

Review of Chronic Graft-Versus-Host Disease in Children After Allogeneic Stem Cell Transplantation: Nursing Perspective

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Abstract

This review presents a summary of the research literature related to the incidence and risk factors for chronic graft-versus-host disease in children following allogeneic hematopoietic stem cell transplantation. The range of incidence of chronic graft-versus-host disease in children found in this review was large, from 0% to 46%. Incidence of chronic graft-versus-host disease was influenced by sample size, time posttransplantation, and stem cell source. Characteristics of the person (eg, child's age and gender) and disease/treatment (eg, sources of transplant) are associated with chronic graft-versus-host disease in children after stem cell transplantation. Person and disease/treatment characteristics provide a framework for understanding the factors associated with chronic graft-versus-host disease symptom experiences in children after stem cell transplantation. Timely assessment of presenting chronic graft-versus-host disease symptoms is critical for treatment and prognosis. Nursing interventions should focus on educating children and parents about the signs and symptoms of chronic graft-versus-host disease. The summary of supportive nursing care for children with chronic graft-versus-host disease provides important information to tailor effective management strategies for children with chronic graft-versus-host disease.

Keywords

allogeneic hematopoietic stem cell transplantation, chronic graft-versus-host disease, children, incidence, risk factors

Introduction

Hematopoietic stem cell transplantation (HSCT) has emerged as an aggressive treatment for life-threatening hematological, oncological, and genetic disorders in children. HSCT ranks as one of the most remarkable therapeutic advances of the past 40 years (Sharma, Singh, Prasad, & Fletcher, 2009). With increasing numbers of long-term survivors, delayed complications, often presenting years after transplantation, are becoming an increasing concern (Leiper, 2002). Chronic graft-versus-host disease (GVHD) is a major complication affecting long-term survivors of allogeneic HSCT. This review of chronic GVHD in children post-HSCT describes the diagnosis and staging, pathobiology, incidence, risk factors, management, and implications for future research.

Diagnosis and Staging of Chronic GVHD

GVHD can be conceptualized as both an acute and chronic illness. On the basis of earlier publications, acute GVHD

was defined as occurring before day 100 posttransplant, whereas chronic GVHD happened after 100 days (Ferrara, Levine, Reddy, & Holler, 2009; Filipovich et al., 2005). However, these previous definitions are not all-inclusive. For example, acute GVHD may present beyond 3 months in patients who have received reduced-intensity conditioning therapy that prevents suppressive rejection reactions, and manifestations of acute and chronic GVHD can be present simultaneously (Filipovich et al., 2005; Mielcarek et al., 2003). The recent National Institutes of Health (NIH) Consensus Conference suggests distinguishing 2 categories of GVHD: (1) acute GVHD (absence of features consistent with chronic GVHD) comprising (a) classic acute GVHD (before day 100) and (b) persistent,

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Table 1. Signs and Symptoms of Chronic GVHD^a

Organ or Site	Diagnostic Sign	Distinctive Sign
Skin	Poikiloderma; lichen planus–like features; sclerotic features; morphea-like features; lichen sclerosus–like features	Depigmentation
Nails		Dystrophy; longitudinal ridging, splitting, or brittle features; onycholysis; pterygium unguis; nail loss (usually symmetric, affects most nails)
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy); scaling, papulosquamous lesions
Mouth	Lichen-type features; hyperkeratotic plaques; restriction of mouth opening from sclerosis	Xerostomia; mucocele; mucosal atrophy; pseudomembranes
Eyes		New onset dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; confluent areas of punctate keratopathy
Genitalia	Lichen planus–like features; vaginal scarring or stenosis	Erosions; fissures; ulcers
GI tract	Esophageal web; strictures or stenosis in the upper to midthird of the esophagus	
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology
Muscles, fascia, joints	Fasciitis; joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis

Abbreviations: GVHD, graft-versus-host disease; GI, gastrointestinal; PFTs: pulmonary function tests.

^aAdapted from Filipovich et al. (2005).

recurrent, or late acute GVHD (after day 100, often on withdrawal of immunosuppression); and (2) chronic GVHD comprising (a) classic chronic GVHD (no signs of acute GVHD) and (b) an overlap syndrome, in which features of both acute and chronic GVHD are present (Filipovich et al., 2005).

It is evident that a consistent classification of chronic GVHD needs to be used. There are differences between the recently published NIH consensus criteria and the traditional 100-day time point on diagnosis of chronic GVHD. Jagasia and others (2007) reported that 73 patients were classified as having chronic GVHD by using the 100-day time point diagnosis criteria. More than one third ($n = 27$) of these patients were reclassified as persistent, recurrent, and delayed acute GVHD by using the NIH criteria. The incidence of chronic GVHD by using the time point may be underestimated.

NIH standardizes the criteria for diagnosis of chronic GVHD (Table 1). The criteria require at least 1 diagnostic sign found only in patients with chronic GVHD and not in acute GVHD or at least 1 distinctive sign that is highly suggestive of chronic GVHD together with laboratory or biopsy confirmation in the same or another organ (Filipovich et al., 2005). Meanwhile, the NIH Consensus recommends a system for scoring chronic GVHD manifestations

in organs and sites, including the skin, mouth, eyes, gastrointestinal tract, liver, lungs, joints and fascia, genital tract, and performance, on a 0 to 3 scale (Filipovich et al., 2005). A global staging of severity (none, mild, moderate, severe) is derived by combining organ-specific scores (Filipovich et al., 2005). This system is intended to assess the clinical severity and functional impact of chronic GVHD.

Chronic GVHD can be progressive, meaning active or acute GVHD merges into a chronic stage; quiescent, meaning acute disease that resolves completely but is followed later by a chronic stage; or a de novo presentation that develops without prior acute GVHD (Bishop, 2009; Ferrara et al., 2009).

The diagnosis and staging of chronic GVHD have significant implications for HSCT nurses. Timely and accurate assessment of presenting specific chronic GVHD symptoms is critical to treatment and prognosis. Chronic GVHD occurs frequently after children are discharged from hospital. Nursing interventions should focus on educating children and parents about the signs and symptoms. In Table 2, we present the signs and symptoms that should be taught to children and parents. It is essential for children and parents to learn the signs and symptoms that should prompt early contact with the physicians responsible for care.

Table 2. Teaching Physical Signs and Symptoms of Chronic GVHD to Children and Parents

Sites	Signs and Symptoms to Observe
Skin	Check for skin changes: skin color may deepen and the texture becomes very hard or thick; a rash and itching may occur; the skin may become scaly; the skin may heal by scarring; hair loss may accompany the skin injury
Eyes and mouth	Look for dry eyes: no tears, constant rubbing and blinking; sensitivity to light; difficulty seeing clearly; the inside of the mouth may become excessively dry and sensitive with sores; ulcers may occur
Breathing	Look for chronic cough; colored sputum; feeling short of breath with either exercise or rest
Eating and digestion	Watch for difficulty swallowing or a sensation that food becomes caught in the throat; nausea/vomiting; diarrhea; poor appetite; abdominal pain; unexplained weight loss
Muscles and joints	Look for joint and muscle aches; the motion of nearby joints may be restricted; muscle cramps; weak muscles
Energy	Watch for being easily fatigued; needs to sleep more

Abbreviations: GVHD, graft-versus-host disease.

Pathobiology of Chronic GVHD

The pathobiology of chronic GVHD is poorly understood because of the lack of highly satisfactory animal models and basic clinical studies in patients (Ferrara et al., 2009; Kansu, 2004). Chronic GVHD presents as a multiorgan and autoimmune-like disease (Kansu, 2004). In children, the thymus plays a critical role in preventing autoimmunity by generating T-cells that are not responsive to autoantigens (Kansu, 2004). Immature T-cell precursors travel from the bone marrow into the thymus and undergo a phase of intense proliferation. Within the thymus, thymocytes give rise to double-positive cells expressing CD4⁺CD8⁺ antigens. These double-positive cells undergo a process referred to as negative selection or apoptosis (Kansu, 2004). Only a few CD4 or CD8 single-positive cells survive this negative selection and leave the thymus (Kansu, 2004). This apoptotic process eliminates the majority of autoreactive lymphocytes. Chronic GVHD may be the result of autoreactive T-cells that escape negative selection in the thymus damaged by a pretransplant conditioning regimen. These T-cells remain alive for a sufficient amount of time to initiate an immune reaction against certain target organs and cause significant and clinically noticeable organ damage (Parkman & Weinberg, 2004). In chronic GVHD, organ-specific autoimmunity develops because autoreactive T helper 2 (Th2) cells can initiate a response against autoantigens leading to B-cell hyperactivity and production of autoantibodies, causing target-organ damage, including skin, mucosa, eyes, joints, and liver (Lee, Vogelsang, & Flowers, 2003).

Once GVHD is initiated, T-cells produce additional proinflammatory cytokines, including tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and interleukin (IL)-2, which in turn attract more T-cells to continue the cycle of tissue destruction (Joseph, Couriel, & Komanduri, 2008).

Fibrosis that often characterizes tissue involvement in chronic GVHD is likely to be mediated by other cytokines, including tissue growth factor (TGF)- β , IL-4, and IL-3; each of these cytokines is both immunomodulatory and fibrogenic (Joseph et al., 2008). Zhang and colleagues (2006) showed that CD25⁺CD4⁺ T- and B-cells are required for chronic GVHD to develop. Although IL-12 may enhance chronic GVHD development, IL-18 may interfere (Kansu, 2004).

Incidence of Chronic GVHD

Based on the findings from a literature review, we see that older recipient age is recognized as a risk factor for chronic GVHD, and a lower incidence of chronic GVHD may be expected in children. On the other hand, there have been significant advances in therapeutic approaches for HSCT over the past decade (Joseph et al., 2008). Decreases in early mortality have led to a greater number of individuals surviving the early post-HSCT period and, thus, having the potential to develop chronic GVHD (Joseph et al., 2008). To present the incidence of chronic GVHD in children postallogeneic HSCT in the past decade, this review was restricted to the current literature from 2000 to 2009. The electronic databases PubMed, CINAHL, and ProQuest Nursing Allied Health were searched using the keywords "chronic GVHD" and "incidence." Limits were set on the searches in children (younger than 19 years) after allogeneic HSCT and restricted to articles that have been published since 2000 in the English language. Review articles and student theses were excluded. In total, 89 references were identified electronically and were read in detail. A total of 13 research studies emerged that were relevant to incidence and chronic GVHD in children postallogeneic HSCT and were summarized in Table 3. Study sample sizes ranged from 8 to 1779.

Table 3. Incidence of Chronic GVHD in Children After Allogeneic Stem Cell Transplantation

Study	Number of Patients	Age Range of Patients (years)	Pretransplant Disease	End Point After HSCT	Cumulative Incidence of Chronic GVHD (%)				
					PBSCT	BMT	UCBT	Overall	Overall
Madero et al., (2000)	8 (BMT), 12 (PBSCT)	<16	ALL	100 days	41.7	37.5			
Rocha et al., (2000)	93 (UCBT), 1779 (BMT)	≤15	Malignant and nonmalignant disease	3 years		15		6	
Thomson et al., (2000)	15	<18	Malignant and nonmalignant disease	365 days				0	
Rocha et al., (2001)	262 (UBMT), 180 (T-UBMT), 99 (UCBT)	2.5-12	Acute leukemia	2 years			46 (UBMT), 12 (T-UBMT)	22	
Zecca et al., (2002)	696	0.3-17	Malignant and nonmalignant disease	3 years					27
Iravani et al., (2005)	140	2-16	β Thalassemia major	1361 days (mean)					30
Wall et al., (2005)	23	0.5-3.9	Leukemia or myelodysplastic syndrome	1 year				26	
Bradley et al., (2007)	13	0.33-20	Malignant and nonmalignant disease	1200 days				16.7	
Satwani et al., (2007)	29	0.5-17.5	ALL	4 years		3.7			
Strahm et al., (2007)	16	1.8-17.3	Myelodysplastic syndrome	100 days					19
Fagioli et al., (2008)	59	0.2-17	Relapsed AML	16 months					29
Kurtzberg et al., (2008)	179	≤18	Hematological malignancy	2 years				20.8	
Huang et al., (2009)	52	3-14	Hematological malignancy	904 days					45.6

Abbreviations: GVHD, graft-versus-host disease; PBSCT, peripheral blood stem cell transplantation; BMT, bone marrow transplantation; UBMT, unrelated bone marrow transplantation; T-UBMT, T-cell-depleted bone marrow transplantation; UCBT, umbilical cord blood transplantation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

The time range for evaluating chronic GVHD was from 100 days to 4 years after transplantation, and incidence in these studies ranged from 0% to 46%. There remains marked heterogeneity in sample size, time posttransplantation, and stem cell source in the pediatric population, making the true estimate of chronic GVHD incidence difficult to quantify (Higman & Vogelsang, 2004). Further research is needed to examine the incidence of chronic GVHD in children after HSCT. Considerations specific to the incidence include sources of transplantation and the time point of assessment.

Risk Factors for Chronic GVHD

The main purpose of this article is to report the evidence of risk factors for chronic GVHD in children postalloge-
neic HSCT. The electronic databases PubMed, CINAHL, and ProQuest Nursing Allied Health were searched using the keywords "risk factors," "chronic GVHD," and "stem cell transplantation." No limits were set on the searches in terms of date or publication type, but only English language articles and studies involving children were selected. In total, 77 references were identified and 10 research studies reported evidence of a relationship between risk factors and chronic GVHD (Table 4). Two categories emerged from the findings of the literature reviewed, including person and disease/treatment.

Person

Person variables that contribute to the rising incidence of chronic GVHD include older age of recipients and transplantation from a female donor to a male recipient (Carlens et al., 1998; Kondo, Kojima, Horibe, Kato, & Matsuyama, 2001; Randolph, Gooley, Warren, Appelbaum, & Riddell, 2004; Remberger et al., 2002; Watanabe et al., 2008). Carlens and others (1998) analyzed 34 risk factors for chronic GVHD after bone marrow transplantation (BMT) in a group of adult and pediatric patients. Older recipient age was the single most important risk factor, consistent with other publications. After adolescence, thymus function deteriorates and places these patients at a high risk for chronic GVHD (Richards, Morgan, & Hillmen, 1999).

Mismatched minor histocompatibility antigens (mHags) that are encoded by genes on the Y chromosome may cause GVHD (Falkenburg, van de Corput, Marijt, & Willemze, 2003). Transplantation of stem cells from a female donor to a male recipient is a special circumstance in which Y-chromosome-encoded proteins may be recognized in the setting of a mismatched gender combination (Falkenburg et al., 2003).

Disease/Treatment

The disease and treatment variables include pretransplant diagnosis, sources of transplant, and history of acute GVHD (Carlens et al., 1998; Cutler et al., 2001; Eapen et al., 2004; Kondo et al., 2001; Randolph et al., 2004; Remberger et al., 2002; Remberger et al., 2005; Rocha et al., 2000; Rocha et al., 2001). The pretransplant diagnosis of chronic myelogenous leukemia was a significant risk factor for chronic GVHD (Carlens et al., 1998; Remberger et al., 2002). Patients with chronic myelogenous leukemia are usually above mean age for HSCT, and in that respect, they are at increased risk for chronic GVHD (Carlens et al., 1998; Remberger et al., 2002).

Chronic GVHD is more common after peripheral blood stem cell transplantation than BMT because it is generally accepted that peripheral blood stem cells contain greater numbers of infused T-cells (Bishop, 2009; Schmitz et al., 2006). T-lymphocytes are most likely responsible for GVHD; depletion of T-lymphocytes decreased the incidence and severity of GVHD (Kolb et al., 1995). A retrospective multicenter study conducted by Rocha and colleagues (2001) compared the outcomes of unrelated umbilical cord blood transplantation, unrelated BMT, and T-cell depleted unrelated BMT in children. Chronic GVHD was decreased after T-cell depleted unrelated BMT and umbilical cord blood transplantation (Rocha et al., 2001). The use of umbilical cord blood appears to be associated with low rates of chronic GVHD (Kurtzberg, 2009; Kurtzberg et al., 2008; Sharma et al., 2009). The immunological properties of lymphocytes from cord blood, which lacks prior antigenic stimulation, suggest that the risk of GVHD may be lower after umbilical cord blood transplantation than after BMT (Madrigal, Cohen, Gluckman, & Charron, 1997).

Thymus function is negatively affected by acute GVHD. It is possible that a damaged thymus that has increased capability of negative T-cell selection will release more autoreactive T-cells. This process leads to more chronic GVHD with autoimmune similarities (Hollander, Widmer, & Burakoff, 1994).

Management of Chronic GVHD

Treatment

Use of corticosteroids (with or without a calcineurin inhibitor) is the standard of initial GVHD treatment (Ferrara et al., 2009). The NIH guidelines suggest consideration of systematic treatment if 3 or more organs are involved or any single organ has a severity score of more than 2, such as major limitation of oral intake (Filipovich et al., 2005). Optimal secondary treatment has not been

Table 4. Risk Factors for Chronic Graft-Versus-Host Disease in Children Postallogeneic Hematopoietic Stem Cell Transplantation

Authors	Sample	Research Approach	Main Findings
Carlens et al. (1998)	451 individuals aged 1-58 years	Prospectively analyzed 34 risk factors for 451 patients who survived more than 3 months and were evaluated for chronic GVHD	Older recipient age was the single most important risk factor. Other significant risk factors in a study evaluated for chronic GVHD were acute GVHD, immune female donor to male recipient, and chronic myelogenous leukemia
Rocha et al. (2000)	1872 children 15 years of age or younger	Retrospective analysis	Chronic GVHD risk was lower after umbilical cord blood transplantation than bone marrow transplantation
Cutler et al. (2001)	16 studies were included	Metaanalysis	Chronic GVHD is more common after peripheral blood stem cell transplantation than bone marrow transplantation
Kondo et al. (2001)	265 individuals aged 1-21 years	Prospective analysis	Acute GVHD, malignant disease, recipient age (>10 years), and a female donor to male recipient were significant risk factors for chronic GVHD
Rocha et al. (2001)	541 children aged 2.5-12 years	Retrospective multicenter study	Chronic GVHD was lower risk after T-cell-depleted unrelated bone marrow transplantation and unrelated umbilical cord blood transplantation than nonmanipulated unrelated bone marrow transplantation
Remberger et al. (2002)	679 individuals aged 0-77 years	Prospectively analyzed 30 potential risk factors for chronic GVHD	Acute GVHD, chronic myelogenous leukemia, and transplantation from an immunized female donor to a male recipient were independent risk factors for moderate-to-severe chronic GVHD
Eapen et al. (2004)	773 individuals aged 8-20 years	Prospective analysis	Chronic GVHD risk was higher after peripheral blood stem cell transplantation than bone marrow transplantation
Randolph et al. (2004)	3238 individuals aged 1-78 years	Retrospective analysis	Compared with other sex combinations, male recipients of female transplants had the greatest odds for chronic GVHD
Remberger et al. (2005)	214 individuals aged 1-56 years	Prospective analysis	Peripheral blood stem cell transplantation results in an increased risk for chronic GVHD compared with bone marrow transplantation
Watanabe et al. (2008)	94 individuals aged 1-15 years	Retrospective analysis	Age at transplantation and a female donor to male recipient were identified as risk factors for chronic GVHD

Abbreviations: GVHD, graft-versus-host disease.

established (Lee & Flowers, 2008). Lee and colleagues conducted a survey of pediatric transplant centers and found that 50% of pediatric physicians use mycophenolate mofetil to treat steroid-refractory multiorgan chronic GVHD (Lee et al., 2008).

Children may require continued treatment with immunosuppressive drugs, which increases their risks for serious infections and other complications. Chronic immunosuppressant treatment has many toxic effects that

include diabetes, muscle weakness, osteoporosis, avascular necrosis, and cushingoid features, which are typical with chronic steroid use (Ferrara et al., 2009). Additionally, calcineurin inhibitors frequently cause renal impairment, hypertension, and neurological paresthesias (Ferrara et al., 2009). The multiple manifestations, varying extent of organ involvement, and difficulty in measuring the response to treatment all contribute to the difficulty of treating chronic GVHD (Couriel et al., 2006; Ferrara et al.,

Table 5. Physical Supportive Nursing Care for Children With Chronic Graft-Versus-Host Disease

Organ System	Nursing Support Care
Dermal	Educate children and parents to prevent further skin injury; develop strategies to manage symptoms, including itching and dry skin
Ocular	Discuss ways to manage relief of dry eyes and sensitivity to light, such as warm compress and protective eyewear and use of moisturizing eyedrops
Oral	Encourage frequent water sipping; maintain good oral/dental hygiene; salivary stimulants (sugar free gum, sugar free candy)
Gastrointestinal	Recommend diet modification as appropriate: for example, soft and moist food when patients are sensitive to foods that have rough and dry textures; maintain appropriate weight of children
Musculoskeletal	Teach stretching exercises and deep muscle massage to improve range of motion
Immunological	Educate about ways to prevent opportunistic infections; stress importance of contacting the physician if children have symptoms of infection, for example, fever more than 38°C and chills

2009). Clinical manifestations of chronic GVHD can persist for prolonged periods, causing significant morbidity, and some symptoms may be irreversible. Supportive care becomes a central component in the long-term management of chronic GVHD (Couriel et al., 2006).

Supportive Care

Successful management and supportive care of children with chronic GVHD require close observation and sufficient understanding of its pathogenic mechanisms to identify complications before they limit function or threaten mortality (Lee et al., 2003). The NIH recently published organ-specific recommendations for ancillary therapy and supportive care of chronic GVHD (Couriel et al., 2006). Because almost half of these recommendations are based on expert consensus rather than evidence, the impact of supportive and ancillary care on quality of life and survival needs to be explored (Couriel, 2008). Evidence-based symptomatic management of chronic GVHD in HSCT nursing practice continues to be a challenge. Supportive nursing care for pediatric chronic GVHD is summarized in Table 5 (Couriel, 2008; Takatsuka, Iwasaki, Okamoto, & Kakishita, 2003; Viale, 2006).

Nurses should focus on preventing further skin injury, such as educating children and parents to avoid direct sun exposure (especially between 10 AM and 4 PM) and to wear a long-sleeved shirt, full-length pants, and hat. Sunscreen cream (SPF 15 or greater) should be used to protect the face, neck, and all uncovered skin. For dry skin, nurses should teach children and parents to use oil in the bath water, lanolin-based lotion, and natural soap for sensitive skin.

Nurses should educate children and parents to control evaporation from the eyes. Occlusive eyewear is helpful when children are outside or in windy conditions, and

warm compresses and humidified environment may be used when dryness of the eyes occurs. For children with salivary gland involvement, frequent water or saline sipping and salivary stimulants are recommended. Children with oral sensitivities should avoid mint-flavored toothpastes and mouthwash. Good oral/dental hygiene should be stressed to prevent tooth decay and infection.

Diarrhea caused by chronic GVHD should be managed with a low-fiber, low-fat, and low-sugar diet. Stress the importance of maintaining or achieving an appropriate weight for the child's growth. Height and weight should be measured every month. If children are underweight, a dietary consult should be initiated to evaluate the child's nutritional intake. Children should drink beverages with calories and protein. Supportive nursing care is focused on rehabilitation for mobility changes associated with fasciitis and contractures. Nurses should encourage daily stretching exercises and deep muscle/fascial massages at home to improve range of motion.

The immune system is profoundly altered by the direct consequences of alloreactivity and indirect effects of immunosuppressive therapy for treatment of chronic GVHD. Infection is the most common cause of morbidity and mortality in patients with chronic GVHD. In the late posttransplantation period (>100 days), patients are at an increased risk for developing encapsulated bacterial infections (eg, pneumococcus) and reactivation of varicella zoster (Kruger et al., 2005). Nurses should educate children and parents on how to prevent infections. Measures include strict hand washing, avoiding contact with crowds, and staying away from foods that contain molds (eg, blue cheese). Childhood vaccinations should be given beginning 1 year after the transplantation and if the child is not on immunosuppressive medications, according to physicians' recommendations. Children who develop fever,

chills, or signs of infection should seek immediate medical attention.

Implications for Future Research

This review of chronic GVHD in children provides support for the need for further research. Supportive nursing care for children with chronic GVHD should be formally established through development of evidence-based practice guidelines. This review also provides insight into risk factors. This is important to provide nurses and researchers with an understanding of how to assess chronic GVHD risk.

No instruments were found designed to measure specific chronic graft-versus-host physical symptoms in children. Further research is needed to develop measures to accurately assess symptoms in children and examine relationships among the symptoms.

Conclusion

The number of HSCT procedures performed yearly continues to increase. Attention must be given to the symptom experience of chronic GVHD, a major complication affecting long-term survivors of allogeneic HSCT. Incidence of chronic GVHD in children reflects a wide variation influenced by sample size, evaluation time, and HSCT source. Understanding the symptom experiences of chronic GVHD in children is needed to guide assessment and interventions to limit symptom occurrence and distress in the future.

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References

- Bishop, M. R. (2009). *Hematopoietic stem cell transplantation*. New York, NY: Springer.
- Bradley, M. B., Satwani, P., Baldinger, L., Morris, E., van de Ven, C., Del Toro, G., . . . Cairo, M. S. (2007). Reduced intensity allogeneic umbilical cord blood transplantation in children and adolescent recipients with malignant and non-malignant diseases. *Bone Marrow Transplantation, 40*, 621-631.
- Carlens, S., Ringden, O., Remberger, M., Lonnqvist, B., Hagglund, H., Klaesson, S., . . . Aschan, J. (1998). Risk factors for chronic graft-versus-host disease after bone marrow transplantation: A retrospective single centre analysis. *Bone Marrow Transplantation, 22*, 755-761.
- Couriel, D. R. (2008). Ancillary and supportive care in chronic graft-versus-host disease. *Best Practice & Research Clinical Haematology, 21*, 291-307.
- Couriel, D., Carpenter, P. A., Cutler, C., Bolanos-Meade, J., Treister, N. S., Gea-Banacloche, J., . . . Flowers, M. E. (2006). Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biology of Blood and Marrow Transplantation, 12*, 375-396.
- Cutler, C., Giri, S., Jeyapalan, S., Paniagua, D., Viswanathan, A., & Antin, J. H. (2001). Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: A meta-analysis. *Journal of Clinical Oncology, 19*, 3685-3691.
- Eapen, M., Horowitz, M. M., Klein, J. P., Champlin, R. E., Loberiza, F. R., Jr., Ringden, O., Wagner, J. E. (2004). Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: The Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry. *Journal of Clinical Oncology, 22*, 4872-4880.
- Fagioli, F., Zecca, M., Locatelli, F., Lanino, E., Uderzo, C., Di Bartolomeo, P., . . . AIEOP-HSCT Group. (2008). Allogeneic stem cell transplantation for children with acute myeloid leukemia in second complete remission. *Journal of Pediatric Hematology/Oncology, 30*, 575-583.
- Falkenburg, J. H., van de Corput, L., Marijt, E. W., & Willemze, R. (2003). Minor histocompatibility antigens in human stem cell transplantation. *Experimental Hematology, 31*, 743-751.
- Ferrara, J. L. M., Levine, J. E., Reddy, P., & Holler, E. (2009). Graft-versus-host disease. *Lancet, 373*, 1495-1576.
- Filipovich, A. H., Weisdorf, D., Pavletic, S., Socie, G., Wingard, J. R., Lee, S. J., . . . Flowers, M. E. (2005). National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biology of Blood and Marrow Transplantation, 11*, 945-956.
- Higman, M. A., & Vogelsang, G. B. (2004). Chronic graft versus host disease. *British Journal of Haematology, 125*, 435-454.
- Hollander, G. A., Widmer, B., & Burakoff, S. J. (1994). Loss of normal thymic repertoire selection and persistence of autoreactive T cells in graft vs host disease. *Journal of Immunology, 152*, 1609-1617.
- Huang, X., Liu, D., Liu, K., Xu, L., Chen, H., Han, W., . . . Zhang, X. (2009). Haploidentical hematopoietic stem cell transplantation without in vitro T cell depletion for treatment of hematologic malignancies in children. *Biology of Blood and Marrow Transplantation, 15*, 91-94.

- Iravani, M., Mousavi, A., Gholibeikian, S., Bahar, B., Samiee, S., Ashouri, A., . . . Ghavamzadeh, A. (2005). Cyclosporin A and mini short-term methotrexate vs cyclosporin A as graft-versus-host disease prophylaxis in patients with beta thalassemia major undergoing allogeneic blood and marrow transplantation. *Bone Marrow Transplantation, 35*, 1095-1099.
- Jagasia, M., Giglia, J., Chinratanalab, W., Dixon, S., Chen, H., Frangoul, H., . . . Schuening, F. (2007). Incidence and outcome of chronic graft-versus-host disease using National Institutes of Health consensus criteria. *Biology of Blood and Marrow Transplantation, 13*, 1207-1215.
- Joseph, R. W., Couriel, D. R., & Komanduri, K. V. (2008). Chronic graft-versus-host disease after allogeneic stem cell transplantation: Challenges in prevention, science, and supportive care. *Journal of Supportive Oncology, 6*, 361-372.
- Kansu, E. (2004). The pathophysiology of chronic graft-versus-host disease. *International Journal of Hematology, 79*, 209-215.
- Kolb, H. J., Schattenberg, A., Goldman, J. M., Hertenstein, B., Jacobsen, N., Arcese, W., . . . European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. (1995). Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood, 86*, 2041-2050.
- Kondo, M., Kojima, S., Horibe, K., Kato, K., & Matsuyama, T. (2001). Risk factors for chronic graft-versus-host disease after allogeneic stem cell transplantation in children. *Bone Marrow Transplantation, 27*, 727-730.
- Kruger, W. H., Bohlius, J., Cornely, O. A., Einsele, H., Hebart, H., Massenkeil, G., . . . Wolf, H. (2005). Antimicrobial prophylaxis in allogeneic bone marrow transplantation. Guidelines of the infectious diseases working party (AGIHO) of the German Society of Haematology and Oncology. *Annals of Oncology, 16*, 1381-1390.
- Kurtzberg, J. (2009). Update on umbilical cord blood transplantation. *Current Opinion in Pediatrics, 21*, 22-29.
- Kurtzberg, J., Prasad, V. K., Carter, S. L., Wagner, J. E., Baxter-Lowe, L. A., Wall, D., . . . COBLT Steering Committee. (2008). Results of the Cord Blood Transplantation Study (COBLT): Clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. *Blood, 112*, 4318-4327.
- Lee, S. J., & Flowers, M. E. (2008). Recognizing and managing chronic graft-versus-host disease. *Hematology, 134*-141.
- Lee, S. J., Joffe, S., Artz, A. S., Champlin, R. E., Davies, S. M., Jagasia, M., . . . Eapen, M. (2008). Individual physician practice variation in hematopoietic cell transplantation. *Journal of Clinical Oncology, 26*, 2162-2170.
- Lee, S. J., Vogelsang, G., & Flowers, M. E. D. (2003). Chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation, 9*, 215-233.
- Leiper, A. D. (2002). Non-endocrine late complications of bone marrow transplantation in childhood: Part I. *British Journal of Haematology, 118*, 3-22.
- Madero, L., Gonzalez Vicent, M., Ramirez, M., Quintero, V., Benito, A., & Diaz, M. A. (2000). Clinical and economic comparison of allogeneic peripheral blood progenitor cell and bone marrow transplantation for acute lymphoblastic leukemia in children. *Bone Marrow Transplantation, 26*, 269-273.
- Madrigal, J. A., Cohen, S. B. A., Gluckman, E., & Charron, D. J. (1997). Does cord blood transplantation result in lower graft-versus-host disease? It takes more than two to tango. *Human Immunology, 56*, 1-5.
- Mielcarek, M., Martin, P. J., Leisenring, W., Flowers, M. E. D., Maloney, D. G., Sandmaier, B. M., . . . Storb, R. (2003). Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood, 102*, 756-762.
- Parkman, R., & Weinberg, K. I. (2004). Immune reconstitution following hematopoietic cell transplantation. In K. G. Blume, S. J. Forman, & F. R. Appelbaum (Eds.), *Thomas' hematopoietic cell transplantation* (3rd ed., pp. 853-861). Oxford, UK: Blackwell Publishing.
- Randolph, S. S. B., Gooley, T. A., Warren, E. H., Appelbaum, F. R., & Riddell, S. R. (2004). Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. *Blood, 103*, 347-352.
- Remberger, M., Beelen, D. W., Fauser, A., Basara, N., Basu, O., & Ringden, O. (2005). Increased risk of extensive chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation using unrelated donors. *Blood, 105*, 548-551.
- Remberger, M., Kumlien, G., Aschan, J., Barkholt, L., Hentschke, P., Ljungman, P., . . . Ringdén, O. (2002). Risk factors for moderate-to-severe chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Biology of Blood and Marrow Transplantation, 8*, 674-682.
- Richards, S. J., Morgan, G. J., & Hillmen, P. (1999). Analysis of T cells in paroxysmal nocturnal hemoglobinuria provides direct evidence that thymic T-cell production declines with age. *Blood, 94*, 2790-2799.
- Rocha, V., Cornish, J., Sievers, E. L., Filipovich, A., Locatelli, F., Peters, C., . . . Gluckman, E. (2001). Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood, 97*, 2962-2971.
- Rocha, V., Wagner, J. E., Sobocinski, K. A., Klein, J. P., Zhang, M. J., Horowitz, M. M., . . . Gluckman, E. (2000). Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. *New England Journal of Medicine, 342*, 1846-1854.
- Satwani, P., Sather, H., Ozkaynak, F., Heerema, N. A., Schultz, K. R., Sanders, J., . . . Cairo, M. S. (2007). Allogeneic bone marrow transplantation in first remission for children with ultra-high-risk features of acute lymphoblastic leukemia: A Children's Oncology Group study report. *Biology of Blood and Marrow Transplantation, 13*, 218-227.
- Schmitz, N., Eapen, M., Horowitz, M. M., Zhang, M. J., Klein, J. P., Rizzo, J. D., . . . European Group for Blood and Marrow Transplantation. (2006). Long-term outcome

- of patients given transplants of mobilized blood or bone marrow: A report from the International Bone Marrow Transplant Registry and the European Group for Blood and Marrow Transplantation. *Blood*, *108*, 4288-4290.
- Sharma, V. K., Singh, U. K., Prasad, R., & Fletcher, S. (2009). Stem cell through present and future. *Indian Journal of Pediatrics*, *76*, 51-56.
- Strahm, B., Locatelli, F., Bader, P., Ehlert, K., Kremens, B., Zintl, F., . . . Niemeyer, C. M (2007). Reduced intensity conditioning in unrelated donor transplantation for refractory cytopenia in childhood. *Bone Marrow Transplantation*, *40*, 329-333.
- Takatsuka, H., Iwasaki, T., Okamoto, T., & Kakishita, E. (2003). Intestinal graft-versus-host disease: Mechanisms and management. *Drugs*, *63*, 1-15.
- Thomson, B. G., Robertson, K. A., Gowan, D., Heilman, D., Broxmeyer, H. E., Emanuel, D., . . . Smith, F. O. (2000). Analysis of engraftment, graft-versus-host disease, and immune recovery following unrelated donor cord blood transplantation. *Blood*, *96*, 2703-2711.
- Viale, P. H. (2006). Chemotherapy and cutaneous toxicities: Implications for oncology nurses. *Seminars in Oncology Nursing*, *22*, 144-151.
- Wall, D. A., Carter, S. L., Kernan, N. A., Kapoor, N., Kamani, N. R., Brochstein, J. A., . . . COBLT Steering Committee. (2005). Busulfan/melphalan/antithymocyte globulin followed by unrelated donor cord blood transplantation for treatment of infant leukemia and leukemia in young children: The Cord Blood Transplantation study (COBLT) experience. *Biology of Blood and Marrow Transplantation*, *11*, 637-646.
- Watanabe, N., Matsumoto, K., Yoshimi, A., Horibe, K., Matsuyama, T., Kojima, S., Kato, K. (2008). Outcome of bone marrow transplantation from HLA-identical sibling donor in children with hematological malignancies using methotrexate alone as prophylaxis for graft-versus-host disease. *International Journal of Hematology*, *88*, 575-582.
- Zecca, M., Prete, A., Rondelli, R., Lanino, E., Balduzzi, A., Messina, C., . . . AIEOP-BMT Group. Italian Association for Pediatric Hematology and Oncology-Bone Marrow Transplant. (2002). Chronic graft-versus-host disease in children: Incidence, risk factors, and impact on outcome. *Blood*, *100*, 1192-1200.
- Zhang, C., Todorov, I., Zhang, Z., Liu, Y., Kandeel, F., Forman, S., . . . Zeng, D. (2006). Donor CD4+ T and B cells in transplants induce chronic graft-versus-host disease with autoimmune manifestations. *Blood*, *107*, 2993-3001.

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