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Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients: Focus on Community Respiratory Virus Infections

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ABSTRACT

Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant (HSCT) recipients, cosponsored by the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Society for Blood and Marrow Transplantation, were issued in October 2000. The guidelines recommend that to minimize transmission of community respiratory virus (CRV) infection, health care workers and visitors with symptoms of upper respiratory tract infection be restricted from having contact with HSCT recipients and candidates undergoing conditioning therapy. To screen HSCT recipients for CRVs, active clinical surveillance for CRV disease should be conducted on all hospitalized HSCT recipients and candidates undergoing conditioning therapy, including daily monitoring for signs and symptoms of CRV infections. Respiratory syncytial virus (RSV) is the most important CRV because it is the most prevalent and because RSV pneumonia has a high case-fatality rate. For this reason, it is recommended that respiratory secretions of any hospitalized HSCT candidate or recipient with signs and symptoms of CRV infection be tested promptly for RSV. If test results are positive, the patient should be treated early and aggressively. Early preemptive therapy with such treatments as aerosolized ribavirin has been proposed, but limited data preclude a recommendation as to the optimal strategy. Lifelong seasonal influenza vaccination is recommended for all HSCT recipients.

KEY WORDS

Hematopoietic stem cell transplant • Community respiratory virus • Opportunistic infection

INTRODUCTION

In October 2000, the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America, and the American Society for Blood and Marrow Transplantation issued guidelines on the prevention of opportunistic infections in hematopoietic stem cell transplant (HSCT) recipients [1]. The guidelines include evidence-based recommendations rated by the strength of the recommendation (Table 1) and the quality of the supporting evidence (Table 2). This rating system is based on that created by the Infectious Diseases Society of America and the United States Public Health Service for guidelines on the prevention of opportunistic infections in those with human immunodeficiency virus [2].

The HSCT guidelines apply to any transplantation of blood- or marrow-derived hematopoietic stem cells, regardless of transplant type (ie, allogeneic or autologous) or cell source (ie, bone marrow, peripheral blood, or placental or umbilical cord blood), and they cover infections caused by many pathogens. The recommendations relating specifically to prevention of community-acquired respiratory virus (CRV) infections are reviewed here.

PREVENTION OF EXPOSURE

The most important step in the prevention of CRV disease among HSCT recipients is limiting their exposure to persons infected with CRVs. The guidelines include the following recommendations to prevent such exposure [1]:

- Health care workers and visitors with upper respiratory tract infection (URTI) symptoms should be restricted from contact with HSCT recipients and with HSCT candidates undergoing conditioning therapy (rating: AIII).
- HSCT recipients and candidates, their family members and visitors, and all health care workers should be educated

Table 1. *Evidence-Based Rating System Used to Determine Strength of Recommendations of the HSCT Guidelines**

Category	Definition	Recommendation
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use	Should always be offered
B	Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use	Pros and cons should be discussed, but should generally be offered
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy may not outweigh the toxicity, drug interactions, or cost of 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

*Adapted from [1].

regarding the importance of following CRV control measures and the potential severity of CRV infection among HSCT recipients (rating: BIII).

- Even when no nosocomial or community outbreak of CRV infections exists, all persons who enter the HSCT center should be screened daily for URTI symptoms, including visitors and health care workers (rating BIII). Some centers place a stop sign at the entrance to remind visitors and health care workers to stop for URTI screening before seeing patients. Other centers use a sign-in sheet for staff members (*see* Nichols, this supplement).
- Visitors with URTI symptoms should be asked to defer their visit to the HSCT center until their symptoms resolve (rating: BIII).
- Health care workers with URTI symptoms should be restricted from patient contact and reassigned to non–patient care duties until symptoms resolve (rating: BIII).

PREVENTION OF NOSOCOMIAL TRANSMISSION

Among the guidelines' recommendations to prevent nosocomial transmission of CRV infection are the following [1]:

- Physicians should institute appropriate precautions and infection control measures for preventing nosocomial pneumonia among hospitalized HSCT recipients and candidates undergoing conditioning therapy, particularly during community or nosocomial CRV outbreaks (rating: AIII).
- When determining the duration of appropriate precautions for CRV-infected HSCT recipients or candidates undergoing conditioning therapy, health care workers should recognize that prolonged CRV shedding can occur (rating: CIII). Viral shedding among HSCT recipients with CRV infection has been reported to last up to 4 months for influenza, up to 2 years for adenovirus, and up to 20 days for RSV (although longer durations for RSV shedding among immunocompromised patients have been reported (*see* Englund, this supplement).
- Active clinical surveillance for CRV disease should be conducted on all hospitalized HSCT recipients and candidates undergoing conditioning therapy. This surveillance should include daily checking for signs and symptoms of CRV infection (rating: AIII). Viral cultures of specimens from asymptomatic candidates for HSCT candidates should *not* be done, however, because they are unlikely to be useful.
- In outpatient waiting rooms, patients with CRV infections should be separated from other patients as much as possible (rating: BIII).
- HSCT recipients with URTI or lower respiratory tract infection (LRTI) symptoms should be placed under contact precautions to avoid transmitting infection to other HSCT candidates and recipients, health care workers, and visitors until the cause of the infection is identified (rating: BIII).
- Optimal isolation precautions should be modified as needed once the cause of the infection is identified (rating: AIII).

PREVENTION OF DISEASE

- HSCT physicians should determine the cause of a URTI, if possible, because such infections can progress to more serious LRTIs, and certain CRV infections can be treated (rating: BIII).
- HSCT candidates with URTI symptoms at the time conditioning therapy is scheduled to start should postpone their conditioning regimen until the URTI is resolved, if possible, because certain URTIs may progress to LRTIs during immunosuppression (rating: BIII).

Table 2.

*Evidence-Based Rating System Used to Determine Quality of Supporting Evidence for Recommendations of the HSCT Guidelines**

Category	Definition
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 analytic studies (preferably from more than 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

*Adapted from [1].

Table 3. *Preventive Regimens for Pediatric HSCT Recipients With RSV Infection**

Indication	First Choice	Alternatives
Prophylaxis for RSV LRTI among patients with hypogammaglobulinemia	RSV-IVIG† can be given in place of standard IVIG during RSV season for those on routine IVIG therapy (rating: CIII) Usual RSV-IVIG dosage is 750 mg/kg per mo or a 1-mg/1-mg dosing substitution of RSV-IVIG for IVIG can be used in those who normally need high IVIG doses to keep serum IgG >400 mg/dL; can give more often than monthly as needed to keep serum IgG >400 mg/dL	None
Preemptive treatment of RSV URTI or early LRTI	Aerosolized ribavirin, 6 g/300 mL sterile water to make concentration of 20 mg/mL; give 18 h/d for 10 d in a tent (rating: CIII) For those with LRTI who cannot tolerate a tent or have RSV URTI, give ribavirin as 2 g for 2 h every 8 h by face mask for 10 d, using SPAG-2	

*Adapted from [1]. IgG indicates immunoglobulin G; IVIG, intravenous immunoglobulin; SPAG, small particle aerosol generator.

†RSV-IVIG is contraindicated among patients with IgA deficiency or who might have allergic reactions or anaphylaxis when receiving blood products containing IgA (DIII). RSV monoclonal antibody is under investigational use among HSCT recipients for treatment with ribavirin but not for prophylaxis.

PREVENTION OF RSV INFECTION

General

RSV is the most important CRV because it is the most prevalent and because RSV pneumonia has a very high case-fatality rate [3-6]. The following recommendations have been made for prevention of RSV transmission [1]:

- Respiratory secretions of any hospitalized HSCT candidate or recipient who experiences signs or symptoms of CRV infection should be tested promptly by viral culture and rapid diagnostic tests for RSV (rating: BIII).
- During RSV season, HSCT recipients and candidates with signs or symptoms should be tested for RSV infection, as indicated by the presence of RSV antigen in respiratory secretions tested by enzyme-linked immunosorbent assay and viral culture, at admission to the HSCT center and regularly thereafter. All patients who are RSV-antigen positive should be treated as a cohort during nosocomial RSV outbreaks, because this practice reduces nosocomial RSV transmission (rating: BII).
- In a hospitalized HSCT candidate or recipient with symptoms of respiratory infection, if 2 diagnostic samples taken >2 days apart do not identify a respiratory pathogen despite persistence of symptoms, a bronchoalveolar lavage (BAL) specimen should be obtained for further testing (rating: BIII).
- HSCT recipients, particularly those who are preengraftment and at highest risk for severe RSV pneumonia, should have RSV infection diagnosed early (during RSV URTI) and treated aggressively to prevent fatal RSV disease (rating: BIII).
- Although a definitive, uniformly effective preemptive therapy for RSV infection among HSCT recipients has not been identified, certain strategies have been proposed, including the use of aerosolized ribavirin, aerosolized ribavirin in combination with RSV antibodies (high–RSV titer immunoglobulin or RSV immunoglobulin), and RSV monoclonal antibody. No recommendation regarding the optimal method of RSV prevention and preemptive therapy can be made because of limited data.

Pediatric Patients

Among the recommendations for the prevention of RSV infections in pediatric (<18 years old) HSCT recipients are the following [1]:

- To prevent RSV disease in pediatric patients, some experts suggest substituting RSV immunoglobulin for standard immunoglobulin during the RSV season (November through April) in children who receive routine immunoglobulin therapy (rating: CIII) (Table 3).
- Other researchers report that pediatric HSCT recipients with RSV infection can be considered for preemptive therapy (during URTI or early LRTI) with aerosolized ribavirin (rating: CIII) (Table 3). This therapy remains controversial.

PREVENTION OF INFLUENZA VIRUS INFECTION

During the 1991-1992 influenza epidemic in Houston, Texas, documented influenza virus infection was the cause of acute URTI among 8 (29%) of 28 HSCT inpatients at M.D. Anderson Cancer Center [7]. URTI was present on admission in 3 patients and was acquired in the hospital by the other 5; mean time to acquisition was 20 days (range, 11-32 days). In 6 (75%) of the 8 infected patients, URTI progressed to pneumonia, and 1 patient died [7].

The guidelines make a number of recommendations for the prevention of influenza, including the following [1]:

- Influenza vaccination of family members and close or household contacts is strongly recommended during each influenza season (October to May), starting the season before HSCT and continuing ≥24 months after HSCT (rating: AI).
- All family members and close or household contacts of HSCT recipients who remain immunocompromised for ≥24 months after HSCT should continue annual influenza vaccination as long as the HSCT recipient remains immunocompromised (rating: AI).
- Seasonal influenza vaccination is strongly recommended for all health care workers who care for HSCT recipients (rating: AI).

- If health care workers, family members, or close contacts of HSCT recipients receive influenza vaccination during an influenza A outbreak, they should receive amantadine or rimantadine chemoprophylaxis for 2 weeks after immunization (rating: BI).
- If a nosocomial outbreak is caused by an influenza A strain not included in the current influenza vaccine, all healthy family members, close and household contacts, and health care workers caring for HSCT recipients and candidates should be given influenza A chemoprophylaxis with amantadine or rimantadine until the end of the outbreak (rating: BIII).
- Health care workers, family members, or other close contacts of HSCT recipients may be offered a neuraminidase inhibitor (zanamivir or oseltamivir) if rimantadine or amantadine cannot be tolerated, if the influenza outbreak is caused by a strain of influenza A resistant to amantadine or rimantadine, or if the outbreak strain is influenza B (rating: BI).
- Lifelong seasonal influenza vaccination is recommended for all HSCT candidates and recipients, beginning during the influenza season before HSCT and resuming ≥6 months after HSCT (rating: BIII). This vaccination schedule differs from the European recommendation, which advises influenza vaccination for all HSCT recipients for only 2 years after transplantation.
- HSCT recipients <6 months after transplantation should receive chemoprophylaxis with amantadine or rimantadine during community or nosocomial influenza A outbreaks (rating: BIII). These drugs are not effective against influenza B. In addition, antiviral-resistant strains of influenza can emerge during treatment with amantadine or rimantadine and can be transmitted to others.

CONCLUSIONS

These evidence-based guidelines for preventing CRVs among HSCT recipients, extracted from the complete guidelines for preventing all opportunistic infections among these patients, provide preventive strategies for HSCT recipients, their household and close contacts, and their health care workers. CRVs, which are generally manageable in healthy immunocompetent individuals, can be difficult to treat and even fatal in HSCT recipients. Therefore, preventing CRVs in this population is preferable to treating them. Adherence to these guidelines should help reduce both the number and the severity of CRVs in HSCT recipients.

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