Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients

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This article contains highlights of "Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients: Recommendations of the CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation," which was published in the *Morbidity and Mortality Weekly Report*. There are sections on the prevention of bacterial, viral, fungal, protozoal, and helminth infections and on hospital infection control, strategies for safe living following transplantation, immunizations, and hematopoietic stem cell safety. The guidelines are evidence-based, and prevention strategies are rated by both the strength of the recommendation and the quality of evidence that supports it. Recommendations are given for preventing cytomegalovirus disease with prophylactic or preemptive gancyclovir, herpes simplex virus disease with prophylactic acyclovir, candidiasis with fluconazole, and *Pneumocystis carinii* pneumonia with trimethoprim-sulfamethoxazole. Hopefully, following the recommendations made in the guidelines will reduce morbidity and mortality from opportunistic infections in hematopoietic stem cell transplant recipients.

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Hematopoietic stem cell transplantation (HSCT) is the infusion of hematopoietic stem cells from a donor into a patient who has received chemotherapy, which is usually marrow ablative. HSCTs are classified as either allogeneic or autologous, depending on the source of the transplanted hematopoietic progenitor cells.

For the purposes of this document, HSCT is defined as any transplantation of blood or marrow-derived hematopoietic stem cells, regardless of transplant type (allogeneic or autologous) or cell source (bone marrow, peripheral blood, or placental/umbilical cord blood). Opportunistic infections (OIs) are defined as any infections that occur with increased frequency or severity in HSCT patients. For the purposes of these guidelines, HSCT patients are presumed immunocompetent if they are at least 24 months post-HSCT, are not receiving immunosuppressive therapy, and do not have graft-versus-host disease (GVHD).

The HSCT OI guidelines were drafted with the assistance of a working group, the members of which are listed at the end of the article. There are 9 sections in the guidelines. Following the introduction are sections on the prevention of bacterial, viral, fungal, protozoal, and helminth infections and on hospital infection control, strategies for safe living following transplantation,

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immunizations, and hematopoietic stem cell safety. The disease-specific sections address prevention of exposure and disease for pediatric and adult autologous and allogeneic HSCT patients.

The purposes of the guidelines are (1) to summarize the current data regarding the prevention of OIs in HSCT patients and (2) to produce an evidence-based statement of recommended strategies for preventing OIs in HSCT patients. These guidelines were developed for use by HSCT patients, their household and close contacts, transplant and infectious disease specialists, HSCT unit and clinic staff, and public health professionals. For all recommendations, prevention strategies are rated by both the strength of the recommendation and the quality of the evidence supporting the recommendation (table 1). This rating system was developed by the Infectious Diseases Society of America and the US Public Health Service for use in the guidelines for preventing OIs in persons infected with HIV [2–5]. The rating system allows assessments of the recommendations to which adherence is most important. As indicated in table 1, the strength of a recommendation is indicated by the letters A–E. The quality and type of evidence that supports a recommendation is indicated by the roman numerals I–II. In this summary, a rating is indicated (in parentheses) for each recommendation.

OIs occur at different phases of immune recovery; therefore, OI prevention strategies will vary by phase. HSCT patients develop various infections at different times posttransplantation, reflecting the predominant host-defense defect(s). There are basically 3 phases of immune recovery for HSCT patients, beginning at day 0, the day of transplantation. Phase 1 is the pre-engraftment phase (<30 days post-HSCT); phase 2, the postengraftment phase (30–100 days post-HSCT); and phase 3, the late phase (>100 days post-HSCT).

PHASES OF IMMUNE RECOVERY

Phase 1: pre-engraftment phase (0–30 days posttransplantation). During the first month posttransplantation, HSCT patients have 2 major risk factors for infection: (1) prolonged neutropenia and (2) breaks in the mucocutaneous barrier due to the HSCT preparative regimens and the frequent vascular access required for patient care. Prevalent pathogens include *Candida* species and, as neutropenia continues, *Aspergillus* species. In addition, herpes simplex virus (HSV) reactivation can occur during this phase. OIs may present as febrile neutropenia. Patients undergoing autologous transplantation are primarily at risk for infection during phase I.

Phase II: postengraftment phase (30–100 days posttransplantation). Phase II is dominated by impaired cell-mediated immunity. The scope and impact of this defect for allogeneic HSCT patients are determined by the extent of and

Table 1. Infectious Diseases Society of America–United States Public Health Service Grading System for evidence-based ranking of recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
B	Moderate evidence of efficacy—or strong evidence of efficacy but only limited clinical benefit—supports recommendation for use. Should generally be offered.
C	Evidence of 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 of lack of efficacy or of adverse outcome supports a recommendation against use. Should generally not be offered.
E	Good evidence of lack of efficacy or of adverse outcome supports a recommendation against use. Should never be offered.
Quality of evidence	
I	Evidence from at least 1 properly randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from >1 center), or from multiple time-series or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from [5].

immunosuppressive therapy for GVHD, a condition which occurs when the transplanted cells recognize the recipient's cells as nonself and attack them. After engraftment, the herpesviruses, particularly cytomegalovirus (CMV), are major pathogens. Other dominant pathogens during this phase include *Pneumocystis carinii* and *Aspergillus* species.

Phase III: late phase (>100 days posttransplantation). During phase III, autologous HSCT patients usually have more rapid recovery of immune function and therefore a lower risk of OIs than do allogeneic HSCT patients. Because of cell-mediated and humoral immunity defects and impaired functioning of the reticuloendothelial system, allogeneic HSCT patients with chronic GVHD and recipients of alternate-donor allogeneic transplants are at risk for various infections during this phase. (Alternate donors include matched unrelated, cord blood, or mismatched family-related donors.) The infections they are at risk for include CMV infection, varicella-zoster virus (VZV) infection, Epstein-Barr virus–related posttransplantation lymphoproliferative disease, community-acquired respiratory virus infection, and infections with encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae.*

The rest of this article summarizes recommendations for preventing specific opportunistic infections in HSCT patients, with ratings of recommendations shown in brackets.

BACTERIAL INFECTIONS

Some experts advise giving routine intravenous immunoglobulin (IVIG) to prevent bacterial infections in the ~20%–25% of HSCT patients with unrelated bone-marrow grafts who develop severe hypogammaglobulinemia (i.e., IgG level <400 mg/dL) within the first 100 days after transplantation (C-III). For example, HSCT patients who are hypogammaglobulinemic might receive prophylactic IVIG to prevent bacterial sinopulmonary infections (e.g., from *Streptococcus pneumoniae*) [6] (C-III). HSCT physicians should *not* routinely administer IVIG products to HSCT patients as prophylaxis for bacterial infection (D-II) (although IVIG has been considered for use by some experts to produce immune modulation for prevention of GVHD).

VIRAL INFECTIONS

CMV infection. All HSCT candidates and all designated allogeneic HSCT donors should be screened for evidence of CMV immunity, such as a positive CMV IgG titer (A-III). CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors (R^-/D^-) should receive only leukocyte-reduced or CMV-seronegative RBCs and/or leukocyte-reduced platelets ($< 1 \times 10^6$ leukocytes/U) to prevent transfusion-associated CMV infection [7] (A-I). HSCT patients at risk for CMV disease post-HSCT (i.e., all CMV-seropositive HSCT patients and all CMV-seronegative recipients with a CMV-seropositive donor) should begin one of two CMV disease prevention programs at the time of engraftment and continue it to day 100 post-HSCT (during phase II) (A-I). Clinicians should use either (1) prophylaxis (A-I) or (2) preemptive treatment (A-I) with ganciclovir for allogeneic HSCT patients.

The first strategy—administration of prophylaxis against early CMV infection (<100 days post-HSCT) to allogeneic HSCT patients—involves administering ganciclovir prophylaxis to all at-risk allogeneic HSCT patients throughout phase II (i.e., from engraftment to day 100 post-HSCT). The induction course is usually started at engraftment (A-I), although some centers may add a brief course of prophylaxis during pre-HSCT conditioning (C-III).

The second strategy—preemptive action against early CMV infection (<100 days post-HSCT) in allogeneic HSCT patients—involves screening HSCT patients routinely after engraftment for evidence of CMV antigenemia or virus excretion. Treatment with intravenous ganciclovir is started if the CMV screening tests become positive (A-I). The preemptive strategy is preferred over the prophylaxis strategy for CMV-seronegative HSCT patients with CMV-seropositive donors (D^+/R^-) because the attack rate of active CMV infection is low when support with screened or filtered blood product is given (B-II). The preemptive strategy restricts ganciclovir recipients to at-risk patients who have evidence of CMV infection post-HSCT. It requires the use of sensitive and specific laboratory tests to rapidly diagnose CMV infection post-HSCT and thus enable immediate administration of ganciclovir once CMV infection has been detected.

HSCT physicians should select $\geq$1 of the following diagnostic methods to determine the need for preemptive treatment: (1) detection of CMV pp65 antigen in leukocytes (antigenemia) [8, 9]; (2) detection of CMV-DNA by use of PCR [10]; (3) isolation of virus from urine, saliva, blood, or bronchoalveolar washings by use of rapid shell-vial culture [11] or (4) routine culture [12, 13]. An HSCT center without access to PCR or antigenemia tests should use prophylaxis rather than preemptive therapy for CMV disease prevention [14] (B-II).

HSV infection. All HSCT candidates should be tested for serum anti-HSV IgG prior to transplantation (A-III). All transplantation candidates who are HSV-seronegative should be informed of the importance of avoiding HSV infection while they are immunocompromised and should be advised of behaviors that will decrease the risk of HSV transmission (A-II). For example, contact with potentially infectious secretions such as cervical secretions and saliva should be avoided (A-II).

Acyclovir prophylaxis should be offered to all HSV-seropositive allogeneic HSCT patients to prevent HSV reactivation during the early posttransplantation period [15–19] (A-I). A

standard approach is to begin acyclovir prophylaxis when the conditioning therapy is initiated and continue until the engraftment occurs or mucositis resolves (whichever is longer, or ~30 days post-HSCT) (B-III). Oral acyclovir may be substituted when patients can tolerate oral medication. However, the optimal dose and duration of acyclovir prophylaxis for prevention of HSV infection post-HSCT have not been defined.

Acyclovir may be considered during phase I for administration to HSV-seropositive autologous HSCT patients who are likely to develop significant mucositis from the conditioning regimen (C-III). Although there have been no well-controlled studies demonstrating its efficacy, acyclovir is routinely administered to HSV-seropositive autologous HSCT patients to prevent HSV reactivation during the early posttransplantation period.

VZV infection. To avoid exposing the HSCT patient to VZV, clinicians should vaccinate susceptible family members, household contacts, and health care workers against VZV. Ideally, VZV-susceptible family members, household contacts, and potential visitors of immunocompromised HSCT patients should be immunized as soon as the decision to perform an HSCT is made. The vaccination dose or doses should be completed at least 4 weeks before the conditioning regimen begins or at least 6 weeks (42 days) before the planned date of HSCT (B-III).

FUNGAL INFECTIONS

During the last decade, with better control of OIs such as CMV infection, invasive fungal disease has emerged as an important cause of death among HSCT patients. The most common fungal infection in HSCT patients is candidiasis. Allogeneic HSCT patients should be given fluconazole prophylaxis to prevent invasive disease with fluconazole-susceptible *Candida* species during neutropenia, especially in health centers where *C. albicans* is the predominant cause of invasive fungal disease pre-engraftment (A-I). Since most candidiasis occurs during phase I [20], fluconazole should be administered [20, 21] from the day of HSCT until engraftment (A-II).

Since autologous HSCT patients generally have an overall lower risk of invasive fungal infection than do allogeneic HSCT patients, many autologous HSCT patients do not require routine antiyeast prophylaxis (D-III). However, experts recommend giving such prophylaxis to a subgroup of autologous HSCT patients who have underlying hematologic malignancies such as lymphoma or leukemia and who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens or graft manipulation or have recently received fludarabine or 2-chlorodeoxyadenosine (2-CDA) (B-III).

Ongoing hospital construction and renovation have been associated with an increased risk of nosocomial mold infection, especially aspergillosis, in severely immunocompromised patients [22]. Therefore, whenever possible, HSCT patients who remain immunocompromised should avoid areas of hospital construction or renovation (A-III).

PROTOZOAL AND HELMINTH INFECTIONS

Clinicians should prescribe prophylaxis for *Pneumocystis carinii* pneumonia (PCP) to allogeneic HSCT patients throughout *all* periods of immunocompromise [23] after engraftment, unless engraftment is delayed. Prophylaxis should be given from engraftment until 6 months post-HSCT (A-II) to *all* patients and beyond 6 months post-HSCT, for the duration of immunosuppression, to those who (1) are receiving immunosuppressive therapy (e.g., with prednisone or cyclosporine) (A-I) or (2) have chronic GVHD (B-II). However, PCP prophylaxis may be initiated before engraftment if engraftment is delayed (C-III). The drug of choice for PCP prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMZ) (A-II). If TMP-SMZ is given before engraftment, the associated myelosuppression may delay engraftment. Some experts recommend an additional 1-week to 2-week course of PCP prophylaxis before HSCT (i.e., day −14 to day −2) (C-III).

PCP prophylaxis should be considered for autologous HSCT patients who (1) have underlying hematologic malignancies such as lymphoma or leukemia, (2) are undergoing intense conditioning regimens or graft manipulation, or (3) have recently received fludarabine or 2-CDA [23, 24] (B-III). The administration of PCP prophylaxis to other autologous HSCT patients is controversial (C-III).

HOSPITAL INFECTION CONTROL

All allogeneic HSCT patients should be placed in rooms that have >12 air exchanges per hour [25, 26] and point-of-use high-efficiency (>99%) particulate air (HEPA) filters that are capable of removing particles $\geqslant 0.3\ \mu$m in diameter [26–29] (A-III). This is particularly important in hospitals and clinics with ongoing construction and renovation [22].

The need for environmental HEPA filtration for autologous HSCT patients has not been established. However, the use of HEPA-filtered rooms should be considered for autologous HSCT patients if they develop prolonged neutropenia, the major risk factor for nosocomial aspergillosis (C-III). The use of laminar-air-flow rooms, if available, is optional for any HSCT patient (C-II). To provide consistent positive pressure in the HSCT patient's room, HSCT units should maintain consistent pressure differentials between the patient's room and the hallway or anteroom, at >2.5 Pascals (0.01 inch by water gauge) [25, 26] (B-III).

STRATEGIES FOR SAFE LIVING AFTER TRANSPLANTATION

HSCT patients should not eat *any* raw or undercooked meat, including beef, poultry, pork, lamb, and venison or other wild game, or combination dishes containing raw or undercooked meats or sweetbreads from these animals, such as sausages or casseroles (A-II). In addition, HSCT patients should not consume raw or undercooked eggs or foods that may contain them (e.g., some preparations of hollandaise sauce, Caesar and other salad dressings, homemade mayonnaise, and homemade eggnog) because of the risk of infection with *Salmonella enteritidis* [30] (A-II). To prevent viral gastroenteritis and exposure to *Vibrio* species and *Cryptosporidium parvum*, HSCT patients should not consume raw or undercooked seafood, such as oysters or clams [31–34] (A-II). In situations where the HSCT patient or his or her caretaker does not have direct control over food preparation (e.g., in restaurants), HSCT patients and candidates should consume only meat that is cooked until well done (A-I).

IMMUNIZATIONS

The guidelines recommend giving 3 doses of DPT or Td, inactivated polio, *H. influenzae*, and hepatitis B vaccines to HSCT patients. These vaccines are to be given at 12, 14, and 24 months post-HSCT. The MMR vaccine, which is a live-virus vaccine, is contraindicated within the first 2 years after HSCT. Administration of MMR vaccine is recommended at 24 months or later post-HSCT if the HSCT patient is presumed immunocompetent (B-II). It is recommended that lifelong seasonal administration of influenza vaccine should be given to HSCT patients, beginning before HSCT and resuming $\geqslant$6 months post-HSCT (B-III). In addition, 23-valent pneumococcal vaccine is recommended for HSCT patients at 12 and 24 months post-HSCT because it may be beneficial to some HSCT patients [B-III). Family, close contacts, and health care providers of HSCT patients should be vaccinated annually against influenza.

HEMATOPOIETIC STEM CELL SAFETY

This section summarizes strategies for the HSCT physician to minimize transmission of infectious diseases, whenever possible, from donors to recipients. To detect transmissible infections, all HSCT donor collection site personnel would follow up-to-date published guidelines and standards for the screening (e.g., obtaining a medical history), physical examination, and serologic testing of donors. All HSCT donors should be in good general health. The medical history of the prospective HSCT donor should obtain information on the following: history of vaccinations during the 4 weeks before donation; travel history, to determine whether the donor has ever resided in or travelled to countries with endemic diseases that might be transmitted through HSCT (e.g., malaria); history of Chagas' disease, leishmaniasis, and viral hepatitis; history of any deferral from plasma or blood donation; history of blood product transfusion, solid organ transplantation, or, in the previous 12 months, transplantation of any tissue; history of risk factors for classic Creutzfelt-Jacob disease; and medical history that indicates the donor has clinical evidence of or is at risk for acquiring a bloodborne infection (e.g., HIV-1 or HIV-2, human T-lymphocytic virus I or II, hepatitis C, or hepatitis B).

CDC/IDSA/ASBMT GUIDELINES FOR THE PREVENTION OF OPPORTUNISTIC INFECTIONS IN THE HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS WORKING GROUP

Chair: Clare A. Dykewicz. *Members:* Raleigh A. Bowden (Fred Hutchinson Cancer Research Center, Seattle), David Emanuel (Indiana University, Indianapolis), David Longworth (The Cleveland Clinic Foundation, Cleveland), Philip A. Rowlings (International Bone Marrow Transplant Registry/Autologous Blood & Marrow Transplant Registry, Milwaukee), Robert H. Rubin (Massachusetts General Hospital, Boston, and Massachusetts Institute of Techmology, Cambridge, MA), Kent A. Sepkowitz (Memorial-Sloan Kettering Cancer Center, New York), Keith Sullivan (Fred Hutchinson Cancer Research Center, Seattle), John R. Wingard (University of Florida, Gainesville, FL). *CDC Members:* Robert T. Chen (National Immunization Program), Brian R. Edlin (National Center for HIV, STD, and TB Prevention [NCHSTP]), Beth Hibbs (National Immunization Program), Harold W. Jaffe (National Center for Infectious Diseases [NCID]), William R. Jarvis (NCID), Jonathan Kaplan (NCID and NCHSTP), Thomas J. Spira (NCID).

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