Cancer survivorship care from the Memorial Sloan Kettering Cancer Center

Adverse Late and Long-Term Treatment Effects in Adult Allogeneic Hematopoietic Stem Cell Transplant Survivors

An evidence-based guide to identification, evaluation, and management.

OVERVIEW: Hematopoietic stem cell transplantation (HSCT) has become the standard of care for many malignant and nonmalignant hematologic diseases that don't respond to traditional therapy. There are two types: autologous transplantation (auto-HSCT), in which an individual's stem cells are collected, stored, and infused back into that person; and allogeneic transplantation (allo-HSCT), in which healthy donor stem cells are infused into a recipient whose bone marrow has been damaged or destroyed. There have been numerous advancements in this field, leading to marked increases in the number of transplants performed annually. This article—the first of several on cancer survivorship—focuses on the care of adult allo-HSCT survivors because of the greater complexity of their posttransplant course. The author summarizes potential adverse late and long-term treatment-related effects, with special focus on the evaluation and management of several cardiovascular disease risk factors that can occur either independently or concurrently as part of the metabolic syndrome. These risk factors are potentially modifiable with appropriate nursing interventions and lifestyle modifications.

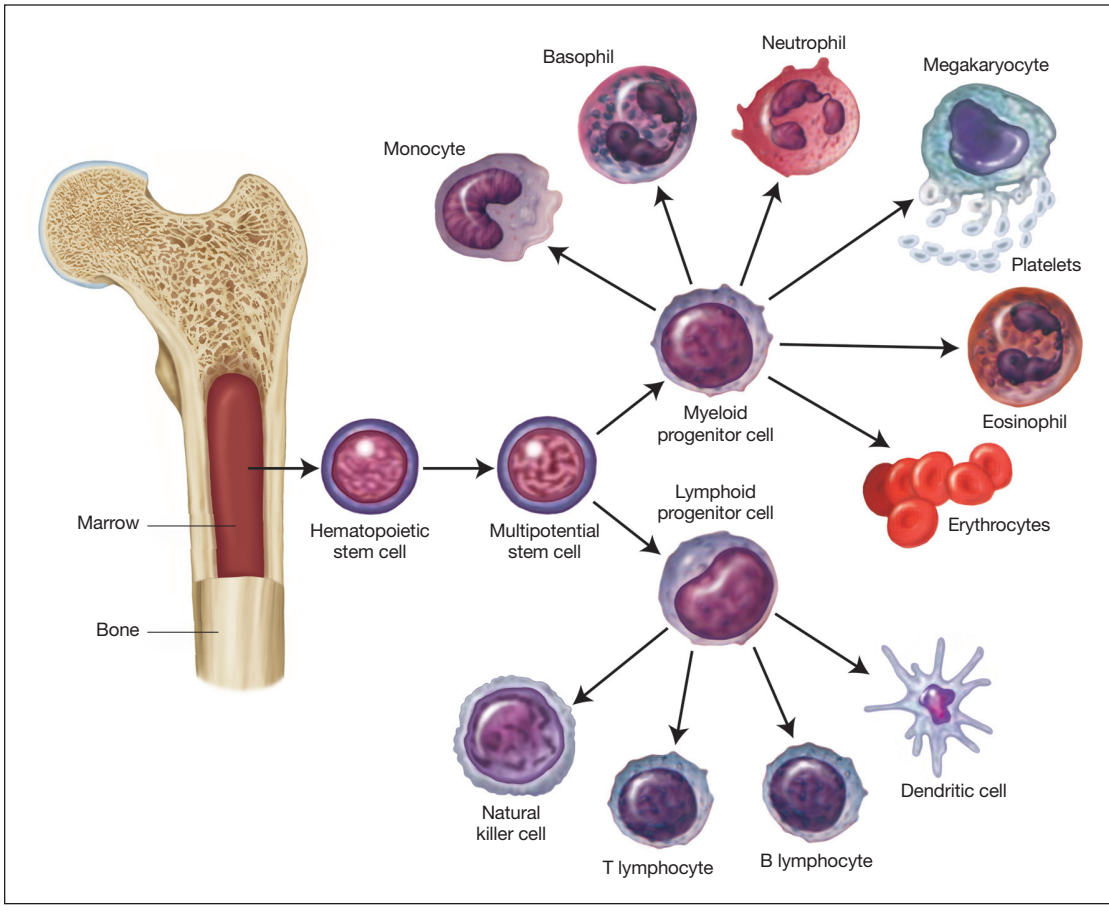
Keywords: allogeneic transplantation, cancer survivorship, cardiovascular disease, hematopoietic stem cell transplantation, metabolic syndrome

Hematopoietic stem cell transplantation (HSCT) has become the standard of care for many malignant and nonmalignant hematologic diseases that don't respond to traditional therapy.[1-3] The procedure involves the intravenous transfusion of stem cells, which originate in bone marrow and give rise to all other types of blood cells (see Figure 1). There are two types of HSCT: autologous transplantation (auto-HSCT), in which an individual's stem cells are collected, stored, and infused back into that person; and allogeneic transplantation (allo-HSCT), in which stem cells are removed from a healthy donor and infused into a recipient whose bone marrow has been damaged or destroyed. Auto-HSCT is routinely performed in cases of lymphoma and myeloma, whereas allo-HSCT is more commonly performed in cases of acute or high-risk leukemias, myelodysplastic syndrome,

and myeloproliferative disorders.[2] HSCT recipients are unique among cancer patients in that, after first receiving chemotherapy or radiation (or both) aimed at achieving a complete remission, they subsequently go on to receive a short course of high-dose chemotherapy, with or without radiation, as part of a pretransplant conditioning regimen. The disease-specific indications and goals for auto- and allo-HSCT procedures vary (see Figure 2[4]), as do the adverse late and long-term treatment-related effects.

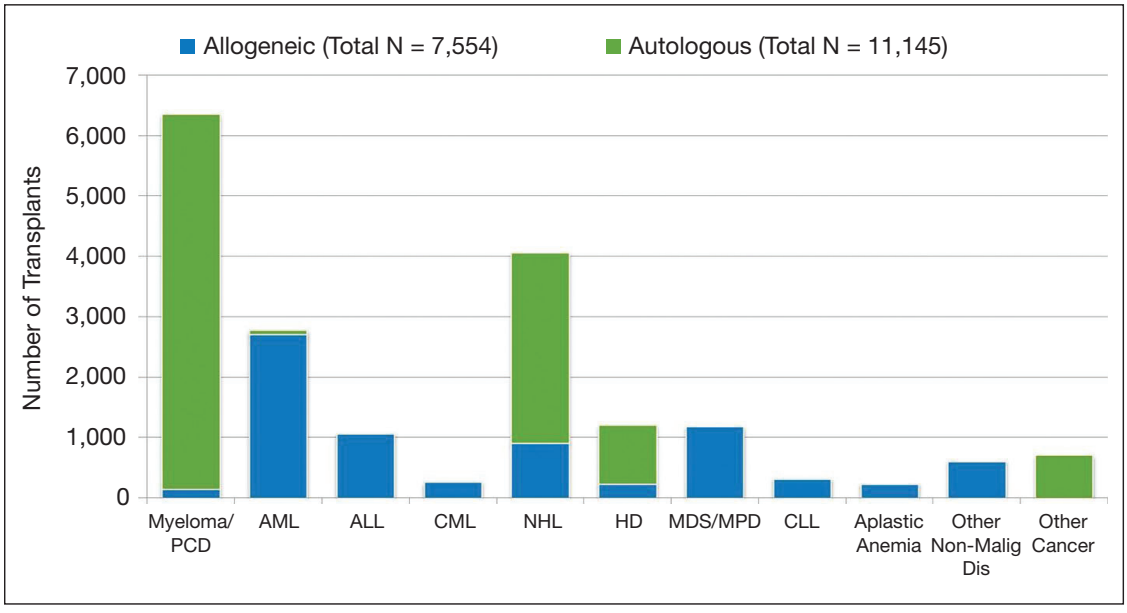
Since the first three successful allo-HSCT procedures in 1968, there have been numerous advancements, leading to marked increases in the number of transplants performed annually and to prolonged life expectancy.[5] It's estimated that, with earlier recognition of posttransplant complications, reduced risk of acute transplant-related death, and improved supportive care, by 2020 there may be as many as half a million long-term allo-HSCT survivors (people living more than two years posttransplant) worldwide.[5] For such survivors, the chances of prolonged survival are excellent (85% at 10 years).[5] That said, mortality rates for allo- or auto-HSCT patients who have survived at least five years are four-to-nine-times higher than those for the general population and remain so for decades after transplantation.[6] And compared with patients who receive auto-HSCT, those who receive allo-HSCT are at higher risk for long-term complications, including graft-versus-host disease (GvHD), in which the donor cells react immunologically to the body of the recipient as foreign and attack one or more organ systems.[2] Other potentially lethal late and long-term treatment effects include infections, secondary

Figure 1. Stem Cell Differentiation



Stem cells are immature "starter" cells produced in bone marrow. As shown here, they differentiate into specialized cells in order to replenish the body's supply of erythrocytes (red blood cells), leukocytes (white blood cells), and platelets. Illustration by Anne Rains.

Figure 2. Indications for Hematopoietic Stem Cell Transplants in the United States, 2012



ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MPD = myeloproliferative disorders; NHL = non-Hodgkin's lymphoma; PCD = plasma cell disorder.

Reprinted from Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: 2014 CIBMTR Summary Slides. Available at www.cibmtr.org.[4]

malignancies, respiratory disease, and cardiovascular disease (CVD).[6-10]

As the number of HSCT survivors grows, the health care system faces increasing challenges in caring for them, including a lack of resources and insufficient patient access to transplantation centers. Many HSCT recipients are transitioned back to the community for posttransplant care, particularly those who have survived beyond two years. So it's crucial for oncology and nononcology providers alike to recognize the specific needs of this population, especially regarding late and long-term treatment effects. The more familiar providers are with the early identification, evaluation, and management of such effects among HSCT survivors, the better their patients' prospects for long-term survival. Although guidelines for post-HSCT care are somewhat limited, providers should be familiar with those that exist. Together with several other transplant organizations, the Center for International Blood and Marrow Transplant Research (CIBMTR) issued joint recommendations for such care in 2006 and updated them in 2011.[11] And in 2013, the National Marrow Donor Program (NMDP) issued guidelines based on the CIBMTR's recommendations and other evidence.[12]

This article focuses on the care of adult allo-HSCT survivors because of the greater complexity of their posttransplant course. It summarizes potential adverse late and long-term treatment effects, and specifically addresses the evaluation and management of several CVD risk factors that can occur either independently of one another or concurrently as part of the metabolic syndrome. These risk factors are potentially modifiable with appropriate nursing interventions and lifestyle modifications. (Although GvHD is a common, significant long-term effect of allo-HSCT, it's often identified and managed earlier, while the allo-HSCT recipient is undergoing treatment at the transplant center, and as such lies beyond the scope of this article.)

OVERVIEW OF ALLO-HSCT

An allo-HSCT has three main components.[13] First, there is a conditioning phase, which involves a combination of high-dose myeloablative or nonmyeloablative chemotherapy, with or without other biologic agents or radiation. (Reduced-intensity doses may be appropriate for some older, more infirm patients.[14]) This phase has two purposes: to destroy cancer cells resistant to conventional chemotherapy, and to cause an immunosuppressive nadir in the recipient and prevent rejection of the donor cells. Second, stem cells that have been collected from the bone marrow, peripheral blood, or umbilical cord blood of a related or unrelated donor are transfused intravenously. A period of engraftment then ensues, in which the recipient begins to make healthy stem cells. Third, a method of GvHD prophylaxis—either graft manipulation or immunosuppressive therapy—is chosen. If graft manipulation through T-cell depletion is chosen, T cells

are removed from the donor cells before transplantation. If immunosuppressive therapy (such as with calcineurin inhibitors) is chosen, patients start to take this medication the day after transplantation. Some patients require both methods.

The main goal of allo-HSCT in treating hematologic malignancies (such as acute myeloid leukemia) is to achieve the graft-versus-tumor effect—"to allow engraftment and development of a donor-derived immune system that can effect an immunologic attack against the recipient['s] lymphohematopoietic system, and in particular against the tumor cells."[13] The engraftment period—in which the transplanted stem cells start to produce new, healthy blood cells in the recipient's marrow—varies. According to Leger and Neville, neutrophil engraftment can be said to have occurred when the absolute neutrophil count is 500/mm^3 or greater for three or more days, which typically happens 10 to 20 days after the transplant.[15] Platelet engraftment, which has been defined as an unsupported platelet count greater than 20,000 platelets per microliter, typically follows, and may take up to eight weeks in umbilical cord blood stem cell recipients.[13, 16] Immune system reconstitution is gradual and variable, depending on individual recipient and donor characteristics and the course of transplantation, with some survivors developing near-normal immune systems one to two years after transplantation and others retaining some degree of long-term immunodeficiency.[8, 17]

ONE PATIENT'S CASE

Paloma Jobin, a 35-year-old teacher, presented to her otolaryngologist in January 2010 with recurrent sinusitis. (This case is a composite based on my experience.) Routine blood work revealed pancytopenia, and she was referred to a hematologist for further evaluation. A bone marrow biopsy performed in February revealed acute myeloid leukemia.

Ms. Jobin underwent induction chemotherapy and, when persistent disease was demonstrated, one cycle of consolidation chemotherapy. By May, complete remission had been achieved, and an allo-HSCT was recommended because of the high risk of disease recurrence. In July, she was admitted to the hospital and underwent conditioning with myeloablative chemotherapy and total body irradiation in preparation for the transplant. Two days after completing the conditioning regimen, she received an allo-HSCT from a human leukocyte antigen–matched unrelated donor, along with GvHD prophylaxis.

Ms. Jobin was first referred to the adult allo-HSCT survivorship clinic by her transplant physician about 14 months after the transplant. Findings from her initial clinic assessment included blood pressure of 134/90 mmHg, weight of 93 kg (205 lbs.), and an abdominal girth of 90 cm (35 in.). Pertinent laboratory results included levels of triglycerides, 334 mg/dL; high-density lipoprotein (HDL) cholesterol, 39 mg/dL; and fasting serum glucose, 127 mg/dL. Her liver function tests were normal except for a mild elevation in alkaline phosphatase. But abdominal imaging revealed hepatic steatosis (nonalcoholic fatty liver disease). Bone densitometry findings indicated osteopenia of the left hip. Results from routine echocardiogram, electrocardiogram, and pulmonary function tests were all unremarkable.

Based on physical examination and laboratory findings, Ms. Jobin was diagnosed with posttransplant metabolic syndrome, meeting all five of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria (see Table 1).[18] Her health care team recognized that expedient management of her metabolic syndrome was crucial to lowering her CVD risk and prolonging survival.

RECOGNIZING NON-CVD–RELATED TREATMENT EFFECTS

Risk factors for adverse late and long-term treatment effects following allo-HSCT include preexisting comorbidities, pretransplant cancer treatment, type of transplant conditioning regimen, recipient characteristics (such as age at transplant), stem cell source, donor characteristics, and type of GvHD prophylaxis and treatment. Non-CVD–related treatment effects, in approximate descending order of frequency, include endocrine abnormalities, loss of vaccine-conferred immunity, skeletal effects, chronic kidney disease, pulmonary complications, ocular complications, and secondary malignancies. Early screening for symptoms of nonrelapse-related complications and recognition of modifiable risk factors for chronic disease can prolong disease-free survival and enhance survivors' quality of life.[19, 20]

Endocrine abnormalities, including posttransplant hypothyroidism and hypogonadism, often occur secondary to pretransplant conditioning.[8] One review puts the long-term prevalence of hypothyroidism in auto- and allo-HSCT survivors at 20% to 40%.[8] Current guidelines recommend performing thyroid function tests (including those that assess thyroid-stimulating hormone and free thyroxine levels) in allo-HSCT survivors annually, and more frequently in those with suspected symptoms.[11, 12] Gonadal failure often occurs following allo-HSCT as a result of radiation-related damage to the hypothalamic–pituitary axis or chemoradiotherapy-related damage to the gonads (or both).[19] In men, many centers screen for hypogonadism at one year posttransplant by assessing free and total testosterone levels, with free testosterone tested before 10 AM.[8] If a male survivor has symptoms of hypogonadism such as fatigue, erectile dysfunction, low libido, or bone loss, testosterone treatment may be initiated after confirmation through repeat testing.[8] It's important to note that, particularly in young male survivors, testosterone replacement can suppress spermatogenesis.[21] The ovaries are also vulnerable to

Table 1. ATP III Criteria for Clinical Identification of the Metabolic Syndrome in Adults

Risk Factor	Defining Level
Abdominal obesity	Waist circumference[a]
Men	> 102 cm (> 40 in.)
Women	> 88 cm (> 35 in.)
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/85 mmHg
Fasting glucose	≥ 110 mg/dL

HDL = high-density lipoprotein.
[a]Some men can develop multiple metabolic risk factors when waist circumference is only marginally increased (94–102 cm or 37–39 in.). These men may have a strong genetic contribution to insulin resistance.
Adapted from the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final Report.[18]

irradiation and chemotherapy. Studies have shown that almost all females who are older than 12 years when undergoing HSCT develop ovarian failure that is usually irreversible.[19,22] When two measurements of serum follicle-stimulating hormone levels, taken at least one month apart, are in the menopausal range, this is diagnostic of primary ovarian insufficiency or failure.[8] Unless contraindicated, hormone replacement therapy should be considered in premenopausal HSCT survivors to manage menopausal symptoms, preserve bone density, and (in those with some ovarian function) prevent endometrial hyperplasia.[8,20]

Loss of vaccine-conferred immunity. Following allo-HSCT, patients often lose immunity conferred by previous vaccinations. It's recommended that all allo-HSCT recipients undergo revaccination after immune system reconstitution has been achieved.[12,20] This is usually initiated around one year posttransplant, or whenever the patient's transplant team determines that the patient is a candidate for vaccine administration. A comprehensive immunization schedule is available free from the NMDP at https://bethematchclinical.org/Post-Transplant-Care/Vaccinations.

Skeletal effects. Loss of bone density is common following allo-HSCT, occurring in about 50% of patients.[23,24] Contributing factors include hypogonadism, glucocorticoid exposure, the use of calcineurin inhibitors, and calcium or vitamin D deficiency.[8] Current recommendations include evaluating bone density via dual photon densitometry within one year of transplantation in all allo-HSCT survivors.[11] Management of osteopenia and osteoporosis are the same as for the general population, but allo-HSCT recipients may need more frequent screening if they're on long-term immunosuppressive therapy or have a history of gastrointestinal (GI) GvHD (which can interfere with calcium absorption).[8] Avascular necrosis of the bone occurs when the blood supply to the bone is disturbed. Risk factors among allo-HSCT recipients include chronic GvHD, male sex, receiving donor cells from an unrelated donor, and taking certain immunosuppressive medications (including prednisone); onset may occur soon after the transplant or several years later.[19] Avascular necrosis is usually seen in areas with terminal circulation (such as the hip) and is painful, often requiring surgery.[19] There are no specific screening recommendations for avascular necrosis, but if a patient presents with new musculoskeletal pain, this should be considered in the differential diagnosis.

Chronic kidney disease in HSCT survivors is typically secondary to transplant conditioning regimens and immunosuppressive therapy.[19] Onset may be early or may be delayed for 10 or more years posttransplant.[25] In one study among HSCT survivors, chronic kidney disease was defined as "sustained elevation of serum creatinine inferring a glomerular filtration rate of < 60 mL/min/1.73 m^2 for three months or longer."[25] In part because definitions and lengths of follow-up have varied, reports of cumulative incidence have varied widely: from 7% to 10% among allo-HSCT survivors at up to five years posttransplant[25,26] and from 18% to 66% among both auto- and allo-HSCT survivors at up to 10 years posttransplant.[27] Current recommendations include regular (at least annual) assessment of blood urea nitrogen and creatinine levels and glomerular filtration rate, as well as urine protein analysis.[8,11] Renal biopsy should be considered in cases of "unclear" posttransplant chronic kidney disease.[8] Although allo-HSCT survivors may be screened more frequently than people in the general population with chronic kidney disease, management recommendations do not differ.

Pulmonary complications include obstructive changes (such as bronchiolitis obliterans syndrome) and restrictive changes (such as declining carbon monoxide diffusion capacity). Such changes occur in 30% to 60% of allo-HSCT survivors and are a major cause of nonrelapse-related mortality.[8,28] Chronic pulmonary changes can be insidious, although these are often detected on routine screening via pulmonary function tests during the first three to 24 months posttransplant. Contributing factors to obstructive changes include the pretransplant conditioning regimen and inflammatory conditions such as viral infections and chronic GvHD, whereas restrictive changes may result from extrinsic causes such as muscle weakness from long-term steroid use, pulmonary fibrosis, or sclerotic GvHD involving the thorax.[8,29] Although pulmonary changes are often identified early, before a patient returns to the community for long-term care, the functional effects

may last for years.[19] New developments in pulmonary symptoms should prompt pulmonary function tests, inspiratory and high-resolution expiratory chest computed tomography, a thorough evaluation for infectious disease, and echocardiography to assess pulmonary artery pressures.[8] Consultation with a pulmonary specialist should also be considered.

Ocular complications of HSCT include cataracts and glaucoma, which can occur secondary to immunosuppressive therapy and total body irradiation, as well as keratoconjunctivitis sicca (also called dry eye syndrome), which is often associated with chronic GvHD.[8, 30] One study found a cumulative incidence of cataracts in about 40% of allo-HSCT survivors at 15 years posttransplant.[31] Recommendations for long-term survivors include annual screening and ophthalmologic evaluation with fundoscopic examination, and more frequent assessments for those who are symptomatic.[11]

Secondary malignancies can have a significant impact on nonrelapse-related survival, with reported cumulative incidence among allo-HSCT survivors from 2% to 6% at 10 years posttransplant.[8] Such malignancies may result from chemotherapy or radiation received before allo-HSCT, the allo-HSCT conditioning regimen, immunosuppression, or immune dysregulation after transplantation.[8] Solid tumors noted most commonly in this patient population include skin, breast, head and neck, and thyroid cancers.[19, 20, 32] A study of more than 28,000 allo-HSCT survivors found that new solid cancers occurred at twice the rate expected in the general population, with the risk increasing over time.[32] Risk factors include having had total body irradiation, male sex, younger age at time of treatment, chronic GvHD, and pretransplant therapy.[8] It's recommended that allo-HSCT recipients should follow general-population screening guidelines for skin, cervical, breast, and colon cancers,[12] and that those with a history of chronic GvHD or who have received radiation should have "more systematic skin evaluations" and should be counseled on the importance of appropriate sun protection.[8] Routine dental evaluations should include assessment for head and neck cancers. Women who have received chest radiation or total body irradiation at levels of 800 cGy or higher should receive annual breast magnetic resonance imaging in addition to annual mammogram screening beginning at age 25 or eight years after radiation, whichever occurs later (but no later than age 40).[8, 12, 33]

For a list of both CVD- and non-CVD–related late and long-term treatment effects and risk factors, see Table 2.[8, 11, 12, 19, 34]

RECOGNIZING CVD AND CVD RISK–RELATED TREATMENT EFFECTS

There are several late and long-term treatment effects associated with a higher risk of CVD that can occur independently or in conjunction with one another, including diabetes mellitus, dyslipidemia, and hypertension.[8] Of particular interest is the metabolic syndrome, which, though not fully understood, has become increasingly common in the general U.S. population,[18] as well as in the allo-HSCT population.

Metabolic syndrome is not a disease, but rather a clustering of risk factors for disease. In the general population, the underlying causes of the metabolic syndrome are overweight or obesity, physical inactivity, and genetic factors.[18] In 2002, the ATP III published the *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*; in these guidelines, the metabolic syndrome was cited as a target for treatment aimed at reducing the risk of coronary heart disease.[18] The ATP III defines the metabolic syndrome as a constellation of metabolic risk factors or components, including insulin resistance with or without glucose intolerance (in which tissue responsiveness to the normal action of insulin is impaired), abdominal obesity, dyslipidemia, hypertension, a prothrombotic state, and a proinflammatory state. There is an increased risk of CVD and type 2 diabetes from the cumulative effect of these individual risk factors.[19] People with the metabolic syndrome are twice as likely to develop atherosclerotic CVD, and the presence of the metabolic syndrome signifies a higher risk of CVD than is predicted by its individual components.[35, 36]

Other components of the metabolic syndrome that aren't routinely measured but are common include elevated levels of apolipoprotein B and C-reactive protein, smaller low-density lipoprotein particle size, hyperuricemia, albuminuria, and variation in coagulation factors (such as plasminogen activator inhibitor and fibrinogen).[37-39] Although not currently considered an independent manifestation of the metabolic syndrome, nonalcoholic fatty liver disease is significantly associated with the components of the metabolic syndrome, and its prevalence increases with the number of such components present.[40]

Compared with the general population, allo-HSCT survivors may be more prone to certain metabolic risk factors. They may have hypothalamic–pituitary axis disturbances that result in hypogonadism and growth hormone deficiency, which in turn can play a role in the development of the metabolic syndrome.[19] Chemotherapy or radiation treatment can damage the vascular endothelium.[19, 36] Furthermore, prolonged immunosuppressive therapy (used to treat or prevent GvHD) with cyclosporine, sirolimus, mycophenolate, tacrolimus, or corticosteroids can induce dyslipidemia, glucose intolerance, and arterial hypertension.[19] Corticosteroids are known to increase insulin resistance, whereas cyclosporine and tacrolimus seem to affect insulin secretion.[41] Chronic liver GvHD may also potentiate dyslipidemia.[42] It's worth noting that in terms

Table 2. Common Adverse Late and Long-Term Treatment Effects and Risk Factors for Allo-HSCT Survivors[8, 11, 12, 19, 34]

Adverse Effects	Risk Factors
Cardiomyopathy	Pre-HSCT anthracyclines, chest radiation
Chronic kidney disease	High-dose methotrexate, calcineurin inhibitors, total body irradiation
Diabetes or impaired glucose metabolism	Total body irradiation, immunosuppressive therapy
Dyslipidemia	Total body irradiation, immunosuppressive therapy
Endocrine complications	Pre-HSCT radiation to thyroid gland, pre-HSCT alkylating agents, total body irradiation, gonadal irradiation, busulfan
GvHD	Unmodified allo-HSCT, mismatched donor
Hypertension	Total body irradiation, immunosuppressive therapy
Ocular complications	Cranial irradiation, total body irradiation, steroids, GvHD
Osteopenia or osteoporosis	Calcineurin inhibitors, corticosteroids, total body irradiation, prolonged hospitalization
Pulmonary dysfunction	Chest radiation, total body irradiation, GvHD
Sarcopenic obesity	Steroids, chemotherapy
Secondary malignancies	Pre-HSCT radiation therapy, total body irradiation, immunosuppressive therapy, GvHD, oncogenic viruses, prolonged immunosuppression

Allo = allogeneic; GvHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplantation.

of body mass index (BMI), long-term auto- and allo-HSCT survivors aren't typically overweight or obese. Indeed, the Bone Marrow Transplant Survivor Study found that the prevalence of obesity was lower in such survivors (16%) than in a sibling comparison group (20%), despite survivors' exposure to radiation, steroids, and prolonged periods of inactivity.[43] But although HSCT survivors may have normal BMIs, their body composition is often significantly altered. Many develop sarcopenic obesity, a condition characterized by increased fat mass and decreased muscle mass, resulting in an increase in adipocyte insulin receptors and a loss of myocyte insulin receptors.[44] The latter are less efficient in binding insulin and clearing glucose, thereby contributing to insulin resistance.

Among adult long-term survivors of HSCT, metabolic syndrome is common. One review reported that 34% to 49% of such survivors had one or more components of the syndrome.[19] And in a cross-sectional study by Majhail and colleagues of allo-HSCT recipients (median follow-up, three years), the overall prevalence of the metabolic syndrome was 49%, more than twice that for age- and gender-matched controls.[36] That study also found that 78% of allo-HSCT recipients had at least two components of the metabolic syndrome. The prevalence of hypertension and hypertriglyceridemia was significantly higher in allo-HSCT recipients than in controls, although there were no significant differences in the prevalence of abdominal obesity, elevated blood glucose, or low HDL cholesterol levels between groups; and no specific patient, donor, or transplant characteristics were associated with the development of the metabolic syndrome. It's important to note that in this study, insulin resistance, hypertension, and dyslipidemia tended not to resolve with time and withdrawal of immunosuppressive therapy.

In an Italian study of auto- and allo-HSCT recipients (median follow-up, nine years), 34% met the ATP III criteria for the metabolic syndrome,[45] more than twice the 15% expected for an age-matched sample from the general population.[41] Another study found the incidence of diabetes in allo-HSCT recipients to be 3.65 times greater than in a sibling comparison group.[43] This risk tended to be associated with exposure to total body irradiation. Metabolic syndrome in allo-HSCT survivors still isn't well understood, and more research is needed to identify which subgroups are at highest risk.[36]

Heart disease. Independently of their greater propensity for the metabolic syndrome, both auto- and allo-HSCT recipients are at increased risk for death from cardiac-related causes—including cardiomyopathy, congestive heart failure, pericarditis, arrhythmias,

and valvular dysfunction, as a result of prior chemotherapy, the pretransplant conditioning regimen, posttransplant immunosuppression, GvHD, or a combination of these.[6, 7, 19, 46, 47] Furthermore, CVD events, including cerebrovascular disease and coronary artery disease, are common and typically occur earlier than is expected in the general population.[19, 43, 48] It's reported that the cumulative incidence of CVD "approaches 23% at 25 years after HSCT in certain high-risk populations" and is highest in allo-HSCT recipients, with incidence rising as time passes.[8, 19] One case–control study in auto- and allo-HSCT recipients (median follow-up, 7.3 years) found that "the presence of two or more of the four targeted cardiovascular risk factors (obesity, dyslipidemia, hypertension, and diabetes) was significantly and independently associated with a greater than five-fold . . . increased risk of CVD."[46]

Over time, HSCT survivors who develop the metabolic syndrome or one or more of its components will be at even greater risk for cardiac complications, making early recognition and management of CVD risk factors crucial for reducing morbidity and mortality. Long-term survivors of allo-HSCT should undergo routine screening for CVD risk factors, including impaired glucose metabolism or diabetes, dyslipidemia, hypertension, and the metabolic syndrome.[8, 11, 19] Tests should include blood pressure measurement at each clinic visit, abdominal girth measurement at least annually, and a fasting lipid panel and comprehensive metabolic panel (with fasting glucose) annually. It's important to note that although glycated hemoglobin (HbA_{1c}) levels are commonly used in evaluating chronic hyperglycemia in the general population, these levels may be falsely depressed in patients with anemia. Patients on long-term immunosuppressive therapy for GvHD treatment or prophylaxis may require more frequent fasting glucose, lipid, and blood pressure monitoring.

MANAGING CVD RISK FACTORS IN ALLO-HSCT SURVIVORS

Because of a lack of randomized trials testing diagnostic and treatment approaches for late and long-term effects specific to allo-HSCT survivors, and only limited published guidelines, relevant general medicine studies are often used to guide treatment of such effects (with the exception of GvHD), including CVD risk factors.[8] Long-term allo-HSCT survivors require earlier intervention for CVD risk factors, regardless of age.[8] Proper management of CVD risk factors such as diabetes, dyslipidemia, and hypertension (whether they occur independently or as part of the metabolic syndrome) has been shown to reduce the risk of CVD events and improve survival in the general population and may help to do the same in allo-HSCT survivors.[8]

Lifestyle modifications. Current guidelines for the management of the metabolic syndrome or its individual components emphasize addressing root causes (specifically obesity and physical inactivity) with therapeutic lifestyle changes—including dietary modifications, decreased alcohol intake, smoking cessation, and regular exercise—as first-line therapy.[38] Although many allo-HSCT survivors with the metabolic syndrome or independent CVD risk factors aren't overweight or obese based on BMI, these lifestyle changes will still help to address sarcopenic obesity and minimize CVD risk factors.

Allo-HSCT survivors who are overweight or obese should be counseled on long-term weight loss. It's well known that "crash" diets or those involving extreme caloric reduction are seldom effective. A more sustainable plan, aimed at achieving a 7% to 10% reduction in weight over the course of six to 12 months, is recommended.[38] According to Grundy and colleagues, a review of several clinical trials "showed that the combination of weight reduction and increased physical activity can halve progression to new-onset diabetes over a period of several years."[38] In the absence of a specific diet shown to have the greatest impact on all of the components of the metabolic syndrome, patients should adhere to a "heart-healthy" diet such as those recommended by the American Heart Association (AHA) and the Physicians Committee for Responsible Medicine.[49, 50] The National Heart, Lung, and Blood Institute and the AHA further recommend limiting total fat to 25% to 35% of daily caloric intake and saturated fat to less than 7% of daily caloric intake; trans fat should be avoided.[35] The National Comprehensive Cancer Network (NCCN) Survivorship Guidelines also recommend that carbohydrates constitute 45% to 65% of daily caloric intake, focusing on vegetables, fruits, and whole grains; and that lean protein constitute 10% to 35% of daily caloric intake (or about 0.8 g/kg of body weight).[51] Consumption of processed foods and simple sugars, sodium, and red or processed meat should be limited.

Allo-HSCT survivors become significantly deconditioned during the transplant process, making a return to an active lifestyle particularly challenging. Yet it's been demonstrated that regular exercise and physical fitness can ameliorate several metabolic risk factors.[38] The NCCN Survivorship Guidelines recommend at least 150 minutes per week of moderate-intensity aerobic activity (such as brisk walking) or 75 minutes per week of vigorous-intensity aerobic activity (such as jogging), or an equivalent combination.[51] Strength training of all major muscle groups should also be performed at least twice weekly to build lean muscle mass (especially important in preventing sarcopenic obesity). Specific recommendations can be individually tailored, taking into consideration factors such as time elapsed since the transplant and immune system function, as well as any transplant-related complications, such as GvHD, steroid-induced myopathy, or peripheral neuropathy, as well as unresolved posttransplant anemia or thrombocytopenia. All patients

should strive to increase their activity level safely and as tolerated. A daily exercise session of 30 minutes could be broken into shorter segments (such as three 10-minute or two 15-minute periods) if need be, although aerobic activity should be performed in segments lasting at least 10 minutes.[11]

Pharmacologic management. In patients for whom lifestyle modifications alone prove insufficient, secondary treatment involves pharmacologic management of CVD risk factors, including dyslipidemia, hypertension, and a prothrombotic state. Generally patients should attempt therapeutic lifestyle changes for three months; if the targeted conditions persist, pharmacologic management can be initiated. Lifestyle modifications should be emphasized both before and in concert with pharmacologic therapy.

In 2013, the American College of Cardiology (ACC) and the AHA jointly issued a new evidence-based guideline specifically aimed at the treatment of blood cholesterol levels to reduce atherosclerotic CVD in adults.[52] According to this guideline, atherosclerotic CVD includes coronary heart disease, stroke, and peripheral arterial disease, "all of presumed atherosclerotic origin." Its recommendations highlight statins as the cornerstone of management; indeed, in a departure from ATP III recommendations, this guideline emphasizes using moderate- or high-intensity fixed-dose statin therapy, rather than titrated doses of statins or other cholesterol-lowering drugs, to address atherosclerotic CVD. Such therapy is recommended for those patients who are most likely to experience a net benefit, considering both the potential for lowering their risk of atherosclerotic CVD and the potential for adverse medication effects. The guideline further identifies four "statin benefit groups"—patients for whom, according to research findings, the benefits of statin therapy outweigh the risks.

Although these groups don't specifically include allo-HSCT recipients, they do include patients with an estimated 10-year risk of atherosclerotic CVD greater than or equal to 7.5%.[52] Since experts consider allo-HSCT to be a CVD risk factor, "similar to hypertension, hyperlipidemia, advancing age, smoking, and family history of CVD, given evidence that HSCT recipients have a 10-year incidence of CVD of more than 10%,"[8] it seems appropriate to apply the ACC/AHA guideline to this patient population. It should be noted that there is some evidence that statins increase the risk of developing type 2 diabetes; but after evaluating data from Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, investigators concluded that "the cardiovascular and mortality benefits of statin therapy exceeded the diabetes hazard."[53] Caution should be used when initiating statins in survivors who are on long-term immunosuppressive therapy, because both statins and immunosuppressants are metabolized through the cytochrome P450 3A4 pathway, which can increase the risk of myopathy and rhabdomyolysis.[54] For the complete ACC/AHA guideline, visit www.guideline.gov/content.aspx?id=48337. A companion tool for estimating 10-year and lifetime risk for atherosclerotic CVD is available at http://bit.ly/1uGpcMK.

The main goal of hypertension treatment is to achieve the target blood pressure, which may require using one or more antihypertensive agents. According to the Eighth Joint National Committee's *2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults*, for adults ages 60 and older with a systolic blood pressure of 150 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher, pharmacotherapy should be initiated to reach systolic and diastolic blood pressure targets of less than 150 mmHg and less than 90 mmHg, respectively.[55] For adults younger than age 60 with a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure of 90 mmHg or higher, pharmacotherapy should be initiated to reach systolic and diastolic blood pressure targets of less than 140 mmHg and less than 90 mmHg, respectively. Patients 18 years of age and older who have diabetes or chronic kidney disease should be treated to reach systolic and diastolic blood pressure targets of less than 140 mmHg and less than 90 mmHg, respectively.

Although this guideline doesn't specifically address treating people with both hypertension and the metabolic syndrome, it recommends that "in the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker" and "in the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker."[55] It also recommends that antihypertensive treatment for all adult patients with chronic kidney disease, regardless of race or diabetes status, include an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for their renal protective effects.

While a prothrombotic state isn't routinely assessed in clinical practice, the AHA recommends low-dose aspirin prophylaxis in most patients—including those with the metabolic syndrome—whose 10-year risk of coronary heart disease is 10% or greater as determined by Framingham risk scoring.[35] Since thrombocytopenia is common in the early posttransplant stages, platelet counts must be taken into account when determining whether aspirin prophylaxis is appropriate.

Although drugs that reduce insulin resistance are often used in clinical practice, as yet there is no clear evidence that they reduce the risk of coronary heart disease in people with impaired glucose metabolism or the metabolic syndrome.[18] That said, the Diabetes Prevention Program, a multicenter study conducted by

the National Institute of Diabetes and Digestive and Kidney Diseases, found that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes.[56] For allo-HSCT survivors with type 2 diabetes and without anemia, hemoglobin variation, or recent transfusions, the treatment goal is generally a reduction in HbA_{1c} levels to less than 7%, with minimal hypoglycemia.[8] In cases when anemia makes HbA_{1c} testing unreliable, fructosamine measurement can be considered.[54] Because insulin doesn't interact with other medications and daily dosage is adjustable, it's the preferred agent for short-term use and for patients who are medically unstable.[8] Oral hypoglycemic agents may be used in medically stable patients unless contraindicated.[41] Patients with both type 2 diabetes and the metabolic syndrome are at particularly high risk for CVD. For such patients, treatment of dyslipidemia and hypertension is essential in mitigating that risk.[38]

Management of endocrine abnormalities such as hypothyroidism and hypogonadism may also help to lower CVD risk. As Rovo and Tichelli have stated, for post-HSCT survivors with such abnormalities, hormonal supplementation "may have a beneficial and additive effect to the standard treatment on lipid profile, glucose tolerance, and body fat."[57] They also note that such treatment "should not be an argument to postpone the specific treatment of dyslipidemia, diabetes, or hypertension."

NURSING IMPLICATIONS FOR CVD RISK FACTORS

Evaluation and management of the metabolic syndrome and its component CVD risk factors in this complex population often requires a multidisciplinary approach. Although management recommendations are generally the same as for the general population, more frequent screening may be necessary, particularly if the survivor is on prolonged immunosuppressive therapy. Early identification and management of existing risk factors is crucial to improving outcomes; and early posttransplant counseling about lifestyle modifications is crucial to prevention. Nurses and other health care providers have vital roles in educating patients on both prevention and management, assessing barriers to lifestyle modifications and supporting behavior change.

Studies have shown that only about 20% to 40% of cancer survivors will be physically active after they recover from treatments.[58,59] Allo-HSCT recipients typically experience extreme deconditioning during the peritransplant period; a return to activity as soon as possible after transplant, with increased activity as tolerated, should be encouraged. Modifications may need to be made for patients who are immunosuppressed, thrombocytopenic, anemic, or similarly challenged. For example, to minimize the risk of infection, a patient who is still severely immunocompromised should avoid gym workouts; walking outside and stretching or strength-training exercises done at home are often acceptable. Patients who are severely anemic should limit exertion to only that necessary for activities of daily living until hemoglobin levels have improved. Patients whose pulmonary function tests indicate restrictive lung disease or declining carbon monoxide diffusion capacity (generally under 40%) are at risk for desaturation with exertion and should be monitored and counseled appropriately.[8]

Allo-HSCT survivors should be routinely assessed for treatment-related effects such as peripheral neuropathy, steroid-induced myopathy, osteoporosis, and avascular necrosis, which may make exercising difficult and unsafe, and should be referred to appropriate specialists for management. Most survivors won't be able to meet long-term exercise goals during the early posttransplant period, but nurses can teach them how to work progressively toward these goals. Nurses can also provide support and encouragement during this time, when patients often become discouraged by the slow pace of recovery and frustrated by their inability to immediately resume their usual daily activities. Referral to a physical therapist or to a personal trainer experienced in working with cancer survivors should be considered, as they can create individualized exercise regimens and facilitate patient adherence. This is especially important in ensuring the safety of patients with long-term treatment-related effects such as steroid-induced myopathy or GvHD-related joint contracture. Patients should also be encouraged to report any new symptoms that arise when they begin an exercise program.

Long-term survivors of allo-HSCT should undergo routine screening for CVD risk factors.

Many allo-HSCT survivors (whether overweight or not) lose a significant amount of weight during the peritransplant period as a result of anorexia, nausea, vomiting, or other GI disturbances, which can be caused by GI GvHD, chemotherapy, or other medications' side effects. In trying to maintain their weight, patients often turn to processed, calorically dense but nutrient-poor foods, and these can further exacerbate the metabolic changes associated with total body irradiation and immunosuppressive therapy. Patients should be counseled about following the aforementioned heart-healthy diet. In particular, they should focus on eating lean protein (such as legumes and lean cuts of meat or fish); complex carbohydrates (such as brown rice); vegetables and fruits; and mono- and polyunsaturated fats (such as olive oil and unsalted nuts). (Note that during the peritransplant period, a

more restricted, low-microbial diet is often advised.) Patients who are overweight or obese may need additional support in reaching and maintaining a healthy weight. Nurses can further advise patients that proper nutrition and good hydration will help them to manage fatigue, and may quicken their progress in meeting physical activity goals.

Although addressing GvHD lies beyond the scope of this article, it's worth noting that many patients with GvHD experience significantly altered body composition, and may require more frequent nutritional assessments. GvHD is a hypercatabolic state characterized by increased circulating proinflammatory cytokines, contributing to extensive loss of lean muscle mass.[60] And patients with GI GvHD will have reduced ability to absorb nutrients and difficulty maintaining weight. Referral to a dietician, ideally a certified specialist in oncology nutrition, may be warranted.

Patients should also undergo routine assessment for tobacco and alcohol use. Those using tobacco should be referred for smoking cessation counseling. Alcohol consumption should be limited to no more than one drink per day for women and two drinks per day for men, if not otherwise contraindicated.

Difficulty sleeping is a common complaint among allo-HSCT survivors (and among cancer survivors in general). The relevant literature suggests that chronic sleep deprivation can increase the likelihood of developing hypertension and obesity, among other health risks.[61,62] Routine assessment of sleep and management of insomnia may help to lower these and other cardiac risk factors.

Thorough evaluation of psychosocial barriers to behavior change, such as depression, anxiety, posttraumatic stress disorder, lack of social support, and financial difficulties, is essential. Nurses can further support patients by teaching them stress management techniques and helping them to identify sources of social support. Some survivors may require evaluation and management by a mental health professional. Social workers can often provide recommendations and resources for managing financial burdens. Cancer support groups can provide peer support and education, offering hope and fostering motivation for behavior change.

Clinician and Patient Resources

American Heart Association
Offers various resources on eating a heart-healthy diet.
www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Nutrition-Center_UCM_001188_SubHomePage.jsp

Blood and Marrow Transplant Information Network
Provides transplant survivors and their loved ones easy-to-understand information, emotional support, and long-term follow-up recommendations.
www.bmtinfonet.org

Center for International Blood and Marrow Transplant Research (CIBMTR)
Together with other transplant organizations, the CIBMTR (www.cibmtr.org) has developed posttransplant care recommendations for survivors of autologous and allogeneic hematopoietic stem cell transplantation. Clinician and patient versions are available at www.cibmtr.org/ReferenceCenter/Patient/Guidelines/pages/index.aspx.

Commission on Dietetic Registration
The commission offers a list of board-certified specialists in oncology nutrition, by state: https://ams.eatright.org/eweb/DynamicPage.aspx?Site=CDRNEW&Webkey=8EADAFE4-F1E1-4309-B21C-66D3C-C2AA112.

National Comprehensive Cancer Network
Provides cancer survivorship guidelines for clinicians, and nutrition and exercise recommendations for cancer survivors.
www.nccn.org

National Marrow Donor Program: Be the Match
Offers various clinician and patient resources, including patient education materials (www.bethematch.org). Clinician and patient guidelines are available at https://bethematchclinical.org/Post-Transplant-Care/Long-Term-Care-Guidelines.

Physicians Committee for Responsible Medicine
Offers *USDA Dietary Guidelines 2015: The Sustainable Power Plate*, a visual guide emphasizing plant-based foods.
www.pcrm.org/health/diets/pplate/dietary-guidelines-usda-sustainable-power-plate

CASE REVISITED: MANAGEMENT

The health care team took several actions aimed at managing Ms. Jobin's metabolic syndrome and lowering her risk of CVD. First, she was extensively counseled on therapeutic lifestyle modifications. Emphasis was placed on increasing exercise, as her daily activity was limited to housework. At the time of her first survivorship appointment, she had achieved near-complete immune system reconstitution and did not have anemia, peripheral neuropathy, or any other musculoskeletal complaints that would make exercise unsafe. She was encouraged to slowly increase her physical activity, with a goal of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity exercise weekly. Given the finding of osteopenia, the importance of weight-bearing exercise was emphasized. It was further recommended that she undertake two to three sessions of strength training weekly to improve her lean muscle mass.

Ms. Jobin was also referred to a dietician specializing in oncology care, who created a meal plan aimed at helping her to lose one to two pounds per week. Other dietary recommendations included limiting

high-calorie snacks, increasing fiber intake, maintaining adequate hydration, and consuming lean protein with all meals and snacks. After three months, physical examination and laboratory findings showed that despite improvement in some areas, she still met three of the five ATP III criteria, indicating persistent metabolic syndrome.

Ms. Jobin was referred to an endocrinologist for further management of the metabolic syndrome and to a gastroenterologist for management of nonalcoholic fatty liver disease. The endocrinologist started her on a statin, taken daily, and she continued working with the dietician by telephone. The gastroenterologist speculated that Ms. Jobin's liver disease was related to the metabolic syndrome, and she was further counseled about the importance of weight loss and limited alcohol intake in preventing progression to cirrhosis and reducing the risk of hepatocellular carcinoma. Because she had expressed persistent fears about the possibility of a recurrence of leukemia, referral to the psychiatry department for evaluation and management of anxiety was offered. But she preferred to minimize hospital appointments, so she was referred for a telephone consultation with a social worker who specialized in working with cancer patients. The social worker helped her to find local resources, including a therapist and a cancer survivors' support group. Ms. Jobin will continue to visit the survivorship clinic every six to 12 months for follow-up.

CONCLUSION

This article has focused mainly on adverse treatment-related effects that contribute to increasing allo-HSCT survivors' risk of CVD, particularly because these may be modified or mitigated with behavior change. The prevention, evaluation, and management of CVD risk factors in this patient population require a multidisciplinary approach. Although allo-HSCT survivors are at higher risk for many medical problems, including diabetes, metabolic syndrome, and CVD, they are no more likely than controls to adhere to recommendations for routine health screenings.[63] Because many allo-HSCT survivors return to the community for posttransplant care, it's imperative for both oncology and nononcology nurses and other providers to recognize the heightened risks faced by these patients and to encourage them not to miss recommended screenings. Dieticians, physical therapists, athletic trainers, mental health specialists, and social workers specializing in oncology care can be useful adjuncts in such efforts.

The NMDP's comprehensive long-term care guidelines include recommendations for CVD risk factor assessment annually or more often.[11] These are broken down by organ system and contain screening recommendations for specific adverse, long-term treatment effects. Experts further recommend lifelong follow-up for this patient population.[7] For links to patient and clinician versions of existing guidelines and recommendations, as well as other resources, see *Clinician and Patient Resources*. ▼

For five additional continuing nursing education activities on topics about cancer survivors, go to www.nursingcenter.com/ce.

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