required to clarify the optimal schedule of immunization with current vaccines. Future developments

**Table 12. Major recommendations for vaccinations for family, close contacts, and health-care workers (HCWs) of hematopoietic stem cell (HSCT) recipients.**

Vaccine	Recommendations for use	Rating
Hepatitis A	Routine vaccination is recommended for persons at increased risk for hepatitis A or its adverse consequences (e.g., persons with chronic liver disease or persons traveling to hepatitis A-endemic countries) and for children aged $\approx$ 24 months living in areas with consistently elevated hepatitis A incidence.	BII
Influenza	Household contacts – Vaccination is strongly recommended during each influenza season (i.e., October-May) beginning in the season before the transplant and continuing to $\approx$ 24 months after HSCT. All household contacts of immunocompromised HSCT recipients should be vaccinated annually as long as these conditions persist. HCWs and home caregivers – Annual vaccination is strongly recommended during each influenza seasons	AI AI
Polio	Vaccination is not routinely recommended for adults but should be administered when polio vaccination is indicated according to published Advisory Committee on Immunization Practices guidelines; when polio vaccine is administered, inactivated polio vaccine should be used.	AI
Measles-mumps-rubella	Vaccination is recommended for all persons who are aged $\approx$ 12 months and who are not pregnant or immunocompromised.	AI
<i>Haemophilus influenzae</i>	Vaccination of pediatric household contacts is recommended to prevent Hib exposure to HSCT patients	All
Rotavirus	Contraindicated because intussusception has been reported among infants during the first 1-2 weeks after rotavirus vaccination with substantially increased frequency.	EII
Varicella	Vaccination should be administered to all susceptible HCWs, household contacts, and family members who are aged $\approx$ 12 months and who are not pregnant or immunocompromised. When varicella vaccination is administered to persons aged $\approx$ 13 years, 2 doses are required, administered 4-8 weeks apart.	AllI

**Table 13. Major recommendations for use of passive immunization for hematopoietic stem cell transplant (HSCT) recipients exposed to vaccine-preventable diseases.**

Preparation	Recommendations for Use	Rating
Cytomegalovirus immunoglobulin	Not recommended for prophylaxis among HSCT recipients because of its lack of efficacy.	DI
Varicella-zoster immunoglobulin	Should be administered to VZV seronegative recipients $\approx$ 96 hours after close contact with a person with varicella or shingles if the HSCT recipient is at a) < 24 months after HSCT or b) $\approx$ 24 months after HSCT and still immunocompromised.	All
Intramuscular immunoglobulin	Should be administered to hepatitis A-susceptible HSCT recipients who anticipate hepatitis A exposure (e.g., during travel to endemic areas) and for postexposure prophylaxis as indicated. Should also be administered after measles exposure among HSCT recipients who were not vaccinated against measles after HSCT.	BIII
Intravenous immunoglobulin	Can be administered to HSCT recipients with severe hypogammaglobulinemia (immunoglobulin G < 400 mg/dl) $\approx$ 100 days after HSCT to prevent bacterial infections	CIII

await licensing of DNA vaccines and newer antigenic agents. However, future plans do not negate the current need for uniformly applied immunization programs to prevent infectious disease following HSCT.

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