Evidence-Based Guideline Recommendations:
Post-Hematopoietic Stem Cell Transplantation

Mary C. Burkhart, MS, CNP, AOCNP®, John Wade, RN, OCN®, and Virginia Lesperance, MSN

Cancer survivorship is expected to increase in coming years. Survivors include recipients of hematopoietic stem cell transplantations, signaling the necessity for evidence-based guidelines that focus on long-term follow-up needs. Studies have shown that evidence-based care can improve cancer survivors’ quality of life and long-term outcomes. The implication is that early identification and intervention in chronic health problems such as graft-versus-host disease result in improved outcomes and a higher quality of survivorship. These discoveries signal a need to provide specific care management with appropriate and timely screening and preventive services. Recommendations for long-term follow-up post-hematopoietic stem cell transplantation are an important guide to direct clinical practice with this patient population and optimize their outcomes.

Mary C. Burkhart, MS, CNP, AOCNP®, is a nurse practitioner at the Mayo Clinic in Phoenix, AZ, and John Wade, RN, OCN®, and Virginia Lesperance, MSN, are blood and marrow transplantation coordinators at the Mayo Clinic in Jacksonville, FL. The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or editorial staff. Burkhart can be reached at burkhart.mary@mayo.edu, with copy to editor at CJONEditor@ons.org. (Submitted February 2013. Revision submitted March 2013. Accepted for publication March 24, 2013.)

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The number of cancer survivors in the United States has exceeded 13 million (Siegel et al., 2012), including post-hematopoietic stem cell transplantation (HSCT) recipients. Allogeneic recipients of HSCT account for about 8,860 of those survivors reported and autologous recipients account for about 9,026 (Pasquini, Wang, Horowitz, & Gale, 2010). As the developments of improved and more targeted treatments are discovered, the number of long-term cancer survivors is expected to increase. Like many cancer survivors, those receiving HSCT have been noted by healthcare providers at some stem cell transplantation centers as being lost to follow-up for various reasons (Majhail et al., 2012). The contributing societal trends identified by Majhail et al. (2012) include an increasingly mobile society, living in healthcare-disparaged locations, and loss of income.

Evidence-based care has been shown to improve the quality of life and long-term outcomes of cancer survivors (Gobel, Beck, & O’Leary, 2006). Principles of ancillary and supportive care studies (i.e., providing interdisciplinary therapies or prescriptive interventions) indicate that early identification and intervention in chronic health problems, such as graft-versus-host disease (GVHD), result in less need for systemic therapy, improved outcomes, and higher quality of survivorship (Carpenter & Couriel, 2009). The reality of those facts supports the need to provide appropriate and timely screening and preventive services to HSCT recipients to optimize their outcomes.

Late Effects

Immune recovery generally occurs gradually during the 12–18 months post-HSCT (Rizzo et al., 2006). Experts agree that good markers for evaluating immune reconstitution include monitoring the CD4 level and the CD4:8 ratio prior to the replacement of immunizations about one year post-HSCT, looking for CD4 greater than 400 as an indication of immune recovery (Rizzo et al., 2006). Late effects and complications can occur in HSCT recipients six months or more after transplantation. After that time, the main complications that remain risks include chronic GVHD, relapsed disease, and infections such as Pneumocystis jiroveci pneumonia, varicella zoster virus, cytomegalovirus, and encapsulated bacteria.

Chronic GVHD occurs in 30%–70% of all allogeneic HSCT recipients. Proper treatment of chronic GVHD is associated with a lower relapse rate and mortality (Tomblyn et al., 2009). Conversely, uncontrolled chronic GVHD is associated with increased impairment of health-related quality of life and higher morbidity.

Other late effects after HSCT can be regimen-related toxicity, prolonged immunodeficiency, and bone disease. Possible
Antifungal Prophylaxis
Candida prophylaxis—conditioning through engraftment (absolute neutrophil count [ANC] less than 1,000)

Preferred
- Fluconazole 400 mg daily
- Fluconazole 200 mg daily (if 400 mg is not tolerated)

Alternatives (consider for high risk [if mold or resistant candida])
- Itraconazole oral solution 200 mg
- Micafungin 50 mg IV daily
- Posaconazole 200 mg TID

Antiviral Prophylaxis
Herpes simplex virus-reactive conditioning until engrafted

Preferred
- Acyclovir 400 mg BID or 800 mg BID if highly immunosuppressed
- Acyclovir 250 mg/m² IV every 12 hours

Alternative
- Valacyclovir 500 mg daily or 500 mg BID if highly immunosuppressed

Bacterial Infection Prophylaxis
Neutropenia for seven days or more and an ANC less than 1,000 until engrafted or IV antibiotic

Preferred
- Levofloxacin 500 mg daily or ciprofloxacin 500 mg BID

Alternative
- Azithromycin 250 mg daily

Varicella Zoster Virus Retinitis—Positive
Day 0 through day 365 if treatment benefit outweighs risk toxicity (autologous day +30, allogeneic day +365)

Preferred
- Acyclovir 800 BID

Alternative
- Valacyclovir 500 mg BID

Cytomegalovirus (CMV)
Engraftment to day 100; pre-emptive transplantation if CMV reactivated

Induction: 14 days
- Ganciclovir 5 mg/kg IV BID or valganciclovir 900 mg BID with CMV detection trend down

Maintenance: 21 days (consider to day 100 if highly immunosuppressed)
- Ganciclovir 5 mg/kg IV daily
- Valganciclovir 900 mg daily

Hold antiviral prophylaxis while on CMV transplantation

Mold Prophylaxis
Previous mold infection

Preferred
- Voriconazole 4 mg/kg IV every 12 hours or PO 200 mg BID

Alternatives
- Amphotericin B 1–1.5 mg/kg IV every 24 hours
- Posaconazole 200 mg four times a day
- Echinocandin in combination therapy

Pneumocystis Jiroveci Pneumonia
Postengraftment until day 180 or longer if highly immunosuppressed

Preferred
- Trimethoprim/sulfamethoxazole one double-strength tablet daily
- Trimethoprim/sulfamethoxazole one double-strength tablet three times weekly

Alternatives
- Trimethoprim/sulfamethoxazole one single-strength tablet daily (consider trimethoprim desensitization)
- Dapsone 50 mg BID or 100 mg every day (consider glucose-6-phosphate dehydrogenase prior)
- Atovaquone 750 mg BID or 1,500 mg daily
- Aerosolized pentamidine 300 mg q 28 days

FIGURE 1. Antimicrobial Guidelines for Post-Hematopoietic Stem Cell Transplantation Recipients

Note. Based on information from Toblyn et al., 2009.

regimen-related toxicities include cataracts, neurologic conditions, gonad dysfunction, endocrine conditions, and growth or development alterations. Overall, late effects and complications may impact entire organ systems. Rizzo et al. (2006) listed the following late effects for each organ system: ocular (cataracts, keratoconjunctivitis sicca, and microvascular retinopathy); oral (sicca syndrome and carries); respiratory (idiopathic pneumonia syndrome, bronchiolitis obliterans syndrome, cryptogenic organizing pneumonia, and sinopulmonary infection); cardiovascular (coronary disease, cardiomyopathy, congestive heart failure, valvular anomaly, and peripheral arterial disease); liver (GVHD, hepatitis B or C, and iron overload); renal or genitourinary (chronic kidney disease, bladder dysfunction, and urinary tract infection); muscular and connective tissue (myopathy, myositis, and fasciitis [scleroderma]); skeletal (osteoarthritis and avascular necrosis); neurologic (leukoencephalopathy, calcineurin neurotoxicity, and cognitive alteration); endocrine (hypothyroid, parathyroid, gonad dysfunction, and growth retardation); and mucocutaneous (cutaneous sclerosis and genital GVHD). In addition, Rizzo et al. (2006) noted late effects for second cancers (e.g., solid tumors, hematologic malignancy, post-transplantation lymphoproliferative disorder), psychosocial issues (e.g., depression, problems regarding fertility dysfunction), and general health (health promotion and maintenance for the general population).

Discussion
In an effort to positively impact quality of life and long-term outcomes of post-HSCT recipients, the current literature was reviewed to determine expert recommendations for follow-up after HSCT, as well as to evaluate current long-term follow-up practices. The topics explored were infection prevention, immunization replacement, interval evaluation for all post-HSCT recipients, and chronic GVHD management.

Substantial evidence supported updates to infection prevention and vaccine replacement schedules (Toblyn et al., 2009). Ongoing study needs were identified in principles of ancillary and supportive care measures for chronic GVHD effects surrounding psychosocial issues (Carpenter & Couriel, 2009). Limited evidence-based data regarding optimal long-term follow-up of HSCT recipients without GVHD was available. Conversely, recommended follow-up has been suggested by a consensus panel formed by the Center for International Blood and Marrow Transplantation Research, the European Group for Blood and Marrow Transplantation, and the American Society of Blood
and Marrow Transplantation that supports follow-up guidelines (Tomblyn et al., 2009). The compiled information led to guideline references for post-HSCT care and follow-up in the following categories: antimicrobial prophylaxis (see Figure 1), chronic GVHD supportive care (see Table 1), and vaccination schedule replacement (see Appendix A). In addition, interval recommendations for screening and preventive practices for all HSCT recipients (see Appendix B) and chronic GVHD monitoring (see Appendix C) were established by a formal Quality Committee meeting with an interdisciplinary team.

Strategies for success of ongoing follow-up care needed for all HSCT recipients depend on providing each recipient with tools that can be used prior to discharge from the transplantation center post-HSCT. Developing care partnerships with a team, including the transplantation care provider, community healthcare provider, and transplantation recipient, also will foster improved quality of life and survivorship (Rizzo et al., 2006).

**Conclusion**

The estimated increase in the number of cancer survivors in coming years signals the need to provide appropriate and timely screening and preventive services for post-HSCT recipients. The National Institute of Health Working Group had identified the need for additional studies surrounding psychosocial issues (Carpenter & Couriel, 2009). Periodic review of evidence-based practice guidelines for this population is important to allow for periodic changes in practice based on experience and new documented evidence.

The limited data to support long-term follow-up needs for all HSCT recipients provide an opportunity for oncology nursing research and multidisciplinary teams of care providers to develop protocols and establish standards of practice that result in overall improved quality of long-term survivorship for all post-HSCT recipients. Advancing information technologies provide additional opportunities for partnerships among oncology nurses, HSCT recipients post-transplantation, and other multidisciplinary teams for the development of tools to supply to discharged patients from transplantation centers. The goal is to guide post-HSCT recipients with a plan for future follow-up care needs and preventive service recommendations in the hopes of leading them to improved quality of life and enduring survivorship. For more information, nurses should send HSCT recipients to the following patient-friendly online resources: [www.mayoclinic.edu](http://www.mayoclinic.edu), [www.nhlbi.nih.gov/health/.../topics/bmsct](http://www.nhlbi.nih.gov/health/.../topics/bmsct), and [http://bethematch.org/Patient/Patients_and_Families.aspx](http://bethematch.org/Patient/Patients_and_Families.aspx).

**References**


**Implications for Practice**

- Periodic review of evidence-based practice guidelines will allow for practice changes based on experience and new documented evidence.
- The limited published data supporting specific long-term follow-up needs for hematopoietic stem cell transplantation recipients signal the necessity for ongoing development of protocols to develop standards of practice for this population.
- Changing complexities in health care promote development of partnerships with an interdisciplinary team including the transplantation healthcare provider, community healthcare provider, and transplantation recipient.

**TABLE 1. Chronic Graft-Versus-Host Disease Monitoring Recommendations**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Interval (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History and physical</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1–12, as clinically indicated</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
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<tr>
<td>Basic blood work</td>
<td>1–6, as clinically indicated</td>
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<tr>
<td>Lipid profile</td>
<td>6–12, as clinically indicated</td>
</tr>
<tr>
<td>Iron indices</td>
<td>6–12, as clinically indicated</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>3–12, as clinically indicated</td>
</tr>
<tr>
<td>Bone health&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12</td>
</tr>
<tr>
<td>Thyroid function tests</td>
<td>12</td>
</tr>
<tr>
<td><strong>Special evaluations</strong></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology (e.g., Schirmer test, glaucoma test)</td>
<td>3–12, as clinically indicated</td>
</tr>
<tr>
<td>Dental and oral medicine&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6–12, as clinically indicated</td>
</tr>
<tr>
<td>Dermatology (e.g., extent and type of lesion)</td>
<td>As clinically indicated</td>
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<tr>
<td>Gynecology (e.g., vulvovaginal examination)</td>
<td>As clinically indicated</td>
</tr>
<tr>
<td>Physical therapy (e.g., range of motion if sclerosis positive)</td>
<td>3–12, as clinically indicated</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td>As clinically indicated</td>
</tr>
</tbody>
</table>

<sup>a</sup>General health, symptoms, medication review, height, weight, and nutrition
<sup>b</sup>Complete blood count and differential, creatinine, magnesium, liver function tests, therapeutic drug levels, and immunoglobulin G level
<sup>c</sup>Dual-energy x-ray absorptiometry densitometry, serum calcium, and 25-OH vitamin D
<sup>d</sup>Soft and hard palate examination; culture, biopsy, and photograph lesions; radiographs

*Note.* Based on information from Carpenter & Couriel, 2009.


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### APPENDIX A. Vaccination Schedule Guidelines for Patients Post-Hematopoetic Stem Cell Transplantation (HSCT)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Month 6</th>
<th>Month 8</th>
<th>Month 10</th>
<th>Month 12</th>
<th>Month 13</th>
<th>Month 14</th>
<th>More Than 24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal conjugate vaccine (PCV) (three doses a minimum of two months apart; fourth dose if patient has graft-versus-host disease)</td>
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<td>X</td>
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<tr>
<td>Pneumococcal polysaccharide (inadequate response if given less than 12 months post-HSCT; given two months after third dose of PCV only if without graft-versus-host disease)</td>
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<td>X</td>
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<tr>
<td>Tetanus, diphtheria, and acellular pertussis (three doses a minimum of one month apart)</td>
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<td>X</td>
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<tr>
<td>Hemophilus influenzae conjugate (three doses a minimum of one month apart)</td>
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<td>X</td>
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<tr>
<td>Meningococcal conjugate (one dose)</td>
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<td>X</td>
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<tr>
<td>Inactivated polio (three doses a minimum of one month apart)</td>
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<td>X</td>
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<tr>
<td>Recombinant hepatitis B (three doses)</td>
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<td>X</td>
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<tr>
<td>Inactivated influenza (annually; consider repeat after three months during flu season)</td>
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<td>X</td>
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<tr>
<td>Measles, mumps, rubella (one to two doses of measles; seronegative more than 24 months post-HSCT; no graft-versus-host disease or immunosuppression)</td>
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<td></td>
<td></td>
<td></td>
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<td>X</td>
</tr>
</tbody>
</table>

*Note.* Varicella (attenuated live virus) and zostavax (shingles) are contraindicated. Varivax (chicken pox) is not mandatory.

*Note.* Based on information from Tomblyn et al., 2009.
Antifungal Prophylaxis

High risk for mold or resistant candida

**Preferred**
- Fluconazole 400 mg daily

**Alternative**
- Voriconazole 200 mg BID
- Posaconazole 200 mg TID with meal

Antiviral Prophylaxis

Duration chronic graft-versus-host disease or immunosuppressant

**Preferred**
- Acyclovir 800 mg BID
- Acyclovir 250 mg/m^2^ IV every 12 hours

**Alternative**
- Valacyclovir 500 mg daily or 500 mg BID if highly immunosuppressed

Bacterial Infection Prophylaxis

Duration of chronic graft-versus-host disease or immunosuppressant

- Monitor immunoglobulin G monthly < 400 mg/kg (and with recurrent infections)
- IV immunoglobulin 400 mg/kg

**Preferred**
- Penicillin V potassium 250–500 mg BID or 500–1,000 mg daily
- Amoxicillin, erythromycin
- Bactrim one single-strength tablet daily
- Levaquin

Cytomegalovirus (CMV)

Monitor one year or more if patient has active chronic graft-versus-host disease or while on immunosuppressive therapy.

**Induction:** 14 days
- Ganciclovir 5 mg/kg IV BID or valganciclovir with CMV detection trend down

**Maintenance:** 21 days
- Ganciclovir 5 mg/kg IV daily
- Valganciclovir 900 mg daily
- CMV nondetectable
  Hold antiviral prophylaxis while on CMV transplantation.

Osteoporosis Prevention

- Calcium with vitamin D 500 mg BID
- Consider alendronate 70 mg every week

Pneumocystis Jiroveci Pneumonia

Continue six months after off immunosuppressant

**Preferred**
- Trimethoprim/sulfamethoxazole one double-strength tablet daily
- Trimethoprim/sulfamethoxazole one double-strength tablet three times weekly

**Alternative**
- Trimethoprim/sulfamethoxazole one single-strength tablet daily
- Dapsone 50 mg BID or 100 mg weekly (consider glucose-6-phosphate dehydrogenase prior)
- Atovaquone 750 mg BID or 1,500 mg daily
- Aerosolized pentamidine 300 mg every 28 days

APPENDIX C. Chronic Graft-Versus-Host Disease Supportive Care Guidelines

*Note.* Based on information from Carpenter & Couriel, 2009; Toblyn et al., 2009.