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# Evaluation of Children with Malignancies for Blood and Marrow Transplantation: A Report from the ASTCT Committee on Practice Guidelines

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A B S T R A C T

Evaluation of a candidate for hematopoietic cell transplantation (HCT) is a complex process with substantial intercenter variability. Although literature providing guidance for evaluating the eligibility of adults is well established, similar guidance for children is lacking. To address gaps between adult recommendations and the specific needs of children, we convened a panel of pediatric HCT experts from a wide geographic range of American Society of Transplantation and Cellular Therapy (ASTCT) member institutions to offer recommendations for pediatric-focused pre-HCT evaluation. In this report from the ASTCT Committee on Practice Guidelines, we present a practical framework for evaluating children with malignancies who are candidates for HCT. We also highlight key differences from adults and emphasize areas of unmet need that require additional research to delineate best practices.


## INTRODUCTION

Indications for hematopoietic cell transplantation (HCT) in children are increasing, with more than 1000 pediatric HCTs performed annually over the past decade in the United States alone [1]. Evaluation of a candidate for HCT is a complex process with substantial intercenter variability. Various opinion pieces have provided guidance for evaluating the eligibility of adult recipients for HCT [2,3], but similar guidance for children is lacking.

Notable clinical differences between pediatric and adult HCT recipients include indications, disease biology, age-related variations in body size and composition, and physiologic differences in organ function and metabolism. Moreover, psychosocial factors that affect children include not only resources and family dynamics, but also the neurodevelopmental status of the child. Pediatric transplantation centers have developed institutional standard operating procedures for pre-HCT evaluation, but there is little harmonization across centers.

To address gaps between adult recommendations and the specific needs of children, we convened a panel of pediatric HCT experts from a wide geographic range of American Society of Transplantation and Cellular Therapy (ASTCT) member institutions to offer pediatric-focused pre-HCT evaluation recommendations. We reviewed pre-HCT evaluations at panel

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member institutions and performed targeted literature searches for data on pediatric-specific organ function assessments and ancillary support services. We confined our focus to HCT for malignancies because the breadth of nonmalignant pediatric indications involves many disease-specific considerations beyond the scope of this project.

Our suggested approach provides a practical framework for evaluating children who are candidates for HCT. We also highlight key differences from adults and emphasize areas of unmet need that require additional research to delineate best practices. Given that data to support pediatric-specific pre-HCT practices can be lacking, often forcing extrapolations from adult approaches, the discussions below incorporate expert opinion but with an attempted harmonization toward commonly performed assessments. Recommendations are summarized in Table 1, and an outline of the pre-HCT planning process is provided in Figure 1.

## Disease-Related Factors

*Indication, disease status, and risk category*

The underlying disease indication for HCT is the main driver of HCT planning and its tempo, donor selection, and preparative evaluation checklists. Allogeneic HCT indications in pediatric malignant disease typically include high-risk acute myeloid leukemia (AML), relapsed or refractory acute lymphoid leukemia (ALL), relapsed or refractory chronic myeloid leukemia, juvenile myelomonocytic leukemia, myelodysplastic syndrome, and some high-risk lymphomas, whereas autologous HCT is indicated for lymphomas and a variety of high-risk solid tumors, with the most common procedure being tandem autologous HCT for high-risk neuroblastoma [4]. These indications have been described in more detail by an ASTCT Committee on Practice Guidelines Task Force [5].

Performing an assessment of disease status before HCT is essential, the components of which are guided by the primary disease, usually in collaboration with the referring oncologist. These are summarized in Table 1 and include close attention to disease status in the central nervous system for leukemia, testing for measurable residual disease, and cross-sectional or functional imaging to assess chemosensitivity when appropriate. Measurable residual disease pre-HCT in patients with acute leukemia is known to be a strong predictor of outcome, and although it has been measured by flow cytometry in recent years, emerging evidence suggests that next-generation sequencing may predict risk more accurately [6].

Disease risk features and remission status guide the pre-HCT estimation of expected outcome and influence pre-HCT evaluation and the HCT plan. The Pediatric Disease Risk Index is a recently validated tool for estimating overall and leukemia-free 5-year survival in children with hematologic malignancy [7].

*Identifying a donor*

As in HCT for adult patients, the donor search process and types of donors considered are driven primarily by the indication for transplantation. Because matched sibling or haploidentical donors are used more frequently, parents may be dealing with the psychological ramifications of treatments and testing not only for their child with severe illness, but also for siblings who are being considered as potential donors. In pediatric related donor HCT, parents may face unique challenges in balancing recipient and sibling donor emotional and psychosocial needs or logistics of their own donor workup and collection while managing a child undergoing arduous cancer treatment. The considerations for choosing one donor or graft type versus another, including donor availability and timeline to HCT, lie outside the scope of this work, but the psychosocial effects that reverberate throughout the family during the donor search are addressed below. Additional layers of complexity are introduced when the patient has a germline predisposition for malignancy, necessitating genetic testing of family members. The preparations for HCT are also affected by the degree of HLA matching, because mismatched grafts warrant additional testing, such as for donor-specific antibodies.

## Patient-Related Factors

*Physiologic*

**Cardiovascular.** Children undergoing HCT for hematologic malignancy often have prior anthracycline exposure, putting them at risk for cardiac complications [8–12]. Prior chest wall irradiation and higher doses of total body irradiation further increase this risk [13–15]. Although cardiac iron deposition from blood transfusions is an even greater concern for patients who undergo transplantation for nonmalignant indications such as hemoglobinopathies, its potential contribution to cardiotoxicity in patients with malignancies remains relevant [16–18]. A baseline routine 12-lead electrocardiogram is recommended to assess for conduction or rhythm abnormalities and QT interval prolongation. Echocardiography is recommended to assess structure and function, with reflexive cardiology consultation if abnormal. Guidelines for cardiac evaluation prior to HCT are mostly arbitrary given limited prospectively collected cardiac outcomes data for children [19]. Although additional research is needed to identify risk cutoffs, a left ventricular ejection fraction of ≥45% is preferred by most transplantation centers and for clinical trials for myeloablative conditioning [2,3,20].

**Renal.** Because normal creatinine values depend on age and muscle mass [21], adopting a uniform serum creatinine cutoff for HCT eligibility is problematic and inadequate for identifying compromised renal function in children undergoing HCT [22]. The glomerular filtration rate (GFR) is more accurate for evaluating kidney function in children, and in the HCT setting, GFR measurement via nuclear radioisotope $^{99m}$Tc-labeled diethylene triamine penta-acetic acid or iohexol is often preferred over GFR-estimating calculations for accurate assessment of renal function [21,23,24]. Cystatin C has emerged as a potentially useful proxy for GFR, but data on its use in the HCT setting for children of all ages remain premature [21,23]. We recommend assessing GFR rather than serum creatinine to determine renal function pretransplantation when there is a history of renal compromise or when nephrotoxic agents are expected to be used in HCT. For patients with suboptimal or borderline renal function, it may be necessary to plan appropriate dosage adjustments in the conditioning regimen and supportive care medications.

**Pulmonary.** Infectious and noninfectious pulmonary complications are major causes of morbidity and mortality after HCT [25–28], and pre-HCT pulmonary function correlates with pulmonary complications and overall survival post-HCT [29–31]. When feasible, pre-HCT pulmonary function tests (PFTs) help establish a baseline and detects obstructive or restrictive lung disease related to prior therapies or prematurity [32]. Of note, children age <6 years are generally unable to perform PFTs. Although research on alternative measures of pulmonary function in this youngest age group is ongoing [33–40], we recommend at least pulse oximetry and consideration given to chest imaging. For those who are capable, pre-HCT PFTs should be performed, as well as pulmonary consultation for any children with abnormal PFTs (eg, low forced

**Table 1**
Summary of Pre-HCT Evaluation Recommendations

| Category | Pretransplantation Recommendations | Unique Pediatric Recommendations/ Other Notes | Focus for Future Research |
|---|---|---|---|
| Disease status | Review all available diagnostic and relapse specimens (as clinically appropriate). | Neuroblastoma:<br>• MIBG scan for MIBG-avid disease | • Further validation and refinement of the Pediatric Disease Risk Index for hematologic malignancies<br>• Development of novel risk assessment and prognostic tools for pediatric solid tumors |
| | Confirm current disease status:<br>• Leukemia: assess marrow MRD by flow, cytogenetics/FISH, molecular and NGS as appropriate based on prior results; assess CSF cell count and/or by flow (if clinically indicated).<br>• Solid tumors or extramedullary leukemia: cross-sectional or functional imaging. | Medulloblastoma:<br>• MRI brain and spinal cord | |
| | | Soft tissue sarcomas:<br>• cross sectional imaging of primary site and metastatic foci | |
| | | JMML:<br>• evaluate size of spleen | |
| Cardiac | ECG and echocardiography:<br>• Left ventricular EF for myeloablative conditioning ideally should be ≥45%. | Consider pediatric cardiology consultation in<br>• prior history of chest wall irradiation<br>• congenital cardiac anomalies<br>• abnormal ECG/echocardiogram. | • Prospective evaluation of EF cutoffs for myeloablative or reduced-intensity conditioning<br>• Age-appropriate metrics for evaluating cardiac function in addition to EF, such as myocardial strain |
| | Cardiac T2*-weighted MRI if heavily transfused with elevated ferritin or known prior elevated liver iron content | | |
| Renal | In stable kidney function over time and no history of significant nephrotoxic agents:<br>• Serum creatinine or noninvasive GFR estimation (eg, 24-hour creatinine clearance may be sufficient) | Serum creatinine may be inadequate to identify compromised renal function in children, as it varies by age and muscle mass. Although an issue for patients of all ages, this can be greater in children due to the wider range of body sizes and composition. Thus, GFR measurement via nuclear isotope methodology may be preferable for patients with a history of renal compromise or in preparation for nephrotoxic agents in HCT. | Validation of cystatin C or other simple noninvasive/inexpensive measurements to estimate GFR in children |
| | In borderline renal function or high risk for renal insufficiency:<br>• GFR estimate by nuclear isotope methods is usual. | | |
| Pulmonary | PFTs (spirometry, plethysmography, DLCO) should be performed when possible. | Patients age <6 years are typically unable to reliably perform FEV1 and plethysmography. | Ongoing trials [112] aim to test more sensitive and reproducible PFT methodologies for children age <6 years, including exploration of FEV .5, multiple breath nitrogen washout, and other techniques more suitable for toddlers. |
| | If lung function compromised pre-HCT:<br>• pulmonology consultation and possibly modification of HCT conditioning. | In significant asthma or chronic lung disease of prematurity:<br>• pulmonology consultation for pretransplantation lung optimization (medications, or nighttime BiPAP or tonsillectomy for sleep apnea). | |
| Nutritional status | Dietician consultation for:<br>• baseline anthropometry and nutritional status to identify overweight or undernourished children at high risk of worse nutritional outcome<br>• baseline electrolytes and vitamin D level. | Enteral nutrition is generally prioritized over parenteral nutrition:<br>• consider early or preemptive nasogastric tube placement. | Markers other than BMI to identify those at risk of poor nutrition and interventions to proactively improve peritransplantation nutrition. |
| Hepatic | Check serum AST, ALT, alkaline phosphatase, bilirubin, and albumin. | Children are at higher risk for VOD than adults. | Screening tests to identify those at higher risk for VOD are under investigation including an active prospective trial evaluating ultrasound elastography. |
| | Assess risks for VOD (eg, inotuzumab, iron overload, prior prolonged TPN use). | Assessment of liver iron content by T2* MRI may identify those at even higher risk. | |
| Endocrine | Consider baseline evaluations of:<br>• hyperlipidemia<br>• thyroid function<br>• early morning cortisol if history of glucocorticoid use, or cosyntropin stimulation testing if high suspicion for adrenal insufficiency but AM cortisol is normal. | Children may experience marked long-term effects on growth and bone health. Particularly with high-dose total body irradiation-based conditioning, or the potential need for chronic glucocorticoid use to treat chronic GVHD, anticipatory counseling should be provided. | • Methods to detect those most at risk of disturbances to growth or pubertal development<br>• Methods to limit these toxicities (eg, steroid-sparing agents) |
| Neurocognitive | If feasible, consider baseline neurocognitive screening to identify areas of dysfunction that may already exist from prior treatment or underlying diagnosis. | Neurocognitive/developmental function assessment can be helpful given its broad variability in children. Data on the neurocognitive impact of HCT on children is mixed, but testing should be considered when brain radiation has been or will be performed in HCT. | How changes in neurocognitive test results truly impact psychosocial outcomes remain undefined and need further investigation. |

(*continued*)

**Table 1** (*Continued*)

| Category | Pretransplantation Recommendations | Unique Pediatric Recommendations/ Other Notes | Focus for Future Research |
|---|---|---|---|
| Dental | A comprehensive dental evaluation to:<br>• identify, minimize, and/or mitigate active or potential sources of infection<br>• provide counseling on oral hygiene. | Conditioning regimens may impact:<br>• craniofacial development<br>• secondary tooth eruptions<br>• loss of primary teeth<br>• orthodontic hardware. | The effects of optimized dental care on the incidence and severity of mucositis and oral flora bacteremia |
| Performance status | Karnofsky Performance Status score for patients age ≥16 years | The Lansky Play-Performance Scale is the most widely used performance status score for patients age <16 years. | Adaptations to the HCT Comorbidity Index to extend applicability to children are needed. |
| Psychosocial | Early patient consultations with at least one of:<br>• social workers<br>• child life specialists<br>• psychologists.<br><br>Young siblings (especially donor) may also benefit from similar consultation. | HCT preparatory assistance may include:<br>• developing an academic catch-up plan<br>• providing age-appropriate explanations or coping strategies<br>• assessing parental financial and social supports to develop a plan for taking leave from work to care for the child. | Best practices for interventions that minimize the emotional and psychological toll that HCT takes on children, as well as their pediatric sibling donors, should be the subject of further research and program development. |
| Fertility | Fertility issues are one of the largest sources of regret for long-term survivors:<br>• Every effort should be made to pursue options for an interested family.<br>• Early referral to a fertility preservation specialist allows patients/families to be maximally informed about options and potentially have time to prepare for any desired interventions. | All children may have experimental or nonexperimental fertility preservation options:<br>• prepubertal ovarian or testicular tissue cryopreservation<br>• postpubertal oocyte or embryo or semen cryopreservation<br>• consideration to gonadal shielding in males or ovarian transposition in females. | Ways to improve:<br>• universal availability of fertility preservation services<br>• the success of post-HCT options for those who suffer from impaired fertility. |
| Palliative care | Early consultation with palliative care to:<br>• lay groundwork of the multidisciplinary team relationship<br>• discuss goals of care: pain management, coping, and other issues. | Although several stages of maturity are represented from infants through young adults, many children have hopes and goals for their own care. | • Improved preemptive goals of care planning<br>• Increased involvement of palliative care teams |
| Infectious disease testing | Universal testing of all recipients for:<br>• HIV, HTLV1/2, CMV, EBV, HSV, VZV, HBV, HCV, West Nile virus, syphilis, Chagas disease, and *Toxoplasma*.<br><br>Additional tests per epidemiologic/social risks:<br>• histoplasma, blastomyces, coccidioides, strongyloides, stool for ova and parasites, tuberculosis, malaria, Zika. | Because asymptomatic upper respiratory infections are more common in children:<br>• Confirming a negative respiratory viral panel is recommended before starting conditioning. | Evidence-based screening plans for primary or reactivated infection through the HCT course are needed, depending on the risk factors each patient brings to HCT. |

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; BiPAP: bilevel positive airway pressure; BMI, body mass index; CMV, cytomegalovirus; CSF, cerebrospinal fluid; DLCO, diffusion capacity of the lungs for carbon monoxide; EBV, Epstein-Barr virus; EF, ejection fraction; ECG, electrocardiography; FEV1, forced expiratory volume in 1 second; FEV.5, forced expiratory volume in .5 second; FISH, fluorescent in situ hybridization; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV1/2, human T lymphotropic virus 1 and 2; HSV, herpes simplex virus; JMML, juvenile myelomonocytic leukemia; MIBG, meta-iodobenzylguanidine; MRD, minimal residual disease; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PFT, pulmonary function test; TPN, total parenteral nutrition; VOD, veno-occlusive disease; VZV, varicella zoster virus.

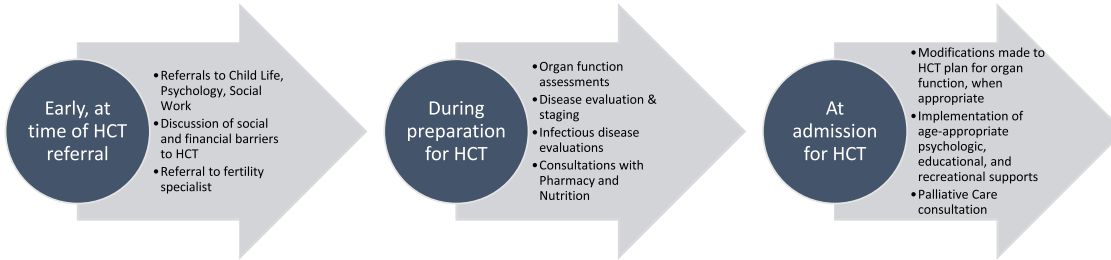


**Figure 1.** Timeline of pre-HCT evaluation.

expiratory volume in 1 second, low diffusion capacity of the lungs for carbon monoxide) or prior history of lung disease. A chest CT to screen for preexisting pulmonary infections is also suggested, especially in patients with hematologic malignancies.

**Nutritional status.** Overweight subjects have inferior survival outcomes after HCT [41,42]. Regimen-related toxicities (vomiting, mucositis, anorexia) and increased catabolism can all contribute to rapid post-HCT nutritional decline [43,44]. Obesity and underweight status have been associated with an increased risk of graft-versus-host disease (GVHD) [45,46], although data are conflicting [47,48]. Although body mass index should not affect the decision of whether to proceed to HCT, it might alter the transplantation approach, supportive care, or conditioning regimen drug dosages [49]. All children should be evaluated by an experienced dietitian, including baseline anthropomorphic measurements and identification of food allergies. Serum albumin and prealbumin biomarkers are used to assess and monitor nutritional status [43,50] but can be confounded by other HCT complications; therefore, no single biomarker has been shown to correlate directly to nutritional status [51]. Baseline electrolyte and vitamin D levels should be obtained as part of nutritional screening to be optimized prior to HCT [52]. Anticipatory guidance should be provided to the child and family regarding an expected decline in oral intake, avoidance of undercooked foods that may be a source of infection, and approaches for nutritional supplementation. This includes enteral feeding via a nasogastric tube and i.v. total parenteral nutrition.

**Hepatic.** During HCT, the liver is subject to increased metabolic demands and is at risk for injury from conditioning chemotherapy and/or radiation, medications, infection, veno-occlusive disease, and GVHD. Current recommendations for assessment of hepatic function rely on measurement of alanine aminotransferase, aspartate aminotransferase, albumin, prothrombin time/international normalized ratio, and total bilirubin. However, appropriate cutoff levels that portend increased hepatic complications post-HCT are unknown. Children can be at increased risk for veno-occlusive disease compared to adults, with an incidence between 10% and 40% [53,54]. Risk factors include young age (<2 years), low body weight, receipt of a mismatched graft [53], prior chemotherapy with inotuzumab ozogamicin or gemtuzumab ozogamicin [55,56], steatohepatitis from long-term steroid use [57,58] or prior liver injury, prior abdominal radiation for solid tumors, and busulfan- or total body irradiation-based conditioning. The significance of an elevated ferritin may vary by patient and disease entity. In heavily transfused patients, estimation of liver iron content can be a more accurate marker of hepatic iron overload and may be used to guide decisions about the utility of pre-HCT chelation.

**Endocrine.** Multiple late endocrine effects are seen after HCT [59], including thyroid dysfunction [60], diabetes [61], dyslipidemia [62], growth and bone health problems [63], adrenal insufficiency [64], and issues with puberty or fertility [65,66]. For all patients, we recommend fasting blood glucose, a lipid panel and triglycerides, and thyroid-stimulating hormone as a baseline pre-HCT. Patients with a history of prolonged exposure to steroids also may require a baseline early morning cortisol level for screening or a cosyntropin stimulation test if there is significant concern for adrenal insufficiency. Preparations also may be made for menstrual suppression, when appropriate.

**Neurocognitive.** Reports on the effect of HCT on neurocognitive development in children are mixed, and additional research is needed [67–77]. Certain factors may portend a higher risk, including younger age at transplantation, chemotherapy that crosses the blood-brain barrier, radiation to the brain, immunosuppressive therapy, and the occurrence of GVHD or infection [73,78]. Pretransplantation screening for neurocognitive function may be considered to provide a baseline and identify areas of dysfunction that may already exist from prior treatment or underlying diagnosis, although the implications of neurocognitive test changes on psychosocial outcomes are unclear and should be the subject of additional research.

**Dental.** As many as 58% of children preparing for HCT have dental issues that necessitate intervention [79]. A comprehensive dental evaluation has been associated with reduced rates of mucositis and febrile neutropenia [80], and minimizing gingivitis and periodontitis may result in less gingival bleeding [81]. The oral evaluation should be performed at least 2 weeks before conditioning to allow for healing [82] and should include cleaning and elimination of active dental infections or sources of trauma [83]. Primary teeth preparing for exfoliation may be extracted, and incipient caries may be temporized with fluoride application and sealants [84]. Orthodontic hardware, which may increase the risk of mucosal trauma and secondary infection, may be removed [83]. Anticipatory guidance about mucositis and proper peri-HCT oral hygiene also can be provided [82,84].

**Performance status.** The Lansky Play-Performance Scale (age, 1 to 16 years) attempts to parallel the Karnofsky Performance Status scale used for patients age ≥16 years and has become the standard assessment for functional fitness and ability of children to tolerate HCT. A single study of adults and children receiving nonmyeloablative conditioning showed that pre-HCT performance score (Karnofsky or Lansky) was independently associated with post-HCT survival [85]. Despite the limitations in applying performance scoring to children who have cognitive delays or are chronically hospitalized, the Lansky Scale remains the sole available functional assessment tool for children. Therefore, we recommend pre-HCT scoring of performance status using the Lansky or Karnofsky Scale as age-appropriate.

To summarize a patient's physiologic condition pre-HCT, the HCT Comorbidity Index (HCT-CI) is often used for adults. The HCT-CI quantifies the patient's pre-HCT comorbidity burden; those with a higher HCT-CI have inferior survival outcomes [86]. However, the HCT-CI can be challenging to apply in children, and its applicability to this age group has not been sufficiently validated [22,87-89]. Efforts for pediatric adaptation of the HCT-CI are ongoing [22] and are expected to yield a useful tool for pre-HCT evaluation [90].

*Psychosocial*

Children exhibit a wide spectrum of emotional capabilities and neurodevelopmental stages, making psychological and social considerations extremely important in the pre-HCT preparations for children. HCT causes an enormous disruption to normal childhood milestones and social development through long hospitalizations, isolation, pain, fear, critical illness, and loss of privacy and control. As a result, children may develop anxiety or a sense of isolation. Their loss of control can lead to behavioral problems, depression, anger, and frustration [91]. For some, there may be long-term consequences of these psychosocial effects, with declines in social competence, self-esteem, and cognitive performance [91]. Preemptive educational assessments and the development of an academic catchup plan may help patients falling behind their

peers from missed school, but the social aspects of missing out may be difficult to recreate in the hospital or in relative isolation at home.

Siblings of HCT recipients also may be affected psychologically by the disruption of family dynamics, loneliness, and limited understanding of the transplantation process [91]. Children who become stem cell donors for a sibling have unique needs; they have been shown to experience a complex mixture of positive and negative feelings about being a donor, feelings that are sometimes not fully appreciated by the parents [92]. Studies on the well-being of sibling donors conclude that pediatric HCT teams must provide adequate education and anticipatory guidance to prepare pediatric donors and the rest of the family for the HCT process [93–95].

Preemptive consultations with psychology, child life, and social work can prepare the parents, the donor, and the other siblings, as well as ameliorate the negative experience of HCT for the recipient. Packages of these interventions are modeled at some centers [94,96] and are recommended early in the HCT consultation process to aid coping and improve the transplantation experience for both patient and siblings. The social worker assists in discussing the immense toll that HCT may take on a family's finances and time, as well as the logistical challenges it will bring. Specific areas to be addressed should include preparations and letters of support for caregivers to take leave from work, arrangements for temporary housing when families live far from the transplantation center, and coordination of appropriate transportation for families who do not have or cannot afford transportation via private car for their frequent appointments.

## *Other Unique Considerations for Pediatric Patients*

*Fertility*

In long-term survivors of HCT, infertility or reduced fertility has long been recognized as a predictor of poor quality of life outcomes [97,98], and the Children's Oncology Group acknowledges the importance of the issue by recommending early discussion of fertility preservation before starting treatment [99]. Barriers that limit the universal provision of comprehensive fertility preservation counseling to patients may include lack of insurance coverage, healthcare team awareness, access to appropriate fertility preservation experts, or patient health/disease-related issues. Studies suggest that access to an institutional fertility preservation program allows for nearly universal fertility preservation counseling prior to gonadotoxic therapy, mirroring a substantial improvement in patient satisfaction [100]. Resources such as Oncofertility Consortium provide information on nearest centers offering these services for children and adults. The sex and pubertal status of the patient will determine whether any treatment delays will result from pursuing fertility preservation, often a key concern for patients and their families. Importantly, options available to male and female patients are continuing to expand, including the recent removal of the experimental label from ovarian tissue cryopreservation [101]. And increasingly encouraging data have been emerging on the return of ovarian/endocrine function and live birth rate following ovarian tissue cryopreservation and subsequent implantation [102]. Options for prepubertal males are less well developed, as evidence is still lacking for successful testicular tissue cryopreservation, reimplantation, or in vitro maturation [103]. Fertility preservation options available to children facing HCT are summarized in Table 1 and are the same for allogeneic and autologous HCT.

*Pharmacy*

Many centers involve pharmacists in the HCT planning process to perform a medication reconciliation, review allergies and potential drug interactions [104,105], and assess medication access or adherence barriers. Pharmacists enhance patient preparedness for the complex post-HCT medication regimens by providing extensive education, help plan dosage adjustments for various conditioning and supportive care agents, and have a critical role in ensuring the success of a HCT because the metabolism of chemotherapeutic and supportive care medications can vary based on a child's age, body weight, surface area, and hepatic or renal function [105,106]. We recommend that each center adopt the practice of collaborating with pharmacists early in the planning process. A template that can be used for an initial pharmacy consult as developed by the team at the University of Minnesota is provided in Supplementary Data.

*Palliative care and symptom management*

The timing of palliative care team involvement for children undergoing HCT varies widely across institutions, with consultations sometimes not requested until close to the end of life. Palliative care team involvement in the care of any child with a life-threatening illness is recommended by the American Association of Pediatrics Section on Hospice and Palliative Medicine guidelines [107]. Their expertise can help elicit and discuss issues related to quality of life, which pairs nicely with symptom management throughout the transplantation process. Palliative care teams also can facilitate communication among patients, caregivers, siblings, and multidisciplinary medical providers [108]. Given that HCT is intense and cure-focused, when that goal is not achieved, patient families and caregivers are at high risk for psychological morbidity. Palliative care functions most effectively when these stakeholders are able to discuss and lay groundwork for goals before discussing symptom management and potentially resuscitation status and end-of-life care. It follows that palliative care is best introduced pretransplantation or at least early in a patient's HCT course [109].

*Infectious history*

Patients undergoing HCT, especially from an allogeneic donor, are at a high risk of infectious complications and mortality, and thus preventive and preemptive monitoring and treatment strategies should be addressed in the pretransplantation evaluation. The risk of various infections depends on disease-, patient- and transplantation-related factors and includes the risk of translocation of the patient's own microbial flora or reactivation of a previously latent infection from the recipient or donor. Pretransplantation evaluation should focus on determination of the HCT recipient's risk, including such variables as immunization history, prior countries lived in, and family member exposures. Infection control measures may be planned based on the identified risks. History should be elicited with attention to cultural, social, and behavioral patterns that may put the patient at risk for future infection (eg, dwelling place and occupational risks of caregivers). Laboratory testing of the transplantation recipient and donor to look for evidence of past infections and current asymptomatic or latent pathogens includes a basic panel of laboratory studies required by regulatory agencies (Table 1) [110,111]. Finally, imaging studies may be required to rule out active infections such as tuberculosis or fungal infections if the evaluation suggests exposure. This process may be aided by Infectious Diseases (ID) team consultation, particularly with ID specialists who

have expertise in HCT. Benefits of preemptive ID consultation include assistance with determining opportunistic infection prophylaxis, as well as establishing treatment plans for patients with a history of multidrug-resistant organisms and automatic approvals within antimicrobial stewardship programs.

## CONCLUSION

Children with malignancy who require HCT for cure have a unique set of psychosocial needs, physical comorbidities, and disease risk features that differentiate them from adults. Given the inability for some of the important pre-HCT risk indices developed for adults to be applied to children, a specialized approach is needed, ideally with harmonization among centers. Although rigorous data on physiologic differences and randomized trials on management are lacking for children, the recommendations provided here are meant to serve as a guide for pre-HCT preparations.

We have summarized considerations for pediatric-specific organ function assessments and disease-specific factors, as well as consultants and ancillary services that should be involved early in the preparations for HCT for malignancy. Looking toward the future, we hope that this document serves as a call for further research into pediatric-specific evaluations and interventions that make the HCT experience safer and more successful for children and their families.

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## SUPPLEMENTARY MATERIALS

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