Chapter 17
Quality and Safety in Hematopoietic Stem Cell Transplant Patients

Kathy Ruble, Christa Krupski, Allen Chen, and Christopher E. Dandoy

Introduction

The field of hematopoietic stem cell transplant (HSCT) has undergone tremendous advancement in the past 60 years since E. Donnall Thomas et al. first attempted to treat leukemic patients with irradiation and marrow grafting [1]. Advances in antiviral therapies [2], extension of graft selection [3–6], establishment of donor registries, and advanced understanding of human lymphocyte antigen (HLA) matching have all contributed to improved outcomes [6–13]. Today, allogeneic HSCT is a treatment modality offered to pediatric patients with a variety of disorders including hematologic malignancies, bone marrow failure syndromes, immunodeficiencies, and hemoglobinopathies [11]. Autologous HSCT can be used in conjunction with high-dose chemotherapy to treat tumors such as neuroblastoma and CNS malignancy [14].

Patients undergoing HSCT have complex medical courses; they undergo prolonged hospitalizations, often require subspecialty consultations, and are at risk for multiple complications in the posttransplant period. Coordinating care for this

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K. Ruble
Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

C. Krupski • C.E. Dandoy (✉)
Department of Bone Marrow Transplantation and Immune Deficiency, Cancer and Blood Disease Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: christopher.dandoy@cchmc.org

A. Chen
Department of Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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group of patients not only necessitates substantial resources but also careful attention in order to ensure patient safety. HSCT patients utilize a substantial amount of resources, as they encounter complications posttransplant (i.e. infection) and utilize measures included in the chronic care model [15, 16]. Both the continuing evolution of clinical care and the diversity of patients and diseases treated with HSCT have led to disagreement regarding the establishment of quality metrics among programs. Additionally, HSCT practices are heterogeneous; substantial variations exist between centers and individual providers.

Although extensive guidelines have been published regarding HSCT, data evaluating barriers to improving delivery of care and adherence to the recommendations is sparse. Despite the lack of published reports, processes at all stages of care should be continuously refined, and strategies for improvement should be shared. As it currently stands, the field of quality and safety in HSCT is in its infancy; extensive opportunities exist to learn and share mechanisms for improving patient care.

Quality can be defined as the best possible science in the context of the patients' wants and needs. Quality improvement describes the process and methods used to assess and implement the best quality care. In this chapter, we will review the following topics:

- HSCT accreditation organizations
- Mechanisms to ensure marrow donor safety
- Strategies to improve coordination of care throughout the HSCT process, including the pre-HSCT evaluation, transplant itself, and the post-HSCT period of survivorship
- Review of selective safety issue opportunities in hospitalized HSCT patients
- Follow-up care, late effects, and improving standardized screening

In our efforts to demonstrate mechanisms for improvement, we will utilize reported data as available from the HSCT literature and, when not available, reports published in relation to the fields of pediatrics and/or oncology. It is important to review briefly the differences between *quality improvement* and *quality assurance*. *Quality assurance* measures compliance against certain necessary standards and is required, and *quality improvement* is a continuous proactive process to improve healthcare delivery systems.

Accreditation: FACT and JACIE

Measurement of quality is critical in the HSCT arena due to the life-threatening nature of the diseases (and, occasionally, the treatment), the opportunity for cure, the intensive resource utilization, and the involvement of healthy donors in HSCT. Standardization of HSCT has been advocated as a way of improving patient care and outcome. Thus, accreditation for transplantation centers has become an accepted standard in the USA and Europe and is required by law in some countries.

The Foundation for the Accreditation of Cellular Therapy (FACT) and JACIE (The Joint Accreditation Committee of the International Society for Cellular Therapy Europe) are advanced quality management systems whose aim is to certify clinical excellence in processes and outcomes within HSCT centers and improve the quality of care in clinical HSCT by the use of well-defined standards and rules and verified through inspections [17, 18].

FACT and JACIE maintain specific standards for accreditation, including: mandating a minimum annual number of transplants centers must perform, guidelines for HSCT center laboratories and clinical oversight, and methodologies for HLA typing and processing. In addition, institutions must maintain adequate nursing and physician staffing, assure institutional standardized policies and procedures, and perform recommended donor evaluations. Centers performing pediatric bone marrow harvests should have appropriate facilities and pediatric anesthesiology specialty care available. Centers performing leukopheresis for peripheral blood stem cell (PBSC) donation should have appropriate equipment and staffing for children [17–25].

In Europe, JACIE implementation has significantly improved patient outcomes, including non-relapse mortality, relapse incidence, and relapse-free survival after allogeneic and autologous HSCT. Gratwohl et al. showed outcomes that were significantly better for patients who received transplantations in accredited centers compared with patients who received transplantation in centers [22]. This was true both in the pre-application baseline, preparation, or application periods and was independent of the year of HSCT [17]. In the USA, after adjusting for patient and center characteristics, FACT centers have shown statistically superior results relative to non-FACT centers, especially for more complex HSCT [18]. Adherence with best practices in evidence-based medicine is likely an underlying driver of the improved outcomes. These examples provide evidence of a quality management system that contributes to the overall survival of patients treated with a highly specific medical procedure and represents significant progress in HSCT quality and safety [26–28].

Although there is significant oversight through accreditation in maintaining minimum standards in HSCT care, there are no specific regulations on clinical care, leading to variation in patient management and supportive care. In 2008, Lee et al. evaluated practice variations in HSCT among transplant centers and countries. A survey administered to 526 adult and pediatric transplant physicians showed wide variation in management approaches to specific clinical scenarios, including chronic myeloid leukemia, acute and chronic graft-versus-host disease, and choice of graft source for patients with aplastic anemia. Among adult transplant physicians, there was little agreement on the patient factors favoring reduced intensity conditioning or myeloablative conditioning [29].

Due to variations in practice and heterogeneity between centers, quality measurements can vary between centers; however, some metrics should be monitored closely (Fig. 17.1) [30]. It is important that institutions have an active and engaged quality assurance team, to measure compliance with the necessary standards that are required. In addition, the committee can mitigate institutional forces impacting the

- Annual volume (number of patients transplanted)
- Disease-free survival
- Engraftment
- Treatment-related complications
- Infectious complications, bloodstream infection rates
- Treatment-related mortality (100-day and 1-year)
- Donar safety
- Hospital length of stay
- Unplanned re-admissions
- Patient satisfaction

Fig. 17.1 Quality and safety metrics in hematopoietic stem cell transplantation. Adopted from Rice and Bailey [31]

HSCT program [31]. HSCT centers should also maintain and support a quality improvement team, to continuously implement processes to ensure quality care.

Donor Safety

As unrelated hematopoietic cell (HC) donation is only reserved for individuals >18 years of age worldwide, we will only review HC donation for related donors. There is no direct medical benefit from serving as a stem cell donor, though there is a psychosocial benefit of helping a sibling or close family member [32]. There are safety, quality, and ethical implications for both donors and recipients; consequently, various processes have been implemented by registries worldwide to minimize the risk to both parties. HLA-matched siblings are considered to be the best HC donors for both practical and biological purposes [33]. However, when the recipient is a child, potential sibling donors are often also children themselves. Today, more than one third of children undergoing allogeneic HSCT receive HC grafts from siblings under the age of 18 years [34, 35].

All stem cell sources, including bone marrow (BM), peripheral blood stem cells (PBSC), and cord blood (CB), can be obtained from pediatric donors, but BM-derived cells are the preferred source for many reasons such as a decreased risk of graft-versus-host disease (GVHD) [34, 35]. PBSC donation requires the donor to receive granulocyte colony-stimulating factor (G-CSF) and then undergo central venous catheter placement under anesthesia and apheresis. BM harvests are generally regarded as safe, but also require general anesthesia and may lead to pain at the harvest site. Although the BM and PBSC collection procedures differ greatly, the main symptoms experienced by BM and PBSC donors were similar: pain, fatigue, insomnia, local reactions, dizziness, anorexia, emesis, rash, and occasional fever or syncope [36] (Fig. 17.2). It is important to note there is no evidence that patients receiving G-CSF have an increased risk for cancer, autoimmune diseases, and/or stroke [37].

In 2010, the American Academy of Pediatrics (AAP) released a policy statement on the use of children as donors. The statement outlined five conditions that the AAP recommends should be met in order for a minor to serve as a stem cell donor [38].

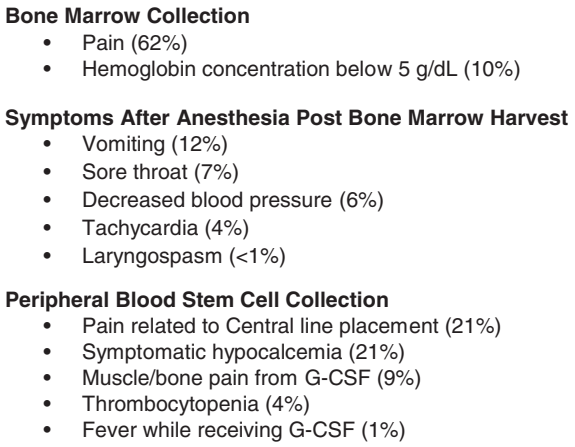

Fig. 17.2 Symptoms associated with hematopoietic cell collect (bone marrow and peripheral blood collection). Adopted from Styczynski [36]

- There is no medically equivalent HLA adult relative who is willing and able to donate.
- A strong personal and positive relationship exists between the donor and recipient.
- There is some likelihood that the recipient will benefit from transplantation.
- The clinical, emotional, and psychosocial risks to the donor must be minimized and reasonable in relation to the benefits expected for both the donor and the recipient.
- Parental permission and donor assent (when developmentally appropriate) must be obtained.

FACT and JACIE have specific guidelines for the collection of cellular products to protect the safety of donors during the process of HC collection. As donor safety is of utmost importance, checklists should be utilized to verify completion of the pre-procedure steps (e.g., testing for hemoglobinopathy, pregnancy, etc.) [39].

Coordination of Care

HSCT care is complex, involving multiple treatment modalities such as chemotherapy, radiation, and surgery; all need to be coordinated among different medical specialties. Treatment regimens can be time-intensive and debilitating and may result in serious, sometimes long-term, complications. Care coordination involves deliberately organizing patient care activities and sharing information between all of the participants involved in a patient's care in order to provide safe and effective care. Simply put, the patient's needs must be known and communicated to the right people at the right time, and this information must then be used to provide quality patient care [40–42]. There are three periods where comprehensive and effective care coordination is needed in the HSCT period: (a) pre-HSCT referral from the

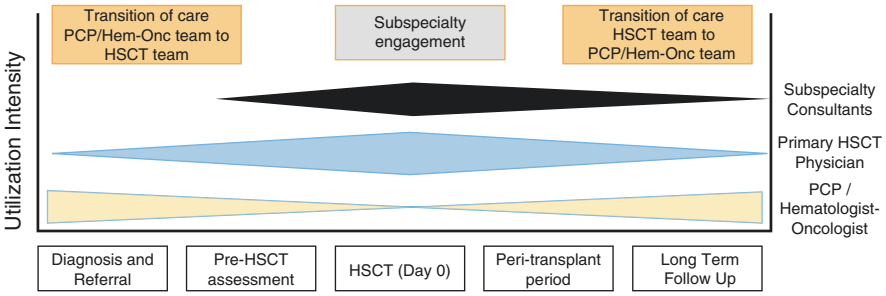

Fig. 17.3 Transitions of care in hematopoietic stem cell transplant (HSCT)

pediatrician or pediatric hematology-oncology physician, (b) during the peri-HSCT period where coordination between the HSCT team and other healthcare providers is needed, (c) in the post-HSCT period when the HSCT survivor is transitioned back to the PCP (Fig. 17.3).

Pre-HSCT Care Coordination

Although the need for care coordination is clear, there are obstacles within our healthcare delivery system that must be overcome in order to provide thorough medical care. The Agency for Healthcare Research and Quality (AHRQ) acknowledges that our healthcare delivery system is often disjointed, and processes vary among primary care and specialty sites. Patients are often not certain of the reasons they are being referred from primary care to a specialist, how to make appointments, and what to do after seeing a specialist. Furthermore, specialists do not consistently receive clear reasons for the referral or adequate information on diagnostic evaluations that have been done prior to the referral [41].

The transfer of care of patients across clinical specialties is a complex process and is made even more challenging by cultural differences, individual expectations, and pressure from patients and families [43]. Oftentimes, referrals fail to meet the needs of either the initiating facility or the receiving provider [40, 43, 44]. Reasons for dissatisfaction include redundancies in the referral process, poor communication between physicians, the time required to write a referral note, and missing information in the referral letter or report [44]. Interestingly, pediatric specialists who received timely patient referral information reported providing optimal care twice as often as specialists who did not [45]. Unfortunately, in pediatric HSCT, there are no published reports relating to the referral process; this leaves opportunity for research and quality improvement in this area.

An effective referral mechanism ensures a close relationship between the initiating facility and the receiving facility. Successful subspecialty referrals require considerable coordination and interaction among the PCP, the subspecialist, and the

patient, which may be challenging in the outpatient setting. Hysong et al. conducted a qualitative study to understand coordination breakdowns related to electronic referrals in an integrated healthcare system [46]. The authors examined work-system factors that affect the timely receipt of subspecialty care. Four overarching themes emerged: lack of an institutional referral policy, lack of standardization in certain referral procedures, ambiguity in roles and responsibilities, and inadequate resources to adapt and respond to referral requests effectively. Marked differences in PCPs' and subspecialists' communication styles and individual mental models of the referral processes likely precluded the development of a *shared* mental model to facilitate coordination and successful referral completion [46].

The AHRQ provides guidelines to improve care coordination with referrals. This approach can be utilized both in pre-HSCT referrals (from the PCP or hematologist/oncologist) or post-HSCT care back to the referring physician. AHRQ recommends that the referral process be designed by key stakeholders (e.g., referring oncology and BMT teams) to include all of the pertinent details necessary for effective and safe management of patients. As checklists have been shown to improve transitions of care through referrals [47], stakeholders should create a formalized checklist for patient referrals. These referral forms should include pertinent demographic, social, and medical information. AHRQ recommends that centers should not rely on patients to relay information, but should discuss and coordinate language barriers, verify that the patient understands the reason of the referral, and maintain a means to communicate progress throughout the HSCT process [41].

Currently, there are no metrics to measure referral effectiveness in HSCT. Physician teams should sample the number of referrals made over a specific time period (denominator) and calculate the percentage of referrals that included all relevant information (numerator). This could be tracked in real time, and QI methodology can then be used to close gaps in care.

Care Coordination in the Peri-transplant Period

HSCT recipients are complex, and their care involves individuals from multiple specialties and services (Fig. 17.4). HSCT providers requesting subspecialist input in the hospitalized patient should provide the following information when requesting a consultation: (1) address the question that is asked, (2) whom to call with the response, (3) and the urgency of the consultation [48]. Physician consultation should be collaborative and multidisciplinary, and include patient and family engagement [49].

HSCT nurse coordinators are instrumental in the overall management of HSCT patients. Nurse coordinators are involved throughout the entire HSCT course; they coordinate HLA typing between patients and potential donors, assure completeness of referral forms, verify insurance coverage, participate in the initial consultation with the transplant physician, schedule necessary procedures, and educate patients and families. Finally, nurse coordinators can assure adequate transition of care to the posttransplant setting and arrange for long-term follow-up [50].

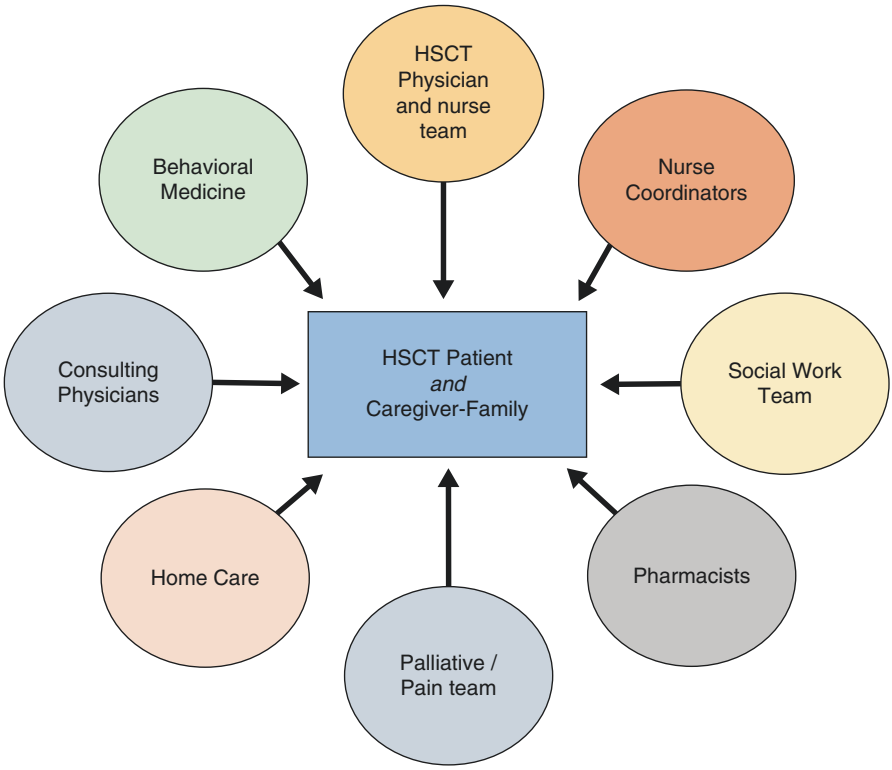

Fig. 17.4 Hematopoietic stem cell transplant (HSCT) care team in the peri-transplant period

Posttransplant Transition

In the absence of relapse and/or active GVHD, most HSCT survivors are eventually able to transition to another set of providers. Ideally, this should be accomplished seamlessly with good communication. However, the vulnerabilities and complexities of such transitions of care have become evident, and medical and/or psychological crises may emerge or resurface among certain groups of patients who are at risk being lost in transition [51]. Oftentimes, HSCT survivors are accustomed to unique living arrangements and receive medical care within a complex healthcare delivery system which includes physicians, social workers, and other pediatric specialists. At times, the transition from the protective environment of the "bone marrow transplant medical home" can be difficult, as pediatric patients may rely on their caregivers well into their 30s and 40s [51–54]. The same requirements and steps described above should be used for the transition of care to the PCP. Cupit et al. recently reviewed the mechanisms to transition care of pediatric and adolescent young adult transition to adult healthcare providers [55]. Important considerations in HSCT transition are reviewed in Fig. 17.5.

Adopted from Cubit et al.[55]

- **Identification of a healthcare provider:** Ensure all HSCT survivors have an identified primary care provider (PCP) who can attend to the challenges of transition and who can assume responsibility for current healthcare, care coordination and future planning.
- **Individualized care plans:** Prepare and maintain a comprehensive medical summary that is accessible and available to both the patient, caregivers/parents, PCP, and subspecialist.
- **Healthcare transition plan:** Create a individualized healthcare transition plan the HSCT survivor and his/her family. Discuss the plan at length with the patient's caregivers/parents to address how their roles may changes. This plan should include the services that need to be provided and who will provide them. This plan should be reviewed at all long term follow up visits.
- **Addressing healthcare coverage:** Ensure affordable, continuous health insurance for all HSCT survivors throughout adolescence and adulthood.
- **Communication:** Engage in regular communication with the patient's PCP prior to, during, and after transition to ensure coordination of care.

Fig. 17.5 Considerations for successful transition of HSCT survivors. Adopted from Cubit et al. [55]

Survivorship and Long-Term Screening

Survivorship of HSCT begins on the day of transplantation [51]. There are few patients who have more complicated survivorship care than those who undergo HSCT in childhood. Quality pediatric HSCT care must include appropriate long-term follow-up to monitor and treat the complications associated with this intensive treatment. Many factors should be considered when determining the risk of long-term complications after HSCT and include the type and intensity of treatments received prior to the transplant, conditioning regimen, type of transplant and product, type and severity of GVHD, early complications, comorbid conditions, genetic factors, and lifestyle. HSCT survivorship tools are available to assist in appropriate screening for complications and include the Children's Oncology Group, Long-Term Follow-Up Guidelines [56], and Pediatric Blood and Marrow Transplant Consortium Consensus Paper [57]. HSCT long-term follow-up teams should include, or have the ability to refer patients to, subspecialists with experience in the care of post-HSCT organ dysfunction (Table 17.1).

Hematologic Complications

Many of the underlying diseases that necessitate HSCT require extensive blood product support prior to transplant, and all patients will require transfusion support in the pre-engraftment period. The cumulative effect of transfusion support is varying degrees of iron overload, which is associated with increased mortality before day 100, acute graft-versus-host disease, and blood stream infections [58–61]. While serum ferritin can be falsely elevated as an acute-phase reactant, elevated levels should serve as an indicator of iron overload and prompt further investigation

Table 17.1 Recommended organ function screening and late-effects multidisciplinary team members

	Screening test	Minimum screening frequency	Multidisciplinary team member
Hematologic	Ferritin Hepatic function	Yearly	Hematologist with experience in chelation therapy
Pulmonary	Pulmonary function tests (PFTs)	Every 6 months for first 2 years	Pulmonologist PFT lab Cardiologist with expertise in pulmonary hypertension
Endocrine	Thyroid function Gonadal function Growth hormone	Yearly	Endocrinologist
Renal	Blood pressure Renal function test Urinalysis Urine protein to creatinine ratio	Blood pressure assessment at each clinic visit Laboratory testing at day +80 and yearly post-HSCT	Nephrologist Pharmacist (to help adjust medications with renal dysfunction)
Ocular	Ophthalmology evaluation	Yearly	Ophthalmologist with experience in the management of cataracts and ocular GVHD
Cardiac	Echocardiography HgA1C Lipid screening	Yearly laboratory testing for metabolic syndrome Echo screening 1 and 5 years post-HSCT	Cardiologist with experience managing heart failure Echocardiography team

Adopted from Dietz et al. [56]

and treatment [58, 62–64]. Multidisciplinary teams should include specialists able to manage chelation therapy if needed.

Pulmonary Complications

Pulmonary complications post BMT vary widely, including both restrictive and obstructive conditions due to acute or chronic GVHD, HSCT preparatory regimens, or infectious sequela. Furthermore, subclinical pulmonary dysfunction may be present in asymptomatic post-HSCT patients [65]. Serial pulmonary function tests (PFTs) are used to monitor survivors post-HSCT. A possible life-threatening pulmonary complication, bronchiolitis obliterans syndrome (BOS), typically occurs within the first few months to years after HSCT and leads to progressive pulmonary fibrosis and obstructive lung disease [66, 67]. In patients who develop BOS, providers should have a low threshold for obtaining echocardiographic screening for pulmonary hypertension [68]. Survivorship multidisciplinary teams should include a pulmonologist, PFT lab, and cardiologist with expertise in pulmonary hypertension.

Endocrine Complications

Endocrinopathies after BMT are common and can result from direct injury to endocrine organs or via disruption of the hypothalamic-pituitary axis. Endocrine dysfunction can include gonadal dysfunction, growth impairment, and thyroid dysfunction; [69–72] and screening for endocrine complications should include monitoring hormone levels and physical exam focusing on appropriate anthropometric and developmental measures including growth velocity and Tanner staging in children [73]. Transplant teams should work closely with endocrinology specialists in the screening and management of endocrine complications after HSCT.

Renal Complications

Three major categories of long-term renal complications are seen in BMT survivors: thrombotic microangiopathy, nephrotic syndrome, and idiopathic chronic kidney disease resulting from nephrotoxic medications used during transplant [74–76]. Screening for renal dysfunction during survivorship involves laboratory monitoring and blood pressure assessment. More comprehensive monitoring with glomerular filtration rate, ultrasonography, or renal biopsy may be warranted for survivors with established or suspected renal disease [56, 77]. Management of CKD during survivorship should focus on mitigating factors; discontinuation of nephrotoxic drugs and aggressive blood pressure control should be prioritized [78].

Ocular Complications

Cataracts are the most common ocular complication and are associated with the preparative regimen and/or a history of GVHD (cumulative steroid dose) [79–81].

Cardiac Complications

Multiple cardiac complications may occur in survivors of HSCT. Echocardiographic findings of elevated right ventricular pressure (pulmonary hypertension) [68, 82], pericardial effusions [83–86], and left ventricular systolic dysfunction [87, 88] have been described in both adult and pediatric patients undergoing HSCT. In addition, HSCT survivors are at risk for early onset metabolic syndrome and coronary artery disease [75, 89–91]. Comprehensive teams should include access to echocardiography and a cardiology subspecialist with experience in the management of heart failure.

Standardized Process for HSCT Survivors

Long-term survivors of HSCT should receive comprehensive routine screening to insure early detection of late effects as it may lessen their long-term consequences. Transplant centers should create a reliable system to adequately screen HSCT survivors including compliance measurements of comprehensive follow-up. These data could be calculated over any specific time.

(a) Multidisciplinary teams should create standard screening protocols that are disease specific, and adaptable to previous treatments and HSCT complications (e.g., GVHD).
(b) Establish a mechanism to identify long-term follow-up patients and measure compliance with screening.
(c) Establish partnerships with subspecialists who have experience managing late HSCT complications.
(d) Barriers to follow-up should be identified. These include inconsistent scheduling of long-term follow-up patients, variability in physician practice with deviations from evidenced-based guidelines, and the lack of accountability and consistent tracking of BMT survivors.
(e) Test and develop intervention and processes to improve long-term follow-up rates. Examples of interventions include creation of a standardized follow-up checklist and processes to identify all survivors, as well as delineated roles and responsibilities for the post-BMT follow-up process.
(f) Establish a standardized mechanism for patients with abnormal post-HSCT screening results including referral to appropriate subspecialty care.
(g) It is important to continuously monitor adherence to the long-term survivor guidelines. Teams should encourage accountability to assure process compliance.

Posttransplant Quality of Life

HSCT is an area rich for the consideration of health-related quality of life (HRQOL) due to the profound impact it has on recipient's physical and emotional well-being [92]. As therapies and associated supportive cares improve and patients experience increased survivorship, the idea of what constitutes a "successful" HSCT continues to evolve. It is not enough to cure the underlying disease; preservation of HRQOL including emotional, social, and physical well-being must also be of utmost importance.

HRQOL is a complex, multifaceted, and dynamic entity influenced by psychological and social functioning [93]. It has been endorsed by the World Health Organization as essential for measuring as a clinical outcome, separate from morbidity and mortality [94, 95]. For the purpose of evaluation, HRQOL is frequently divided into physical, social, and emotional/mental domains [96–101]. HRQOL is

compromised even before patients undergo HSCT, likely due to prior treatment, underlying disease, and physical symptoms; it then worsens with the preparative regimen [93, 102, 103]. Although medical factors impact HRQOL, certain demographic factors are also potent predictors of HRQOL [103]. A 2009 review article by Tremolada et al. examined 47 studies on pediatric HSCT recipients relating to psychosocial sequelae and HRQOL; many studies showed that older age at HSCT, late effects, female gender, and more proximal time to transplant were risk factors found to be associated with poor HRQOL [93].

Recent studies show variable effects of age at HSCT on HRQOL [95, 103–107]. Patients who are older at the time of HSCT may experience more disruption to their daily lives; they may also more concretely anticipate future distress and prolonged illness than younger children [103]. Additionally, younger patients may not remember the HSCT experience as vividly as older patients do later in life [95]. Additionally, even after controlling for socioeconomic status, ethnicity impacts HRQOL with African-American children reporting the highest HRQOL, while children of Asian descent report the worst decline in HRQOL [103]. It is thought that the patients' culture, behaviors, and values, in combination with their pre-HSCT experience, impact their expectations related to HSCT. Religion, spirituality, and social support, which are often culturally mediated, also impact HRQOL.

When compared to pediatric patients with hematologic malignancies who have been treated with chemotherapy alone, patients who have undergone HSCT have lower overall HRQOL scores [108]. Several studies have shown that these patients generally do not experience decreased social or emotional functioning post-HSCT; it is physical functioning that is most impaired [108–110]. Pediatric HSCT survivors also report more severe chronic health conditions later in life versus patients who received only chemotherapy [111–113]. As social and emotional functioning is essentially unchanged, they seem to adapt emotionally well to their limitations; it is the severity of physical dysfunction that appears to determine HRQOL in this patient population [114, 115].

In the absence of GVHD and late effects, HRQOL does ultimately improve post-HSCT. Studies have shown the timing of improvement to be variable, around 4–12 months post-HSCT [93, 103]. As early as 6 months post-HSCT, HRQOL can be comparable to, and sometimes better than, population normative data [93, 105]. Due to the lack of data investigating quality improvement in HRQOL, more research and investigation is needed.

Impact of Late Effects and GVHD

Post-HSCT late effects are common; they are well documented in the literature and negatively impact HRQOL [116–121]. Monitoring for late effects in pediatric patients post-HSCT is essential and is reviewed separately. Studies comparing childhood cancer survivors treated with chemotherapy alone versus those treated with HSCT demonstrate a significantly higher risk of late effects in those treated

with HSCT [91, 114]. Additionally, physical dysfunction or limitations, psychological stress, and problems with social interactions are common in patients' post-HSCT [91].

QOL in patients with late effects may vary by age, partly because some medical causes of impaired QOL, for example, gonadal failure or other organ damage, may not be fully realized until adulthood [114]. Therefore, QOL may be more preserved in children and adolescents but impaired once the patients reach adulthood.

Additionally, when patients experience GVHD, HRQOL declines. The Chronic GVHD Consortium has extensively studied the impact of chronic GVHD on HRQOL in adult post-HSCT patients [122]. Within HSCT recipients, patients with GVHD have significantly worse HRQOL, both clinically and statistically, versus those without GVHD [123].

Challenges to Measuring HRQOL in Pediatric Patients

The National Institutes of Health (NIH) Consensus Conference on Criteria for Clinical Trials in chronic GVHD recommended the use of health-related QOL (HRQOL) tools in adult patients for a standardized measure of the impact of disease burden and patient outcomes [124–126]. A unidimensional measure of global HRQOL has also been developed as part of the Patient-Reported Outcomes Measurement Information System (PROMIS) project [127]. Despite these efforts, there have been no formal recommendations for a pediatric-specific HRQOL tool.

The use of varying HRQOL surveys for assessment in pediatric patients, along with a wide spectrum of diseases and a limited number of patients, leads to inconsistent results among pediatric HRQOL studies [93, 123]. Another major challenge of measuring HRQOL in pediatric patients is that these patients are dynamic; physical, emotional, social, and cognitive development changes occur with time and must be accounted for in a measurement tool [128].

Parent-Patient Concordance

In addition to the lack of age-appropriate QOL measures, another historic limitation in the evaluation of pediatric HR QOL was the belief that children did not have the ability to reflect on their own QOL, necessitating parents as proxy QOL raters. However, HRQOL ratings differ between patients and parents, perhaps due to information variance, the unequal understanding of and/or access to information, effects of age on processing and interpretation of information, and the child's ability to understand the gravity of both the underlying diagnosis and treatment modalities [92]. Criterion variance, the difference in weight given by each to the available information, also impacts proxy HRQOL scores; parents may compare the child's current health status to his/her potential future status, the health status of siblings or peers [92].

New Tools

Using the Child Health Rating Inventories (CHRIs) tool, Rodday et al. created child, adolescent, and parent surveys to evaluate seven HRQOL modalities in pediatric HSCT recipients: physical health, mental health, family life, friendship, self-confidence, fun, and life enjoyment [129, 130]. Its brevity yields simplicity, ease of use, and decreased responder burden, making it an ideal tool for which to screen patients who may require more in-depth HRQOL evaluation.

Lawitschka et al. developed the PedsQL Stem Cell Transplant module, an HSCT-specific tool for HRQOL assessment in children and adolescents [128]. The instrument was based on the PedsQL Generic Core Scale [131, 132]. It contains the following domains: pain and hurt, fatigue, nausea, worry or anxiety about disease and/or treatment, nutritional problems, thinking and remembering, communication about disease and/or treatment, and chronic GVHD symptoms. A multicenter validation trial is currently underway.

Selected Topics in HSCT Quality and Safety

Bloodstream Infections (BSIs)

HSCT patients are at increased risk for developing bacterial bloodstream infections (BSIs), which are among the most serious infectious complications and a known cause of increased non-relapse mortality (NRM) in this patient population [133–135].

BSIs in the healthcare setting are classified as primary BSI, related to either a central venous line (CVL) or other hospital-acquired source, or secondary BSI, a bacteremia related to another site of infection (e.g., abscess or pneumonia) [136]. Thus, unless an alternative source is identified, all BSIs in patients with a CVL are considered central line-associated bloodstream infections (CLABSIs). CLABSIs are serious complications in HSCT recipients and lead to prolonged hospitalization, intensive care admissions, and antibiotic treatment [133, 134, 137]. Some patients with CVLs experience BSIs that do not arise from the catheter, but rather originate from translocation of bacteria through non-intact oral and gut mucosa [136, 138]. To address this type of BSI, the Centers for Disease Control and Prevention defined a specific CLABSI type known as "mucosal barrier injury laboratory-confirmed bloodstream infection" (MBI-LCBI) on the basis of literature review and expert opinion. In 2013, the MBI-LCBI definition was integrated into the National Healthcare Safety Network (NHSN) methods for primary BSI surveillance to identify a subset of BSIs reported as CLABSIs that were likely related to MBI in the mouth and gut and not the presence of the CVL itself and that occurred most frequently in patients with neutropenia [136]. Currently, primary BSIs in patients with a CVL are defined as "laboratory-confirmed bloodstream infection (LCBI)" and

subcategorized as “CLABSI” or “MBI-LCBI” [139]. Inherent to this distinction is emerging evidence showing that improved CVL maintenance is effective at reducing CLABSI rates [140–142], but not in preventing MBI-LCBIs [143].

Catheter Care Bundles

Catheter care bundles, for both CVL insertion and maintenance, consist of a standard combination of evidence-based interventions that have been shown to be effective in preventing CLABSIs and improving patient outcomes [144, 145]. Germane bundle components include performance of hand hygiene, full-barrier precautions including the use of sterile technique and chlorhexidine cleansing during insertion, and proper procedures for CVL access, manipulation, and dressing changes. Standardization of bundle elements coupled with systematic implementation and compliance has been shown to significantly reduce CLABSI rates across multiple studies of pediatric oncology and HSCT patients [146–150]. Best practice bundle implementation with particular focus on maintenance strategies also reduces CLABSI rates in the ambulatory setting [146, 151]. As part of a multicenter quality improvement initiative, 32 pediatric hematology/oncology and bone marrow transplant centers across the USA implemented a standardized bundle of CVL care practices. Average compliance with the CVL care bundle across the institutions was greater than 80% during the study period, and the collaboration demonstrated a decrease in CLABSI rates from 2.85 CLABSI/1000 CVL days to 2.04 CLABSI/1000 CVL days, a reduction of 28% (RR, 0.71; 95% CI, 0.55–0.92) [152]. This multiinstitutional collaborative improvement effort succeeded at reducing CLABSI rates through standardized CVL bundle care in immunocompromised patients. In a recent study from Memorial Sloan Kettering Cancer Center (MSKCC), rates of hospital-acquired CLABSI in high-risk adult patients, including HSCT recipients, after implementing the use of a disinfection cap were 2.3/1000 days, representing 34% decrease from previous periods and resulted in substantial cost savings [153].

Microsystem Stress

Microsystem stress can arise from high patient volumes and acuity and is associated with increased mortality, failure-to-rescue rates, and increased nurse burnout [154, 155]. Additionally, increased workload can influence the provider’s decision to perform various procedures [156], reduce patient satisfaction [157], decrease communication between nurses and patients [158], and decrease collaboration between providers [159].

Dandoy et al. evaluated the effects of microsystem stress on CLABSI rates. Over a 1-year period of time, their institution saw increased stressors to their healthcare delivery system: the average daily float nurse hours increased nearly 400%, average daily census increased 30%, the number of new relapsed or refractory patients

increased 200%, and the percentage of nurses with less than 1 license year increased 100%. Corresponding with these acute stressors, the CLABSI rate increased from 1 to 2 CLABSIs/1000 CVL days. The multidisciplinary team identified key processes to mitigate potential drivers to the increased CLABSI rate and, through small tests of change, implemented a standardized process for daily hygiene, increased awareness of high-risk patients with CLABSI, improved education/assistance for nurses performing high-risk central venous catheter procedures, and developed a system to improve allocation of resources to de-escalate system stress. After implementation of the interventions, the CLABSI rate decreased nearly 70% (0.39 CLABSIs/1000 CVL days).

Microsystem stress, caused by increased census and acuity, can be extended to physicians as well. Neuraz et al. performed a multicenter analysis evaluating workload and mortality in eight adult ICUs. The risk of death was increased by 2.0 (95% CI, 1.3–3.2) when the patient-to-physician ratio exceeded 14. High patient turnover (adjusted relative risk, 5.6 [2.0–15.0]) and the volume of life-sustaining procedures performed by staff (adjusted relative risk, 5.9 [4.3–7.9]) were also associated with increased mortality [160]. Additional studies, including hospitalists, intensivists, and surgeons, report that excessive attending physician workload has a negative impact on patient care [161–163]. These studies suggest that hospitals should provide mechanisms to provide greater staffing assistance and systems responsive to acuity and census fluctuations to improve safety and quality of care.

Cardiac Monitor Alarms and Alarm Fatigue

Alarm fatigue, the lack of response due to excessive numbers of alarms resulting in sensory overload, can create desensitization and result in missed alarms [164, 165]. In addition, high alarm rates can lead to decreased response to alarms, discomfort for patient families, and unnecessary resource utilization [166]. Due to the risk for acute decompensation, cardiac monitor alarms are frequently utilized in pediatric HSCT inpatients.

Dandoy et al. determined the impact of implementation of a standardized cardiac monitor care process on the rate of cardiac monitor alarms, and alarm fatigue in the Bone Marrow Transplant Unit at Cincinnati Children's Hospital Medical Center [166]. The team measured the number of alarms per monitored day on patients. The cardiac monitor care process was developed through evaluation of the existing literature, and through Plan-Do-Study-Act testing. The standardized process included measurement of four components:

(a) Age-appropriate parameters for patients upon placement on a cardiac monitor
(b) Daily electrode changes
(c) Daily evaluation of cardiopulmonary monitor parameters
(d) Timely discontinuation of the monitor once the patient was off patient-controlled analgesia or clinically stable

In addition, customized monitor delays and increased parameter threshold settings were evaluated and utilized. The nursing staff also utilized an "excessive monitor algorithm" when patients or staff felt that alarms were too frequent (Fig. 17.6).

The unit's overall compliance with the process increased to a median of 95% (from 30%). As compliance improved, there was a decrease in the number of alarms, from a median of 180 to 40. During the implementation, the median number of false alarms on the floor fell from 95% to 50%. In addition, the median time that individual nurses spent addressing frequent alarms decreased from 25 min per shift to 10 min per shift, including the time it took each nurse to complete the monitor log.

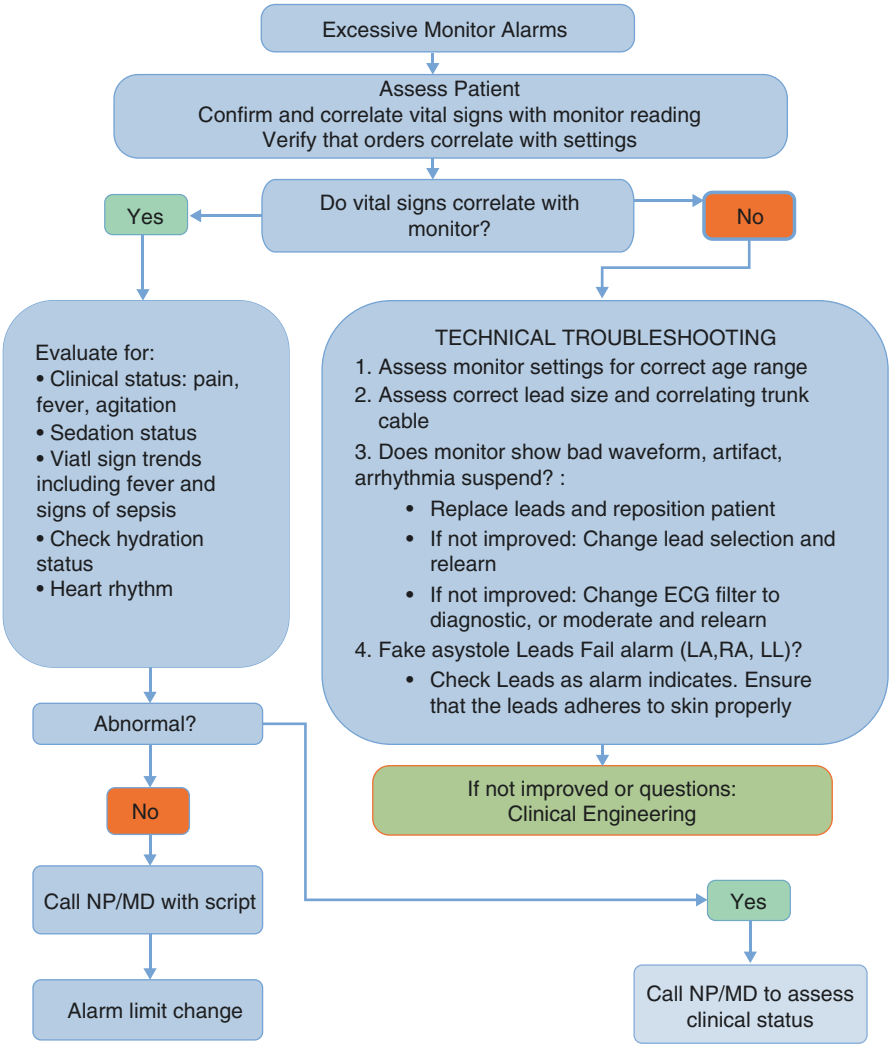

Fig. 17.6 Excessive monitor algorithm. Adopted from Dandoy et al. [166]

Finally, no acute decompensations, code, or staff emergency occurred or were missed because of the cardiac monitor care process.

Hospital Readmission After HSCT

Pediatric HSCT recipients are typically discharged to the outpatient setting shortly after engraftment. However, full immune reconstitution does not occur for many months afterward, especially following an allogeneic transplant [167]. Shulman et al. reviewed the records of pediatric patients who underwent HSCT over a 3- year period of time at Dana-Farber/Boston Children's Hospital Cancer Center to determine the incidence and risk factors for hospital readmission [168]. Their group found 63% of patients had at least on readmission in the first 6 months after transplant (78% of allogeneic, 38% autologous) for mean length of hospital stay of 10.7 days (range of 1–129 days). The majority of patients were readmitted for fever (72% in autologous, 52% in allogeneic) with 30% of allogeneic recipients readmitted for gastrointestinal symptoms. There are no published reports investigating mechanisms to decrease hospital readmission after HSCT, neither in the pediatric nor adult literature. Further investigation could include enhanced predischarge education by nurses and pharmacists and ongoing outpatient education and follow-up [169]. Additional strategies could focus on outpatient management of fever in low-risk patients and early removal of CVLs after HSCT [168].

Future Steps in Pediatric Quality

Long after therapy for a malignancy is over, survivors face ongoing physical, emotional, and practical challenges. Patient-centered research is now focusing more on the development of the best content for, and models of, comprehensive, posttreatment follow-up care. Currently, the only way to determine HSCT success is to evaluate survival at varying time points post-HSCT. We must also focus on outcomes most important to the patients themselves. Through the Patient-Centered Outcomes Research Institute (PCORI), the National Marrow Donor Program (NMDP) is conducting a patient-centered initiative to determine which HSCT outcomes are most important to patients and decide which research questions must be pursued.

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