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Late Effects Surveillance Recommendations among Survivors of Childhood Hematopoietic Cell Transplantation: A Children's Oncology Group Report

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Abstract

Hematopoietic cell transplantation (HCT) is an important curative treatment for children with high-risk hematologic malignancies and solid tumors, and increasingly, non-malignant diseases. Given improvements in care, there is a growing number of long-term survivors of pediatric HCT. Compared with non-transplanted childhood cancer survivors, HCT survivors have been shown to have a substantially increased burden of serious chronic conditions and impairments involving virtually every organ system and overall quality of life. This likely reflects the joint contributions of pre-transplant treatment exposures and organ dysfunction, the transplant conditioning regimen, and any post-transplant graft versus host disease (GVHD). In response, the Children's Oncology Group (COG) has created Long-Term Follow-Up Guidelines (www.survivorshipguidelines.org) for survivors of childhood, adolescent, and young adult cancer, including those treated with HCT. Guidelines taskforces, consisting of HCT specialists, other pediatric oncologists, radiation oncologists, organ-specific subspecialists, nurses, social workers, other healthcare professionals, and patient advocates have systematically reviewed the literature with regards to late effects after childhood cancer and HCT since 2002, with the most recent review completed in 2013. For the most recent review cycle, over 800 articles from the medical literature relevant to childhood cancer and HCT survivorship were reviewed, including 586 original research articles. Provided here-in is an organ system-based overview that emphasizes the most relevant COG recommendations (with accompanying evidence grade) for the long-term follow-up care of childhood HCT survivors (regardless of current age) based on a rigorous review of the available evidence. These recommendations cover both autologous and allogeneic HCT survivors, those transplanted for non-malignant diseases, and those with a history of chronic GVHD.

INTRODUCTION

Hematopoietic cell transplantation (HCT) has long been an important curative treatment for children with high-risk hematologic malignancies and solid tumors, and increasingly, non-malignant diseases. Given improvements in care, there is a growing number of long-term survivors of pediatric HCT.[1] At the same time, given the joint contributions of pre-transplant treatment exposures and organ dysfunction, the transplant conditioning regimen, and any post-transplant graft versus host disease (GVHD), HCT survivors are at increased risk of developing a wide range of adverse late effects (Table 1). Compared with non-transplanted childhood cancer survivors, HCT survivors have been shown to have a substantially increased burden of serious chronic conditions and impairments involving virtually every organ system and overall quality of life.[2–5]

In 2011, the National Cancer Institute, the National Heart, Lung and Blood Institute, and the Pediatric Blood and Marrow Transplant Consortium organized an international conference on late effects following childhood HCT.[6] One of the sessions focused on existing oncology guidelines with relevance to the pediatric HCT survivor population.[7] While different national or professional groups have issued guidelines for this high risk population,[8–10] it was recognized that each had limitations (Table 2).[7]

Recognizing these limitations, the Children's Oncology Group (COG) guidelines taskforces herein provide an organ system-based overview that emphasizes the most relevant

recommendations for the long-term follow-up care of childhood HCT survivors based on a rigorous review of the available evidence. However, it is important to note that in many instances, the recommendations are based on studies of general childhood cancer survivors and not exclusively HCT survivors, but given the overlap in exposures, we believe data from general cancer survivors can still be highly informative. Recommendations for exposures that are uncommon to HCT survivors are not discussed, but can be found in the full guidelines (www.survivorshipguidelines.org).[11] The COG guidelines also are designed for individuals who are ≥2 years off therapy. However, recognizing the importance of the one-year post-transplant assessment for HCT survivors, and the fact that many HCT survivors have had many years of treatment prior to their transplant, we have benchmarked the following guidelines to start at one-year post-transplant unless otherwise specified. These guidelines cover both autologous and allogeneic HCT survivors, apply to survivors transplanted during childhood, adolescence, or as young adults (regardless of current age), and include those transplanted for non-malignant diseases and those with a history of chronic GVHD. However, we will not discuss the diagnosis and management of chronic GVHD itself, nor do we make surveillance recommendations related to the original indication for transplant (e.g., monitoring for cancer recurrence or specific complications of non-malignant diseases not corrected by HCT). Finally, while adherence to existing general population health screening guidelines is still recommended for all HCT survivors,[12] the COG recommendations are designed to supplement areas where survivors of childhood HCT have unique needs different from the general population.

METHODS

The COG began systematically reviewing the literature with regards to late effects after childhood cancer in 2002.[8] Taskforces, consisting of pediatric oncologists including HCT specialists, radiation oncologists, organ-specific subspecialists, nurses, social workers, other healthcare professionals, and patient advocates have systematically reviewed the literature on a biennial cycle, most recently in 2013. For the most recent cycle, across 13 taskforces, over 800 articles from the medical literature relevant to childhood cancer survivorship were reviewed, including 586 original research articles (26 systematic reviews, 36 clinical trials, 273 cohort studies, and 251 cross-sectional or case-control studies; additional literature reviewed included smaller case series, expert opinion pieces, and non-systematic reviews). The HCT taskforce, specifically conducted its search using MEDLINE with the keywords “childhood cancer therapy”, “complications”, “late effects”, combined with keywords for each therapeutic exposure, including “stem cell transplant”, “bone marrow transplant”, “autologous”, and “allogeneic”. References from bibliographies of selected articles also were reviewed. The taskforce reviews were then further curated by a Guidelines Expert Panel, which scored each specific recommendation linking a therapeutic exposure to a late effect from 1 (highest level evidence and consensus that recommended screening is appropriate) to 3 (lowest level and major disagreement that screening is appropriate; Table 3; Appendix Table 1). Only recommendations scored 2B or stronger are included in the current guidelines. The initial guidelines were released in 2003; the 4th version was released October 2013, and form the basis of this overview (Appendix Table 1 lists the sections reviewed).[11]

ENDOCRINE

Endocrine late effects are among the most prevalent chronic conditions seen following HCT in children.[5;13;14] Most endocrine abnormalities are due to primary end organ damage by chemotherapy or radiation, but central endocrine deficiencies due to hypothalamic/pituitary dysfunction can be seen among patients who have received myeloablative total body irradiation (TBI), especially if additional cranial radiation was given either prior to or as part of HCT. Growth impairment has been reported in 50% to 85% of children undergoing HCT, while other central endocrine deficiencies are unlikely to occur unless cumulative radiation doses to the hypothalamus exceed 30 Gy.[10;13] Primary hypothyroidism also is common, seen in 30% to 50% of patients after TBI.[13] In addition, HCT survivors often have disrupted gonadal function, although the degree of dysfunction varies by gender. Infertility tends to be very common in both genders, while hormonal dysfunction is more likely in females compared with males.[13] Finally, HCT survivors are at increased risk of developing metabolic syndrome, characterized by adiposity, dyslipidemia, glucose intolerance, and hypertension.[15]

Growth Hormone Deficiency

Poor growth following HCT can be due to many factors, including chronic GVHD, malnutrition, and corticosteroid use, as well as growth hormone (GH) deficiency. GH deficiency can occur after 10 Gy single fraction TBI or 12 Gy fractionated TBI, and is more common among patients exposed to additional cranial radiation (especially if ≥18 Gy).[2] Additional risk factors include younger age at exposure, time since treatment, and surgery in the parasellar region.[16] Some patients who are treated with GH may still grow poorly after TBI due to poor response to GH (end organ resistance) as well as concurrent hypothyroidism and hypogonadism. Early pubertal onset (more common after cranial radiation alone) can accelerate growth and initially mask GH insufficiency.

Concerns have been raised with respect to rates of original cancer recurrence and second cancers among pediatric cancer survivors treated with GH. Studies have not supported an increased risk for recurrence while data have been more mixed with regards to GH treatment and risk of second cancers.[17] Analyses from the Childhood Cancer Survivor Study showed an initial 3-fold increased risk for second cancers associated with GH treatment which subsequently declined over time, with no risk associated with subsequent brain tumors.[18–20] Optimal management of GH deficiency among adult-aged survivors of childhood cancer and HCT remains an active area of inquiry.

Growth Hormone Deficiency Recommendations *[Evidence: level 1 for radiotherapy]*

1. All survivors who have not attained skeletal maturity should have evaluations including height, weight, body mass index (BMI), and Tanner staging every 6 months.
2. Survivors who are growing poorly should have thyroid function and bone age evaluated, and should be referred to endocrinology if their growth rate is abnormal based on their bone age and pubertal stage.

3. While GH deficiency can occur after 10 Gy TBI or 18 Gy cranial radiation, survivors who have received ≥30 Gy of cranial radiation (inclusive of TBI) should be routinely referred to endocrinology regardless of signs or symptoms due to a high risk for central endocrine disorders which can adversely affect growth.
4. Adult GH replacement should be discussed with an endocrinologist.

Thyroid Disease

Primary hypothyroidism, hyperthyroidism (rarely), and the occurrence of thyroid nodules (and thyroid cancer) can be seen after TBI exposure. Risk is further increased by prior radiation exposure to the thyroid (especially cumulative doses ≥20 Gy), and increased time since exposure.[14;21;22] In general, females are at higher risk of thyroid disease compared with males, and younger age at exposure has been implicated as an additional risk factor in some studies.[23;24] Notably, for thyroid cancer, risk may begin to decrease at radiation doses beyond 30 Gy compared with lower doses due to ablation and fibrosis of thyroid tissue.[25] The additional utility of thyroid ultrasound to detect thyroid nodules versus palpation as a screening modality for thyroid cancer remains an active area of inquiry.[26]

Thyroid Disease Recommendation *[Evidence: level 1 for radiotherapy]*

1. Survivors with any neck radiation exposure, including TBI, should have an annual history to elicit symptoms of thyroid dysfunction, and measurement of free T4 and TSH.
2. These survivors also should have annual palpation of the thyroid gland for nodules, recognizing that the use of ultrasound as a first-line screening modality remains controversial in this population.

Gonadal Function

Gonadal function can be impaired by TBI, alkylating and similar DNA inter-strand crosslinking agents (i.e., platinum-based agents) when used as components of HCT preparative regimens. Exposure to these chemotherapy agents and gonadal radiation pre-transplant further enhance the likelihood of gonadotoxicity. Gonadal damage may manifest as delayed/arrested puberty, post-pubertal gonadal insufficiency, or impaired fertility.[14;27;28] Precocious puberty can be seen after lower doses of cranial radiation, though not typically after TBI.[18;19]

In males, alkylating and similar DNA-inter-strand crosslinking agents are toxic to spermatogonial germ cells (particularly at cumulative doses exceeding cyclophosphamide ≥7.5 gm/m^2, ifosfamide ≥60 mg/m^2, MOPP ≥3 cycles, or busulfan ≥600 mg/m^2).[27] Leydig (testosterone producing) cells tend to be more resilient, and may only manifest dysfunction at doses ≥20 gm/m^2 of cyclophosphamide (or when given as part of HCT conditioning) and ifosfamide (≥60 mg/m^2).[27] Germ cells also are more sensitive to damage from radiation with

permanent azoospermia likely after 6 Gy to 10 Gy while testosterone insufficiency in Leydig cells may not occur until ≥20 Gy.[27]

Females are particularly sensitive to gonadotoxic therapies due to the finite reserve of the primordial follicle pool. In contrast to males, in females there also is less of a differential gonadotoxic effect on oocyte production relative to hormone production. Older age and pubertal status at time of exposure increase the risk of ovarian dysfunction, with infertility associated with lower radiation doses among pubertal versus prepubertal girls (≥5–10 Gy versus ≥10–15 Gy, respectively).[28–30] In addition, radiation including TBI is a risk factor for uterine vascular insufficiency, which can affect fertility.[28] Radiation as well as chronic GVHD also can increase the risk of vaginal fibrosis and stenosis.[28;31] Finally, ovarian failure and infertility also can occur after exposure to alkylating or similar DNA inter-strand crosslinking agents, including those used as part of HCT preparative regimens, but dose thresholds are less well-established for females.[28–30] Ovarian failure can occur soon after transplant or manifest later as premature menopause.[29;30;32]

Gonadal Function Recommendations *[Evidence: level 1 for alkylating agents, radiotherapy; level 2A for DNA inter-strand crosslinking agents]*

1. Survivors exposed to TBI, cranial radiation, alkylating agents, or similar DNA inter-strand crosslinking agents should have an annual assessment of pubertal development, and sexual and reproductive function.
2. In at-risk males: a) morning testosterone beginning no later than age 14 and as clinically indicated; b) semen analysis is most informative to assess risk for infertility, but FSH has been suggested as a possible surrogate measure of germ cell damage in those unable/unwilling to give a semen specimen. However, this remains an active area of inquiry.[33]
3. In at-risk females: a) LH, FSH and estradiol beginning no later than age 13 and as clinically indicated; b) those with a history of radiation to the female reproductive system or chronic GVHD should be evaluated for vaginal fibrosis and stenosis.
4. Both males and females with evidence of abnormal pubertal timing or gonadal dysfunction should be referred to endocrinology, gynecology, or urology as indicated. Survivors who are experiencing difficulties conceiving should receive referral to reproductive specialists.

Obesity, Dyslipidemia, and Diabetes

Cranial radiation is a well-documented risk factor for obesity among childhood cancer survivors,[34] and while TBI itself does not appear to lead to increased BMI, survivors treated with TBI tend to have increased central adiposity (which may not always closely correlate with BMI).[15] TBI exposure also has been strongly associated with subsequent dyslipidemia and impaired glucose intolerance, and a greater risk of developing diabetes mellitus and metabolic syndrome.[15;34] Separate from TBI, any abdominal radiation also has been associated with an increased risk of diabetes.[34;35] The presence of untreated

endocrinopathies such as GH deficiency, hypothyroidism, and hypogonadism can further exacerbate these comorbid conditions.[15]

Obesity, Dyslipidemia, and Diabetes Recommendations *[Evidence: level 1 for radiotherapy]*

1. All survivors should have weight status assessed annually, especially after cranial radiation (including TBI).
2. Survivors treated with any abdominal radiation (including TBI) should be screened with a fasting blood glucose (or hemoglobin A1c) and a lipid profile every 2 years.

BONE HEALTH

Childhood HCT survivors are at increased risk of reduced bone mineral density (defined in children as z-score >2 standard deviations below age and gender-matched population norms) and avascular necrosis (AVN). Low bone mineral density has been reported in up to one-quarter of childhood HCT survivors.[13;36–38] Rates of avascular necrosis (AVN) are not as well described, although not all children with MRI findings have clinically significant symptoms.[39;40]

Host risk factors for abnormal bone mineral density include younger age at primary diagnosis and at transplant, Caucasian ethnicity, GVHD therapy, and lower weight/BMI.[36–38;41] Health behaviors such as inadequate calcium and vitamin D intake, use of alcohol and carbonated beverages, smoking, and insufficient weight bearing exercise have been found to adversely affect bone mineral formation in some studies.[37;38] Relevant pre- and post-HCT drug exposures include corticosteroids (especially dexamethasone and/or cumulative exposure to ≥9 g/m^2 prednisone equivalents), methotrexate (particularly ≥40 g/m^2), and calcineurin inhibitors (e.g., cyclosporine, tacrolimus).[36;38] TBI and cranial/craniospinal radiation further enhance the risk of low bone mineral density.[36–38;41] Untreated endocrinopathies such as GH deficiency, hyperthyroidism and hypogonadism can also adversely impact bone mineral density.[13] Risk factors for AVN post-HCT include age ≥5 years at HCT, female sex, being treated for malignancy, myeloablative conditioning regimens, and corticosteroid (especially dexamethasone) exposure.[40] Hip and knee joints are the most commonly involved sites.[13;39;40]

Bone Health Recommendations *[Evidence: level 1 for AVN and HCT; level 2B for reduced bone mineral density and HCT]*

1. All survivors should undergo a bone mineral density evaluation using either DEXA scanning or quantitative CT at one-year post-transplant. There are age-specific limitations to both modalities, and repeat testing should be performed only as clinically indicated.
2. Endocrine consultation is advised for children with a bone mineral density z-score >2 SD below the mean for age (or adult-aged survivors with T-score >1 SD below the mean for age), or if multiple fractures.

3. MRI should be considered for suspected areas of AVN, with orthopedic consultation if identified.

4. All survivors are encouraged to have adequate calcium and vitamin D (recommended minimum daily allowance for children is 400 IU/day) intake,[42] along with regular physical activity (with consideration for any appropriate weight-bearing restrictions).

SENSORY

Ocular Toxicity

Cataracts and dry eye syndrome are the primary ocular late effects following HCT. Overall, one-quarter to half of pediatric HCT survivors have been reported to develop posterior subcapsular cataracts over time, but significant vision impairment is uncommon[43–45]. Cataracts have mainly been associated with TBI-based conditioning (or prior cranial radiation) and to a lesser degree with busulfan and corticosteroid exposures.[43;44;46] Pediatric data on dry eye syndrome (xerophthalmia; keratoconjunctivitis sicca) following HCT are limited. Among pediatric allogeneic HCT survivors, 12.5% were affected in one study; acute or chronic GVHD was present in most and risk was further increased among those who had received prior cranial/eye radiation.[43] Similar associations have been reported among survivors of adult HCT.[47]

Eye Recommendation *[Evidence: level 1 for corticosteroids, radiotherapy; level 2B for busulfan]*

1. Survivors exposed to corticosteroids, TBI or cranial radiation, busulfan, and those with history of chronic GVHD, should be asked about impaired vision, diplopia, halos, dry eyes, and eye irritation, and should have acuity and funduscopic evaluations annually. Among those exposed to radiation and/or have a history of chronic GVHD, these annual screening exams should be specifically conducted by an ophthalmologist at least every 1 to 3 years.

Ototoxicity

Ototoxicity data specifically following HCT are limited. However, at least 50% of general childhood cancer survivors treated with DNA inter-strand crosslinking agents (cisplatin, increased risk with higher cumulative dose; carboplatin given as HCT conditioning) may experience sensorineural hearing loss.[48;49] Ototoxicity following these exposures first affects higher frequencies (>4 KHz) and with continued exposure can progress to involve lower (speech) frequencies.[50] Hearing loss also can continue to worsen after completion of therapy and be accompanied by tinnitus and vertigo.[50] Radiation alone with cumulative cochlear dose ≥30 Gy (inclusive of any TBI or cranial radiation) also is associated with sensorineural hearing loss, which may develop and/or progress years after exposure.[48;51] Additionally, radiotherapy also can result in conductive hearing loss, tympanosclerosis, otosclerosis, and Eustachian tube dysfunction.[48;52] Younger age, pre-existing hearing loss,

and use of other ototoxic agents (e.g., aminoglycosides) further increase risk and intensity of hearing loss.[48]

Hearing Recommendations *[Evidence: level 1 for DNA inter-strand crosslinking agents, radiotherapy]*

1. All survivors should be screened annually for hearing difficulties (with/without background noise), tinnitus and vertigo along with an otoscopic exam. Those with concerns and all survivors exposed to DNA inter-strand crosslinking agents and cumulative pre- and HCT cranial radiation ≥30 Gy should have a complete audiology evaluation (pure tone audiometry, speech audiometry and tympanometry) at one-year post-transplant. If hearing loss is detected, audiology testing should be performed yearly (or per audiologist recommendations).
2. Survivors exposed to cumulative cranial radiation ≥30 Gy should undergo complete audiology evaluations yearly for 5 years after completion of therapy or until age 10 (whichever is later); it is recommended that these patients continue to be tested every 5 years thereafter.

NEUROCOGNITIVE

Subsets of survivors are at risk for neurocognitive late effects including deficits in executive function, sustained attention, memory, learning deficits in math and reading, diminished IQ, and behavioral changes.[53–56] Risk factors for developing neurocognitive deficits include CNS-directed treatments for leukemia/lymphoma including TBI or any other radiation to the brain, high-dose intravenous cytarabine (single dose ≥1000 mg/m^2), high-dose intravenous methotrexate (single dose ≥1000 mg/m^2), or any intrathecal methotrexate.[53–56] The greatest risks are seen among children treated at a young age (especially those age <3 years), female survivors, those who received cranial radiation doses ≥24 Gy or single fraction TBI (10 Gy), and radiation to the temporal lobe.[53–55]

Neurocognitive Recommendations *[Evidence: level 1 for methotrexate, radiotherapy; level 2A for high-dose cytarabine]*

1. All survivors should be screened yearly for educational and/or vocational progress. Among survivors with concerns, formal neuropsychological evaluation should be considered at one-year post-transplant, and then periodically as clinically indicated. Formal neuropsychological evaluation should include tests of processing speed, computer-based attention, visual motor integration, memory, comprehension of verbal instructions, verbal fluency, executive function and planning.
2. Survivors with neurocognitive deficits should be referred to a school liaison or an appropriately resourced medical center to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication may be considered and/or evidence-based rehabilitation training.

PULMONARY

Chronic pulmonary dysfunction after HCT can present as obstructive or restrictive lung disease, as a diffusion abnormality, or a combination of all three, months to years following completion of therapy.[57;58] Overall, childhood cancer survivors have a nearly nine-fold excess risk of dying due to respiratory causes when compared to age- and sex-matched individuals without a history of cancer, an excess risk that is second only to that due to subsequent malignancies.[59] For HCT survivors, the intensity of HCT-related therapy and the additive effects of previous therapies magnify the risk.[57;58] Patients who received unfractionated single-dose TBI ≥6 G, fractionated TBI ≥12 Gy, or TBI at high-dose rates have the highest risk for late pulmonary complications; use of more fractionated and lower-dose rate TBI has reduced the risk for these complications.[57] Dose-related pulmonary fibrosis can also develop after bleomycin, busulfan, and nitrosurea exposures, and survivors conditioned with carmustine (BCNU) and lomustine (CCNU) appear to be at highest risk.[57;58] As with cardiovascular disease, the risk of chemotherapy-related pulmonary injury is magnified in survivors with a history of radiation exposure to the lung.[57;58] Unique to allogeneic HCT survivors, bronchiolitis obliterans is a chronic, irreversible, obstructive lung disease, and a well-recognized complication of HCT and chronic GVHD.[60] The treatment of bronchiolitis obliterans remains a challenge and many patients with bronchiolitis obliterans will still succumb to their pulmonary disease.[60]

Pulmonary Recommendations *[Evidence: level 1 for select chemotherapy agents, radiotherapy, GVHD]*

1. Survivors exposed to bleomycin, busulfan, nitrosureas, any chest radiation (including TBI, mantle, mediastinal fields; notably, spinal radiation alone is not a risk factor), or have a history of chronic GHVD, should be assessed annually for signs and symptoms of pulmonary dysfunction (e.g., chronic cough with and without fever, shortness of breath, and dyspnea on exertion).
2. These survivors should undergo pulmonary function testing at one-year post-transplant or once age-appropriate, whichever is later. Most children are able to perform spirometry by age 6, although measurement of diffusion capacity may not be possible until older ages. If a patient is unable to perform standard pulmonary function testing and clinical concerns exist, providers are advised to discuss alternative testing methods with pulmonology. Re-evaluation of pulmonary function is per clinician discretion and guided by initial findings.
3. Counsel regarding tobacco avoidance/smoking cessation.

CARDIOVASCULAR

Cardiovascular complications such as premature coronary artery disease, stroke, congestive heart failure, conduction abnormalities, and valvular disease have emerged as leading causes of treatment-related morbidity and mortality in long-term survivors of childhood cancer.[61;62] Exposures such as anthracycline (doxorubicin, daunorubicin, epirubicin, idarubicin) and anthraquinone (mitoxantrone) chemotherapy, and chest radiation increase the risk of many

of these complications.[61–63] Comorbidities such as hypertension, diabetes, dyslipidemia, and abnormal body composition further increase cardiovascular disease risk.[61–63] A recent study evaluating long-term health-related outcomes in three cohorts (conventionally treated childhood cancer survivors, survivors of childhood HCT, and sibling controls) revealed that while survivors of HCT were at a nearly 13-fold risk of severe or life-threatening cardiovascular complications when compared to siblings, after adjusting for cardiotoxic exposures, the risk among HCT survivors was equivalent to that seen in conventionally treated patients.[5] A possible explanation may be that the risk for late-occurring cardiovascular complications following HCT is largely driven by pre-transplant therapeutic exposures, with little additional risk from conditioning-related exposures or GVHD. As such, knowledge of pre-transplant exposures is important in guiding surveillance among HCT survivors.[61;62;64]

Cardiovascular Recommendations *[Evidence: level 1 for anthracyclines, radiotherapy]*

1. Survivors treated with anthracyclines/anthraquinones and/or chest radiation (including TBI, spinal, and upper abdomen/flank fields) should have an annual history and examination to screen for cardiac symptoms such as dyspnea, chest pain, palpitations, or exertion intolerance.
2. Furthermore, these survivors should have routine assessment of cardiac function (systolic and diastolic) using two-dimensional echocardiography at intervals ranging from yearly to every 5 years, depending on their exposure doses and age at exposure (see www.survivorshipguidelines.org for more specific recommendations).
3. Those exposed to cranial radiation, including TBI, should be screened for neurologic signs and symptoms concerning for cerebrovascular disease, including concerns for neurocognitive decline.
4. Survivors at risk should be screened for modifiable cardiovascular risk factors such as diabetes and dyslipidemia (see Endocrine section), hypertension (see Renal section), and smoking/tobacco use to help minimize subsequent cardiovascular disease risk.

RENAL

The use of chemotherapy and radiation as part of pre-transplant treatments, conditioning regimens, and additional exposures to calcineurin inhibitors, nephrotoxic antibiotics, combined with infectious complications, GVHD, and concurrent hypertension can all affect renal function after HCT. More than half of HCT survivors may experience some degree of chronic kidney disease.[65] Among pre-transplant exposures relevant to HCT recipients, ifosfamide and similar DNA inter-strand crosslinking agents (e.g., cisplatin), and to a lesser extent methotrexate, have been implicated in acute and chronic glomerular and renal tubular injury.[66] Persistent tubulopathy has been reported in up to 30% of children treated with ifosfamide, while chronic magnesium-wasting is more common following cisplatin

exposure, frequently requiring electrolyte replacement.[66] Risks are particularly increased among those treated with combinations of these chemotherapies or with the addition of nephrotoxic antimicrobials and calcineurin inhibitors. Abdominal or flank radiation at doses ≥ 15Gy, fractionated TBI doses ≥12 Gy, or unfractionated TBI doses ≥6 Gy confer yet additional risks for chronic renal injury.[66]

Besides side effects from immunosuppressants, chronic GVHD itself may contribute to kidney disease. While the pathophysiology remains to be fully elucidated, investigators have hypothesized that direct T cell mediated injury to the renal tubules results in release of inflammatory cytokines and may lead to renal injury, manifesting as albuminuria or frank proteinuria.[65] The presence of early albuminuria (at day 100 post-transplant) has been associated with subsequent progressive renal disease and increased non-relapse mortality in HCT survivors.[67]

Renal Recommendations *[Evidence: level 1 for all HCT survivors]*

1. All survivors should be screened for hypertension annually, using national definitions;[68] if age <18 years, use appropriate age-, sex-, and height-based thresholds to define hypertension.[69]
2. All survivors should have annual urinalyses, with measurement of blood urea nitrogen, creatinine, and electrolytes (including calcium, magnesium, and phosphate) at one-year post-transplant, and then as clinically indicated.
3. Those with hypertension, proteinuria, or progressive renal insufficiency should be referred to a nephrologist for further evaluation.

GASTROINTESTINAL

Due to the effects of pre-transplant exposures, toxicity from the HCT conditioning process, and GVHD, HCT survivors may have a 5-fold greater burden of significant gastrointestinal complications compared with other cancer survivors.[5] Autologous and allogeneic survivors (even those without active chronic GVHD) can be at increased risk for strictures and liver dysfunction. Lumen stricture formation can occur in both the esophagus as well as lower parts of the GI tract.[70] Radiation dose ≥30 Gy (inclusive of any TBI) is a risk factor for stricture formation.[70;71] Additional risk factors for esophageal stricture specifically include chronic GVHD, prior candida esophagitis, and gastroesophageal reflux.[70;72] Late bowel obstruction can be seen many years after abdominal surgery.[70;72]

Liver disease in long-term survivors of childhood cancer treated with HCT may be the result of sinusoidal obstruction syndrome (SOS; also termed veno-occlusive disease), GVHD, chronic infection with hepatotrophic viruses, and iron overload.[73] Survivors with a history of SOS may manifest persistent hepatomegaly, reversal of flow in the portal system and subsequent splenomegaly with thrombocytopenia for years after therapy. Risk factors for SOS are primarily myeloablative chemotherapy used prior to or during conditioning, especially cyclophosphamide, carmustine, and busulfan.[73] Receipt of anti-metabolites such

as mercaptopurine or thioguanine prior to HCT may also be a contributing factor in some patients.[74]

Liver GVHD is associated with hepatocellular necroinflammatory changes, paucity of interlobular bile ducts, and interhepatic cholestasis.[73] Chronic hepatitis infections, most commonly Hepatitis C, and siderosis, noted in approximately 90% of long-term survivors of HCT, may also accelerate the course of liver injury and result in cirrhosis, portal hypertension, and hepatocellular carcinoma.[73;75] Finally, focal nodular hyperplasia is being increasingly found on radiographic screening, although it is thought to be a benign process which may be associated with high doses of alkylating agents, history of SOS, or radiation.[70]

Gastrointestinal Recommendations ***[Evidence: level 1 for anti-metabolite chemotherapy, radiotherapy, GVHD; recommendations related to transfusion-associated infections are listed in the Immunologic section below]***

1. All survivors should have ALT, AST, bilirubin, and serum ferritin assessed at one-year post-transplant, with repeat testing or hepatology consultation as clinically indicated. Among those with abnormal values, the prothrombin time can be an indicator of hepatic synthetic function. Among those with persistently increased ferritin, consider further evaluation of iron burden and treatment of any iron overload with phlebotomy or chelation therapy.
2. Survivors exposed to radiation and/or with a history of chronic GVHD should be screened for dysphagia, heartburn, or relevant lower gastrointestinal tract symptoms, which need to be distinguished from GVHD manifestations.
3. All survivors should be counseled on limiting alcohol use and immunization against Hepatitis A and B if immunity is not established.

DENTAL

Primary central incisors develop as early as 6 months with most children having complete primary dentition by 6 years of life. The formation and eruption of permanent dentition follows between 6 and 12 years of life.[76] Given this timing, structural abnormalities of teeth are increasingly seen following childhood cancer treatment. These include hypodontia, microdontia, enamel hypoplasia, and root malformation.[77] Risk factors include younger age at treatment (e.g., age <5 years), higher doses of alkylating agents (especially cyclophosphamide), and radiation exposure.[76] Radiation doses as low as 10 Gy have resulted in permanent damage to tooth development.[78] HCT conditioning regimens, especially those containing TBI and alkylating agent chemotherapy can lead to tooth agenesis and root abnormalities.[76] Children with dental abnormalities often have increased risk of cavities due to increased colonization with Streptococcus mutans and other bacteria.[79]

Xerostomia can both be a consequence of TBI or other radiation to the salivary glands, as well as chronic GVHD. The salivary glands are highly radiosensitive; receipt of concurrent radiomimetic chemotherapy such as doxorubicin may further increase the risk of xerostomia. Xerostomia increases the risk of caries, oral infections, sleep disturbances and difficulties with chewing, swallowing and speaking.[80]

Dental Recommendations *[Evidence: level 1 for all HCT survivors]*

1. All survivors should have dental exams and cleaning every 6 months, and annual oral exams, including special attention for those with a history of radiation or chronic GVHD for xerostomia and second cancers (discussed further below).
2. A baseline panorex should be considered in all survivors to evaluate root development prior to dental procedures.

SKIN

Skin health can be adversely affected following HCT due to effects from radiation as well as GVHD. The skin is the most commonly affected organ in chronic GVHD and its involvement may be predictive of poor prognosis.[81] It is important to recognize that skin manifestations of chronic GVHD extend well beyond the traditional lichenoid and sclerodermatous subtypes, to include poikiloderma, ichthyosis, keratosis pilaris, eczematous dermatitis, and a spectrum of sclerotic changes, including peripheral edema.[81] Survivors with any history of chronic GVHD should be counseled about potential long term issues with alopecia, nail dystrophy, and vitiligo. While these late effects are relatively benign, they may significantly affect one's quality of life.[82] In addition, survivors with sclerotic GVHD may experience joint contractures and genital complications including vaginal stenosis.[31;81] Finally, as discussed further below, radiation and chronic GVHD are risk factors for both melanoma and non-melanoma skin cancers.

Skin Recommendations *[Evidence: level 1 for radiation, GVHD]*

1. Survivors with a history of TBI should have, at minimum, annual full skin examinations.
2. Those with a history of chronic GVHD should also have full skin examinations, including hair, nails, and external genitalia.
3. Sun protective behaviors, including avoiding excessive sun exposure and tanning booths, are recommended.

IMMUNOLOGIC

Infectious complications remain an important cause of late morbidity and mortality in long-term survivors of childhood HCT.[83–85] For example, long-term survivors treated with TBI had nearly an eight-fold increased risk of death due to infection compared with population norms.[85] Patients with active chronic GVHD are considered functionally asplenic and have impaired lymphocyte function, making them at risk of life threatening infections with

encapsulated organisms, as well as from viruses, fungi, and other opportunistic pathogens.[83;84] However, even after chronic GVHD has resolved some patients still remain significantly immunocompromised for many months or years afterwards with evidence of ongoing T and/or B cell dysfunction, manifesting as hypogammaglobulinemia, secretory IgA deficiency, and recurrent chronic sino-pulmonary infections.[83–85] Other exposures that may potentiate risk for infectious-related morbidity and mortality include transfusion-acquired viruses. Among U.S. survivors, those treated between 1977 and 1985 are at risk for HIV infection, while those treated before 1993 are at risk for hepatitis C infection.[86]

Immunologic Recommendations ***[Evidence: level 1 for transfusions, GVHD. Evidence for IVIG replacement beyond 100 days post-transplant was not reviewed as part of the COG guidelines, but joint recommendations from the US Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), and ASBMT are listed below[87]]***

1. Survivors with active chronic GVHD should be considered for antibiotic prophylaxis against encapsulated organisms for the duration of immunosuppressive therapy and receive broad spectrum parenteral antibiotics for fevers ≥101°F (38.3°C).
2. Survivors with resolved chronic GVHD may still not be immunologically normal, and annual evaluations should include a history and exam to assess for chronic conjunctivitis, sinopulmonary infections, or other recurrent, unusual, or severe infections.
3. Survivors should be screened for HIV and hepatitis C if exposed to blood products prior to universal testing for those viruses.
4. All survivors should receive vaccinations according to guidelines previously released by other national and professional societies.[88]
5. **Per the CDC, IDSA, and ASBMT:** many HCT centers provide routine IVIG replacement in the first 100 days post-transplant to high-risk patients (e.g., unrelated marrow, haploidentical, and unrelated cord blood donors) when serum IgG levels fall below 400 mg/dL. However, routine use after day 100 is only supported in the setting of severe hypogammaglobulinemia (IgG level <400 mg/dL). Data do not support the routine use of IVIG for patients after related donor or autologous transplantation.[89]

SECOND CANCERS

A potentially devastating complication of HCT is the occurrence of subsequent malignant neoplasms (SMNs). SMNs can be classified into 3 groups: (1) therapy-related myelodysplasia and acute myeloid leukemia (t-MDS/AML); (2) lymphoma, including lymphoproliferative disorders; and (3) solid tumors (Table 4). Although secondary leukemias and lymphomas develop relatively early in the post-transplantation period, secondary solid tumors have a longer latency.[90]

Myelodysplasia and acute myeloid leukemia

T-MDS/AML is a major cause of non-relapse mortality following autologous HCT, and less common after allogeneic HCT. Anywhere from 1 to nearly 25% of autologous transplant recipients have been reported to develop subsequent t-MDS/AML.[90;91] Transplant-specific risk factors include use of peripheral blood stem cells (compared to bone marrow), stem cell mobilization with etoposide, conditioning with TBI, low number of $CD34^+$ cells infused, and multiple transplants.[92;93] Pre-transplant exposure to alkylating agents, topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines), or radiation also increase risk.[90] Notably, latency of t-MDS/AML development can be longer following alkylating agents or radiation compared with topoisomerase II inhibitors (4 to 7 years versus <5 years).

Lymphomas

Post-transplant lymphoproliferative disorders (PTLD) are the most common new malignancy in the first year (often within the first 6 months) after allogeneic HCT, with a 10-year cumulative incidence of 1% to 2%.[94] Most of these cases occur after T cell depleted transplants and are related to EBV infection. These lymphomas typically have a B cell origin, but are otherwise clinically and morphologically heterogeneous. Other risk factors include use of antithymocyte globulin or anti-CD3 monoclonal antibody for conditioning or acute GvHD prophylaxis, unrelated or HLA-mismatched related donor, TBI, and a prior primary immunodeficiency diagnosis.[94] Later-onset lymphomas, including Hodgkin lymphoma, have also been reported.[95;96] Extensive chronic GVHD remains an important risk factor for these lymphomas.[90]

Solid tumors

The cumulative incidence of solid tumors after allogeneic HCT has been reported to range as high as 11% at 15 years post-transplantation, more than two-fold what would be expected in the general population matched on age and sex.[97;98] The overall risk as reported by pediatric-only HCT cohort studies may be lower, although risk also increases with further time from HCT, and appears to be greater following allogeneic versus autologous HCT.[91;99] Types of solid tumors reported in excess among HCT recipients include skin cancers (melanomas, basal cell and squamous cell carcinomas), cancers of the oral cavity and salivary glands, brain, liver, uterine cervix, thyroid, breast, bone, and connective tissue.[97;98] Other risk factors for solid tumors following HCT include exposure to radiation at a younger age, higher radiation doses (thyroid gland being one exception[25]), any underlying host predisposition (Table 4), infectious agents like hepatitis and human papilloviruses, and chronic GVHD (especially in relation to cancers of the oral cavity).[100]

Second Cancer Recommendations *[Evidence: level 1 for all HCT survivors]*

1. Second cancer-specific screening recommendations that account for pre-HCT therapy, transplant conditioning therapy, chronic GVHD status, and host factors are detailed in Table 4.

2. All survivors should be counseled with regards to lifestyle factors that influence future cancer risk (e.g., alcohol abuse, high fat/low fiber diet, smoking/tobacco use, excess sun or ultraviolet light exposure).

PSYCHOSOCIAL

HCT survivors are at risk for a number of adverse psychosocial and quality of life late effects, including: social withdrawal, educational problems, dysfunctional marital relationships, under-employment or unemployment, and dependent living.[101;102] Besides the HCT experience itself, female sex, younger age at diagnosis, physical limitations, neurocognitive problems, family history of mental illness, and lower socioeconomic status have been identified as risk factors.[101;102] Chronic fatigue and pain also may be concerns.[103] Survivors also are at increased risk for mental health disorders including depression, anxiety, post-traumatic stress, and suicidal ideation.[102;104] Those with chronic pain and perceived poor physical health are particularly high risk.[104] In general, survivors of HCT appear less likely to report risky health behaviors such as excessive alcohol use or smoking, and have similar or better health screening than siblings but, younger survivors, those without health insurance, and with lower education may be more likely to engage in high-risk behaviors.[105]

Psychosocial Recommendations *[Evidence: level 2A for all HCT survivors]*

1. As part of an annual evaluation, all survivors should receive a psychosocial assessment with attention to social withdrawal and educational/vocational progress, as well as chronic fatigue, pain, risk behaviors, and mental health concerns (e.g., depression, anxiety, post-traumatic stress, and suicidal ideation).
2. Finally, all survivors should be asked about their access to insurance and healthcare, particularly in light of recent changes to healthcare regulations.

CONCLUSION

Survivors of childhood HCT need ongoing, lifelong monitoring since many late adverse effects may not manifest for years or even decades, and often increase with age (Table 1). Earlier detection may mitigate the long-term consequences of some these late effects. The importance of long-term follow-up requires educating survivors and their families, as well as their pediatric and future adult primary healthcare providers. In addition to producing guidelines for healthcare providers, COG has produced a series of informational materials for patients and families on multiple health topics related to treatment late effects (www.survivorshipguidelines.org). The COG also is participating in an ongoing international effort to systematically review the evidence base for childhood cancer and HCT late effects, including a goal of trying to harmonize the guidelines for consistent use across national groups.[106] These efforts support the Institute of Medicine's recommendation that all survivors receive treatment summaries and individualized care plans.[107] Given the complexity of care that most childhood HCT survivors have received, and the lack of familiarity most adult primary care providers have with survivorship care, survivor care

plans may be especially important as survivors transition from pediatric to adult-based care.[108;109]

Nevertheless, important knowledge gaps remain, where the quality of evidence that informs the COG guidelines in relation to HCT survivors is limited (e.g., grade 2A and 2B recommendations; Appendix Table 1). It also will be important to follow children now receiving newer agents such as fludarabine, treosulfan, and molecular-targeted drugs (e.g., tyrosine kinase inhibitors) and immune-based therapies. While these treatments offer the promise of reduced late effects, children who receive them will still need to be followed long-term to determine their ultimate toxicity profile, including effects on immune reconstitution. Given the growing appreciation of the financial toxicity associated with cancer treatment and HCT,[110;111] the cost-effectiveness of surveillance recommendations also deserves greater study.[112;113] Finally, the optimal management of many late effects, once detected, remains unclear. This includes management of adult growth hormone deficiency, low bone mineral density, insulin resistance and the metabolic syndrome, and subclinical renal insufficiency and cardiomyopathy, among other important late effects. These and other topics are currently the focus of a renewed effort by the National Institutes of Health to identify and prioritize late effects research important for both childhood and adult HCT survivors.

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References

1. Pasquini, MC.; Zhu, X. [accessed November 1, 2015] Current use and outcome of hematopoietic stem cell transplantation. 2014 CIBMTR Summary Slides. Available at: http://www.cibmtr.org
2. Sanders, JE. Growth and development after hematopoietic cell transplantation. In: Appelbaum, FR.; Forman, SJ.; Negrin, RS.; Blume, KG., editors. Thomas' Hematopoietic Cell Transplantation. West Sussex: Wiley-Blackwell; 2008. p. 1608-19.
3. Perkins JL, Kunin-Batson AS, Youngren NM, et al. Long-term follow-up of children who underwent hematopoeitic cell transplant (HCT) for AML or ALL at less than 3 years of age. Pediatr Blood Cancer. 2007; 49(7):958–63. [PubMed: 17474113]
4. Baker KS, Bresters D, Sande JE. The burden of cure: long-term side effects following hematopoietic stem cell transplantation (HSCT) in children. Pediatr Clin North Am. 2010; 57(1):323–342. [PubMed: 20307723]
5. Armenian SH, Sun CL, Kawashima T, et al. Long-term health-related outcomes in survivors of childhood cancer treated with HSCT versus conventional therapy: a report from the Bone Marrow Transplant Survivor Study (BMTSS) and Childhood Cancer Survivor Study (CCSS). Blood. 2011; 118(5):1413–1420. [PubMed: 21652685]
6. Baker KS, Bhatia S, Bunin N, et al. NCI, NHLBI first international consensus conference on late effects after pediatric hematopoietic cell transplantation: state of the science, future directions. Biol Blood Marrow Transplant. 2011; 17(10):1424–1427. [PubMed: 21723224]
7. Pulsipher MA, Skinner R, McDonald GB, et al. National Cancer Institute, National Heart, Lung and Blood Institute/Pediatric Blood and Marrow Transplantation Consortium First International Consensus Conference on late effects after pediatric hematopoietic cell transplantation: the need for

pediatric-specific long-term follow-up guidelines. Biol Blood Marrow Transplant. 2012; 18(3):334–347. [PubMed: 22248713]

8. Landier W, Bhatia S, Eshelman DA, et al. Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline. J Clin Oncol. 2004; 22(24):4979–4990. [PubMed: 15576413]
9. Skinner R, Wallace WH, Levitt GA. Long-term follow-up of people who have survived cancer during childhood. Lancet Oncol. 2006; 7(6):489–498. [PubMed: 16750499]
10. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012; 18(3):348–371. [PubMed: 22178693]
11. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent and young adult cancers, Version 4.0. Monrovia, CA: Children's Oncology Group; 2013. Available at: http://www.survivorshipguidelines.org [accessed November 1, 2015]
12. US Preventative Services Task Force. [accessed November 1, 2015] Available at: http://www.uspreventiveservicestaskforce.org
13. Dvorak CC, Gracia CR, Sanders JE, et al. NCI, NHLBI/PBMTC first international conference on late effects after pediatric hematopoietic cell transplantation: endocrine challenges-thyroid dysfunction, growth impairment, bone health, & reproductive risks. Biol Blood Marrow Transplant. 2011; 17(12):1725–1738. [PubMed: 22005649]
14. Chow EJ, Liu W, Srivastava K, et al. Differential effects of radiotherapy on growth and endocrine function among acute leukemia survivors: a childhood cancer survivor study report. Pediatr Blood Cancer. 2013; 60(1):110–115. [PubMed: 22628201]
15. Baker KS, Chow E, Steinberger J. Metabolic syndrome and cardiovascular risk in survivors after hematopoietic cell transplantation. Bone Marrow Transplant. 2012; 47(5):619–625. [PubMed: 21643022]
16. Mulder RL, Kremer LC, van Santen HM, et al. Prevalence and risk factors of radiation-induced growth hormone deficiency in childhood cancer survivors: a systematic review. Cancer Treat Rev. 2009; 35(7):616–632. [PubMed: 19640651]
17. Raman S, Grimberg A, Waguespack SG, et al. Risk of Neoplasia in Pediatric Patients Receiving Growth Hormone Therapy--A Report From the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab. 2015; 100(6):2192–2203. [PubMed: 25839904]
18. Sklar CA, Mertens AC, Mitby P, et al. Risk of disease recurrence and second neoplasms in survivors of childhood cancer treated with growth hormone: a report from the Childhood Cancer Survivor Study. J Clin Endocrinol Metab. 2002; 87(7):3136–3141. [PubMed: 12107213]
19. Ergun-Longmire B, Mertens AC, Mitby P, et al. Growth hormone treatment and risk of second neoplasms in the childhood cancer survivor. J Clin Endocrinol Metab. 2006; 91(9):3494–3498. [PubMed: 16822820]
20. Patterson BC, Chen Y, Sklar CA, et al. Growth hormone exposure as a risk factor for the development of subsequent neoplasms of the central nervous system: a report from the childhood cancer survivor study. J Clin Endocrinol Metab. 2014; 99(6):2030–2037. [PubMed: 24606096]
21. Vogelius IR, Bentzen SM, Maraldo MV, Petersen PM, Specht L. Risk factors for radiation-induced hypothyroidism: a literature-based meta-analysis. Cancer. 2011; 117(23):5250–5260. [PubMed: 21567385]
22. Bailey HK, Kappy MS, Giller RH, Gralla J. Time-course and risk factors of hypothyroidism following allogeneic hematopoietic stem cell transplantation (HSCT) in children conditioned with fractionated total body irradiation. Pediatr Blood Cancer. 2008; 51(3):405–409. [PubMed: 18523993]
23. Ishiguro H, Yasuda Y, Tomita Y, et al. Long-term follow-up of thyroid function in patients who received bone marrow transplantation during childhood and adolescence. J Clin Endocrinol Metab. 2004; 89(12):5981–6. [PubMed: 15579747]

24. Sanders JE, Hoffmeister PA, Woolfrey AE, et al. Thyroid function following hematopoietic cell transplantation in children: 30 years' experience. Blood. 2009; 113(2):306–308. [PubMed: 18838614]
25. Sigurdson AJ, Ronckers CM, Mertens AC, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet. 2005; 365(9476):2014–2023. [PubMed: 15950715]
26. Brignardello E, Corrias A, Isolato G, et al. Ultrasound screening for thyroid carcinoma in childhood cancer survivors: a case series. J Clin Endocrinol Metab. 2008; 93(12):4840–4843. [PubMed: 18812481]
27. Kenney LB, Cohen LE, Shnorhavorian M, et al. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol. 2012; 30(27):3408–3416. [PubMed: 22649147]
28. Metzger ML, Meacham LR, Patterson B, et al. Female reproductive health after childhood, adolescent, and young adult cancers: guidelines for the assessment and management of female reproductive complications. J Clin Oncol. 2013; 31(9):1239–1247. [PubMed: 23382474]
29. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab. 2006; 91(5):1723–1728. [PubMed: 16492690]
30. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst. 2006; 98(13):890–896. [PubMed: 16818852]
31. Hirsch P, Leclerc M, Rybojad M, et al. Female genital chronic graft-versus-host disease: importance of early diagnosis to avoid severe complications. Transplantation. 2012; 93(12):1265–1269. [PubMed: 22466789]
32. Sanders JE, Hawley J, Levy W, et al. Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. Blood. 1996; 87(7):3045–3052. [PubMed: 8639928]
33. Green DM, Zhu L, Zhang N, et al. Lack of specificity of plasma concentrations of inhibin B and follicle-stimulating hormone for identification of azoospermic survivors of childhood cancer: a report from the St Jude lifetime cohort study. J Clin Oncol. 2013; 31(10):1324–1328. [PubMed: 23423746]
34. Meacham LR, Chow EJ, Ness KK, et al. Cardiovascular risk factors in adult survivors of pediatric cancer--a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 2010; 19(1):170–181. [PubMed: 20056636]
35. de Vathaire F, El-Fayech C, Ben Ayed FF, et al. Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study. Lancet Oncol. 2012; 13(10): 1002–1010. [PubMed: 22921663]
36. Petryk A, Bergemann TL, Polga KM, et al. Prospective study of changes in bone mineral density and turnover in children after hematopoietic cell transplantation. J Clin Endocrinol Metab. 2006; 91(3):899–905. [PubMed: 16352681]
37. Ruble K, Hayat MJ, Stewart KJ, Chen AR. Bone mineral density after bone marrow transplantation in childhood: measurement and associations. Biol Blood Marrow Transplant. 2010; 16(10):1451–1457. [PubMed: 20417715]
38. Le Meignen M, Auquier P, Barlogis V, et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities. Blood. 2011; 118(6):1481–1489. [PubMed: 21596857]
39. Kaste SC, Shidler TJ, Tong X, et al. Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. Bone Marrow Transplant. 2004; 33(4):435–441. [PubMed: 14716354]
40. Li X, Brazauskas R, Wang Z, et al. Avascular necrosis of bone after allogeneic hematopoietic cell transplantation in children and adolescents. Biol Blood Marrow Transplant. 2014; 20(4):587–592. [PubMed: 24388803]
41. Petryk A, Polgreen LE, Zhang L, et al. Bone mineral deficits in recipients of hematopoietic cell transplantation: the impact of young age at transplant. Bone Marrow Transplant. 2014; 49(2):258–263. [PubMed: 24121211]

42. Greer FR, Krebs NF. Optimizing bone health and calcium intakes of infants, children, and adolescents. Pediatrics. 2006; 117(2):578–585. [PubMed: 16452385]
43. Suh DW, Ruttum MS, Stuckenschneider BJ, Mieler WF, Kivlin JD. Ocular findings after bone marrow transplantation in a pediatric population. Ophthalmology. 1999; 106(8):1564–1570. [PubMed: 10442905]
44. Gurney JG, Ness KK, Rosenthal J, Forman SJ, Bhatia S, Baker KS. Visual, auditory, sensory, and motor impairments in long-term survivors of hematopoietic stem cell transplantation performed in childhood: results from the Bone Marrow Transplant Survivor study. Cancer. 2006; 106(6):1402–1408. [PubMed: 16453335]
45. Horwitz M, Auquier P, Barlogis V, et al. Incidence and risk factors for cataract after haematopoietic stem cell transplantation for childhood leukaemia: an LEA study. Br J Haematol. 2015; 168(4): 518–525. [PubMed: 25284463]
46. Fahnehjelm KT, Tornquist AL, Olsson M, Winiarski J. Visual outcome and cataract development after allogeneic stem-cell transplantation in children. Acta Ophthalmol Scand. 2007; 85(7):724–733. [PubMed: 17725615]
47. Baker KS, Gurney JG, Ness KK, et al. Late effects in survivors of chronic myeloid leukemia treated with hematopoietic cell transplantation: results from the Bone Marrow Transplant Survivor Study. Blood. 2004; 104(6):1898–1906. [PubMed: 15172972]
48. Grewal S, Merchant T, Reymond R, McInerney M, Hodge C, Shearer P. Auditory late effects of childhood cancer therapy: a report from the Children's Oncology Group. Pediatrics. 2010; 125(4):e938–e950. [PubMed: 20194279]
49. Landier W, Knight K, Wong FL, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group. J Clin Oncol. 2014; 32(6):527–534. [PubMed: 24419114]
50. Bertolini P, Lassalle M, Mercier G, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004; 26(10):649–655. [PubMed: 15454836]
51. Merchant TE, Gould CJ, Xiong X, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. Int J Radiat Oncol Biol Phys. 2004; 58(4):1194–1207. [PubMed: 15001264]
52. Young YH, Lu YC. Mechanism of hearing loss in irradiated ears: a long-term longitudinal study. Ann Otol Rhinol Laryngol. 2001; 110(10):904–906. [PubMed: 11642420]
53. Phipps S, Dunavant M, Srivastava DK, Bowman L, Mulhern RK. Cognitive and academic functioning in survivors of pediatric bone marrow transplantation. J Clin Oncol. 2000; 18(5):1004–1011. [PubMed: 10694550]
54. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. J Natl Cancer Inst. 2010; 102(12):881–893. [PubMed: 20458059]
55. Willard VW, Leung W, Huang Q, Zhang H, Phipps S. Cognitive outcome after pediatric stem-cell transplantation: impact of age and total-body irradiation. J Clin Oncol. 2014; 32(35):3982–3988. [PubMed: 25385724]
56. Iyer NS, Balsamo LM, Bracken MB, Kadan-Lottick NS. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. Blood. 2015; 126(3):346–353. [PubMed: 26048910]
57. Gower WA, Collaco JM, Mogayzel PJ Jr. Pulmonary dysfunction in pediatric hematopoietic stem cell transplant patients: non-infectious and long-term complications. Pediatr Blood Cancer. 2007; 49(3):225–233. [PubMed: 17029245]
58. Liles A, Blatt J, Morris D, et al. Monitoring pulmonary complications in long-term childhood cancer survivors: guidelines for the primary care physician. Cleve Clin J Med. 2008; 75(7):531–539. [PubMed: 18646589]
59. Armstrong GT, Liu Q, Yasui Y, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009; 27(14):2328–2338. [PubMed: 19332714]

60. Uhlving HH, Buchvald F, Heilmann CJ, Nielsen KG, Gormsen M, Muller KG. Bronchiolitis obliterans after allo-SCT: clinical criteria and treatment options. Bone Marrow Transplant. 2012; 47(8):1020–1029. [PubMed: 21874057]
61. Shankar SM, Marina N, Hudson MM, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the Cardiovascular Disease Task Force of the Children's Oncology Group. Pediatrics. 2008; 121(2):e387–e396. [PubMed: 18187811]
62. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: A scientific statement from the American Heart Association. Circulation. 2013; 128(17):1927–1995. [PubMed: 24081971]
63. Armenian SH, Sun CL, Vase T, et al. Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease. Blood. 2012; 120(23):4505–4512. [PubMed: 23034279]
64. Chow EJ, Chen Y, Kremer LC, et al. Individual prediction of heart failure among childhood cancer survivors. J Clin Oncol. 2015; 33(5):394–402. [PubMed: 25287823]
65. Nieder ML, McDonald GB, Kida A, et al. National Cancer Institute-National Heart, Lung and Blood Institute/pediatric Blood and Marrow Transplant Consortium First International Consensus Conference on late effects after pediatric hematopoietic cell transplantation: long-term organ damage and dysfunction. Biol Blood Marrow Transplant. 2011; 17(11):1573–1584. [PubMed: 21963877]
66. Jones DP, Spunt SL, Green D, Springate JE. Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2008; 51(6):724–731. [PubMed: 18677764]
67. Hingorani SR, Seidel K, Lindner A, Aneja T, Schoch G, McDonald G. Albuminuria in hematopoietic cell transplantation patients: prevalence, clinical associations, and impact on survival. Biol Blood Marrow Transplant. 2008; 14(12):1365–1372. [PubMed: 19041058]
68. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014; 311(5):507–520. [PubMed: 24352797]
69. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004; 114(2 Suppl 4th Report):555–76. [PubMed: 15286277]
70. Castellino S, Muir A, Shah A, et al. Hepatobiliary late effects in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2010; 54(5):663–669. [PubMed: 19890896]
71. Rodriguez ML, Martin MM, Padellano LC, Palomo AM, Puebla YI. Gastrointestinal toxicity associated to radiation therapy. Clin Transl Oncol. 2010; 12(8):554–561. [PubMed: 20709653]
72. Lal DR, Foroutan HR, Su WT, Wolden SL, Boulad F, La Quaglia MP. The management of treatment-related esophageal complications in children and adolescents with cancer. J Pediatr Surg. 2006; 41(3):495–499. [PubMed: 16516623]
73. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology. 2010; 51(4):1450–1460. [PubMed: 20373370]
74. De Bruyne R, Portmann B, Samyn M, et al. Chronic liver disease related to 6-thioguanine in children with acute lymphoblastic leukaemia. J Hepatol. 2006; 44(2):407–410. [PubMed: 16226335]
75. Strasser SI, Sullivan KM, Myerson D, et al. Cirrhosis of the liver in long-term marrow transplant survivors. Blood. 1999; 93(10):3259–3266. [PubMed: 10233877]
76. Effinger KE, Migliorati CA, Hudson MM, et al. Oral and dental late effects in survivors of childhood cancer: a Children's Oncology Group report. Support Care Cancer. 2014; 22(7):2009–2019. [PubMed: 24781353]
77. Cubukcu CE, Sevinir B, Ercan I. Disturbed dental development of permanent teeth in children with solid tumors and lymphomas. Pediatr Blood Cancer. 2012; 58(1):80–84. [PubMed: 21254371]
78. Kaste SC, Goodman P, Leisenring W, et al. Impact of radiation and chemotherapy on risk of dental abnormalities: a report from the Childhood Cancer Survivor Study. Cancer. 2009; 115(24):5817–5827. [PubMed: 19834960]

79. Selwitz RH, Ismail AI, Pitts NB. Dental caries. Lancet. 2007; 369(9555):51–59. [PubMed: 17208642]
80. Jensen SB, Pedersen AM, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer. 2010; 18(8):1039–1060. [PubMed: 20237805]
81. Martires KJ, Baird K, Steinberg SM, et al. Sclerotic-type chronic GVHD of the skin: clinical risk factors, laboratory markers, and burden of disease. Blood. 2011; 118(15):4250–4257. [PubMed: 21791415]
82. Kinahan KE, Sharp LK, Seidel K, et al. Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor study. J Clin Oncol. 2012; 30(20):2466–2474. [PubMed: 22614987]
83. Bunin N, Small T, Szabolcs P, Baker KS, Pulsipher MA, Torgerson T. NCI, NHLBI/PBMTC first international conference on late effects after pediatric hematopoietic cell transplantation: persistent immune deficiency in pediatric transplant survivors. Biol Blood Marrow Transplant. 2012; 18(1): 6–15. [PubMed: 22100979]
84. Fuji S, Kapp M, Einsele H. Challenges to preventing infectious complications, decreasing re-hospitalizations, and reducing cost burden in long-term survivors after allogeneic hematopoietic stem cell transplantation. Semin Hematol. 2012; 49(1):10–14. [PubMed: 22221780]
85. Perkins JL, Chen Y, Harris A, et al. Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2014; 120(16): 2514–2521. [PubMed: 24824782]
86. Stramer SL. Current risks of transfusion-transmitted agents: a review. Arch Pathol Lab Med. 2007; 131(5):702–707. [PubMed: 17488155]
87. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000; 49(RR-10):1–125.
88. Centers for Disease Control and Prevention. [accessed November 1, 2015] Vaccination of hematopoietic stem cell transplant (HSCT) recipients. Available at: http://www.cdc.gov/vaccines/pubs/hemato-cell-transplts.htm
89. Raanani P, Gafter-Gvili A, Paul M, Ben-Bassat I, Leibovici L, Shpilberg O. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol. 2009; 27(5):770–781. [PubMed: 19114702]
90. Socie G, Baker KS, Bhatia S. Subsequent malignant neoplasms after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012; 18(1 Suppl):S139–S150. [PubMed: 22226098]
91. Danner-Koptik KE, Majhail NS, Brazauskas R, et al. Second malignancies after autologous hematopoietic cell transplantation in children. Bone Marrow Transplant. 2013; 48(3):363–368. [PubMed: 22964594]
92. Friedberg JW, Neuberg D, Stone RM, et al. Outcome in patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. J Clin Oncol. 1999; 17(10):3128–3135. [PubMed: 10506609]
93. Krishnan A, Bhatia S, Slovak ML, et al. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. Blood. 2000; 95(5):1588–1593. [PubMed: 10688812]
94. Socie G, Curtis RE, Deeg HJ, et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol. 2000; 18(2):348–357. [PubMed: 10637249]
95. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood. 1999; 94(7):2208–2216. [PubMed: 10498590]
96. Rowlings PA, Curtis RE, Passweg JR, et al. Increased incidence of Hodgkin's disease after allogeneic bone marrow transplantation. J Clin Oncol. 1999; 17(10):3122–3127. [PubMed: 10506608]

97. Rizzo JD, Curtis RE, Socie G, et al. Solid cancers after allogeneic hematopoietic cell transplantation. Blood. 2009; 113(5):1175–1183. [PubMed: 18971419]

98. Majhail NS, Brazauskas R, Rizzo JD, et al. Secondary solid cancers after allogeneic hematopoietic cell transplantation using busulfan-cyclophosphamide conditioning. Blood. 2011; 117(1):316–322. [PubMed: 20926773]

99. Pole JD, Darmawikarta D, Gassas A, et al. Subsequent malignant neoplasms in pediatric cancer patients treated with and without hematopoietic SCT. Bone Marrow Transplant. 2015; 50(5):721–726. [PubMed: 25706885]

100. Curtis RE, Metayer C, Rizzo JD, et al. Impact of chronic GVHD therapy on the development of squamous-cell cancers after hematopoietic stem-cell transplantation: an international case-control study. Blood. 2005; 105(10):3802–3811. [PubMed: 15687239]

101. Barrera M, Atenafu E, Hancock K. Longitudinal health-related quality of life outcomes and related factors after pediatric SCT. Bone Marrow Transplant. 2009; 44(4):249–256. [PubMed: 19234504]

102. Sanders JE, Hoffmeister PA, Storer BE, Appelbaum FR, Storb RF, Syrjala KL. The quality of life of adult survivors of childhood hematopoietic cell transplant. Bone Marrow Transplant. 2010; 45(4):746–754. [PubMed: 19718073]

103. Mulrooney DA, Ness KK, Neglia JP, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: a report from the childhood cancer survivor study (CCSS). Sleep. 2008; 31(2): 271–281. [PubMed: 18274275]

104. Stuber ML, Meeske KA, Krull KR, et al. Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. Pediatrics. 2010; 125(5):e1124–e1134. [PubMed: 20435702]

105. Armenian SH, Sun CL, Francisco L, et al. Health behaviors and cancer screening practices in long-term survivors of hematopoietic cell transplantation (HCT): a report from the BMT Survivor Study. Bone Marrow Transplant. 2012; 47(2):283–290. [PubMed: 21423125]

106. Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Pediatr Blood Cancer. 2013; 60(4):543–549. [PubMed: 23281199]

107. Committee on Cancer Survivorship. Improving Care and Quality of Life, National Cancer Policy Board. In: Hewitt, M.; Greenfield, S.; Stovall, E., editors. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C: Institute of Medicine and National Research Council, National Academies Press; 2006.

108. Suh E, Daugherty CK, Wroblewski K, et al. General internists' preferences and knowledge about the care of adult survivors of childhood cancer: a cross-sectional survey. Ann Intern Med. 2014; 160(1):11–17. [PubMed: 24573662]

109. Shankar SM, Carter A, Sun CL, et al. Health care utilization by adult long-term survivors of hematopoietic cell transplant: report from the Bone Marrow Transplant Survivor Study. Cancer Epidemiol Biomarkers Prev. 2007; 16(4):834–839. [PubMed: 17416780]

110. Kirchhoff AC, Leisenring W, Krull KR, et al. Unemployment among adult survivors of childhood cancer: a report from the childhood cancer survivor study. Med Care. 2010; 48(11):1015–1025. [PubMed: 20940653]

111. Khera N, Chang YH, Hashmi S, et al. Financial burden in recipients of allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2014; 20(9):1375–1381. [PubMed: 24867778]

112. Yeh JM, Nohria A, Diller L. Routine echocardiography screening for asymptomatic left ventricular dysfunction in childhood cancer survivors: a model-based estimation of the clinical and economic effects. Ann Intern Med. 2014; 160(10):661–671. [PubMed: 24842413]

113. Wong FL, Bhatia S, Landier W, et al. Cost-effectiveness of the children's oncology group long-term follow-up screening guidelines for childhood cancer survivors at risk for treatment-related heart failure. Ann Intern Med. 2014; 160(10):672–683. [PubMed: 24842414]

HIGHLIGHTS

- For survivors of childhood autologous/allogeneic hematopoietic cell transplantation
- Comprehensive review from the Children's Oncology Group
- Organ-system-based guideline of recommended late effects surveillance

TABLE 1

Overview of late effects, organized by treatment exposures commonly seen among survivors of childhood hematopoietic cell transplantation.

Exposure	Late effect*
HCT experience in general	• Dental abnormalities • Renal toxicity • Hepatic toxicity • Low bone mineral density • Avascular necrosis • Increased risk of second cancers • Adverse psychosocial/quality of life effects • Mental health disorders, risk behaviors • Psychosocial disability due to pain, fatigue
Transplant conditioning Alkylating agent	• Cataract (busulfan) • Pulmonary fibrosis (busulfan) • Renal toxicity • Urinary tract toxicity • Gonadal dysfunction • Therapy-related AML/MDS • Bladder cancer
Epipodophyllotoxin	• Therapy-related AML/MDS
DNA inter-strand crosslinking agents (i.e., platinum/heavy metal)	• Ototoxicity • Renal toxicity • Gonadal toxicity
Total body irradiation (TBI)†	• Neurocognitive deficits • Leukoencephalopathy • Cataract • Dental abnormalities • Growth hormone deficiency • Hypothyroidism, thyroid nodule • Pulmonary toxicity • Breast tissue hypoplasia • Cardiac toxicity • Renal toxicity • Gonadal dysfunction • Uterine vascular insufficiency • Diabetes • Dyslipidemia • Musculoskeletal growth problems

Exposure	Late effect*
	• Second cancers
Pre-transplant exposures, not listed above Anthracycline/ anthraquinone	• Cardiac toxicity • Therapy-related AML/MDS
Bleomycin	• Pulmonary toxicity
Cytarabine	• Neurocognitive deficits • Leukoencephalopathy
Methotrexate	• Neurocognitive deficits • Leukoencephalopathy • Renal toxicity • Low bone mineral density
Corticosteroid	• Cataract • Low bone mineral density • Avascular necrosis
Cranial radiation≠	• Neurocognitive deficits • Leukoencephalopathy • Cerebrovascular disease • Cataract • Craniofacial abnormalities • Dental abnormalities, xerostomia • Growth hormone deficiency • Hypothyroidism, thyroid nodule • Increased obesity • Precocious puberty • Brain tumor
Spinal radiation (in addition to cranial dose)	• Cardiac toxicity • Scoliosis/kyphosis, musculoskeletal problems
Post-transplant, not listed above Chronic GVHD	• Xerophthalmia • Xerostomia, dental abnormalities • Pulmonary toxicity • Gastrointestinal strictures • Genitourinary strictures • Skin and joint changes • Immune deficiency • Second cancers, especially skin, oral, cervical, lymphoma
Tyrosine kinase inhibitor	• Acute cardiac toxicity reported, but not known to cause late cardiotoxicity

Exposure	Late effect*
Other exposures	
Blood transfusions	• Hepatitis C, HIV

*Focused on those late effects which can develop or persist even after cessation of therapy.

†At given total dose, risks greater for single fraction vs. fractionated TBI; single fraction myeloablative TBI (>500 cGy) now rarely used

‡Effects listed are those more likely to be associated with doses used in HCT survivors (i.e., those given for leukemia treatment, <25 Gy); late effects are more likely if TBI also given.

TABLE 2

Overview of existing long-term follow-up guidelines with relevance to survivors of pediatric hematopoietic cell transplantation.

Sponsor	Perceived strengths	Perceived limitations	Other comments
Children's Oncology Group (COG) [8] Children's Cancer Study Group (UK) [9]	Comprehensive, pediatric- focused with a HCT- specific section.	May be overly complex, not exclusive to HCT patients; primarily focused on patients treated for underlying malignancy (vs. non- malignant processes)	Exposure- based
CIBMTR, ASBMT, EBMT, APBMT, BMTSANZ, EMBMT, SBTMO [10]	HCT-focused, relatively concise	Not pediatric focused, less comprehensive compared with pediatric-specific guidelines; does not always fully account for pre-HCT exposures	Systems- based

TABLE 3

Overview of evidence scoring system used by the Children's Oncology Group Long-Term Follow-Up guidelines.

Evidence score	Statement of consensus
1	Uniform consensus of the review panel that: 1) high-level evidence links the late effect with the therapeutic exposure; 2) screening recommendation is appropriate based on the collective clinical experience of panel members
2A	Uniform consensus of the review panel that: 1) lower-level evidence links the late effect with the therapeutic exposure; 2) screening recommendation is appropriate based on the collective clinical experience of panel members
2B	Non-uniform consensus of the review panel that: 1) lower-level evidence links the late effect with the therapeutic exposure; 2) screening recommendation is appropriate based on the collective clinical experience of panel members
3	Major disagreement that the recommendation is appropriate

TABLE 4

Second malignant neoplasm screening considerations among survivors of pediatric hematopoietic cell transplantation.

Neoplasm type* [Corresponding COG guideline section number]	Exposure/predisposing factor	Screening
Myelodysplasia/acute myeloid leukemia [14, 32, 43, 44, 103]	• Radiation including TBI • Autologous HCT • Chemotherapy: epipodophyllotoxins, alkylating agents, anthracyclines • Other: older host age, peripheral blood stem cell source, lower CD34 cell count	• Annual history & physical exam up to 10 years after transplant; laboratory studies only as clinically indicated.
Lymphoma [106]	• Chronic GVHD • HCT-related factors: HLA mismatch, unrelated donor, anti-T cell serotherapy • Other: primary immune deficiency	• Annual history & physical exam
Solid tumors in general [44, 104]	• Radiation including TBI • Chronic GVHD • Younger age at treatment • Other: cancer predisposition syndrome (e.g., Li Fraumeni, neurofibromatosis, Fanconi's anemia, germline RB1); hepatitis C infection, human papillomavirus infection	• Annual history & physical exam, including the oral cavity
Specific solid tumors: In addition to above exposures, also:		
Bladder [18]	• Alkylating agents • Alcohol use, smoking	• Urinalysis with history of any hematuria, dysuria, or change in urinary flow
Brain [48]	• Neurofibromatosis, ataxia telangiectasia	• Consider brain MRI every other year in patients with neurofibromatosis who received any radiation to the head
Breast [77]	• ≥20 Gy radiation (for 10–19 Gy or TBI alone, recommend discussion of potential benefits/risks of screening first) • Positive family history, BRCA1/2 or ATM mutation carrier	• Yearly breast exam beginning at puberty until age 25 years; then every 6 months • Yearly mammograms and breast MRI beginning 8 years after radiation or age 25 years (whichever occurs last)
Colon/rectum [90]	• ≥30 Gy radiation • Lynch syndrome, familial adenomatous polyposis, or inflammatory bowel disease	• Colonoscopy every 5 years (minimum) beginning 10 years after radiation or age 35 years (whichever occurs last) • Those with one of the listed predisposing conditions may

Neoplasm type* [Corresponding COG guideline section number]	Exposure/predisposing factor	Screening
		require earlier initiation of screening.
Skin [45]	• Sun exposure/tanning • Gorlin's syndrome	• Annual full skin exam • Dermatology consultation to evaluate and monitor atypical findings
Thyroid [72]	• Female	• If any palpable nodules detected, consider ultrasound and fine needle aspiration

*Neoplasm types only highlight those occurring most commonly or associated with greater risks following HCT; survivors should receive standard screening for other tumors not listed per recommendations for the general population. More details can be found at www.survivorshipguidelines.org.

APPENDIX TABLE 1

List of Children's Oncology Group Guidelines sections specifically covered by this hematopoietic cell transplant guidelines review.

Section number	Treatment exposure	Late effect	Evidence score
1	All survivors	Psychosocial/quality of life issues	2A
2	All survivors	Mental health disorders	2A
3	All survivors	Risky behaviors	2A
4	All survivors	Chronic pain	2A
5	All survivors	Fatigue	2A
6	All survivors	Healthcare insurance barriers	2A
8	Transfusion	Hepatitis C	1
9	Transfusion	HIV infection	1
10	Chemotherapy-any	Dental abnormalities	1
11	Alkylating & similar DNA inter-strand crosslinking agents	Reduced fertility (male)	1/2A
12	Alkylating & similar DNA inter-strand crosslinking agents	Reduced testosterone (male)	1/2A
13	Alkylating & similar DNA inter-strand crosslinking agents	Ovarian dysfunction	1/2A
14	Alkylating & similar DNA inter-strand crosslinking agents	Acute myeloid leukemia / myelodysplasia	1/2A
15	Busulfan	Pulmonary fibrosis	1
16	Busulfan	Cataract	2B
17	Alkylating agent	Urinary tract toxicity	1
18	Alkylating agent	Bladder cancer	2A
19	Alkylating agent	Renal toxicity	1
20	DNA inter-strand crosslinking agent	Ototoxicity	1
22	DNA inter-strand crosslinking agent	Renal toxicity	2A
23	Cytarabine	Neurocognitive deficits	2A
24	Cytarabine	Leukoencephalopathy	2A
26	Mercaptopurine & thioguanine	Hepatic dysfunction	2A
27	Methotrexate	Low bone mineral density	2B
28	Methotrexate	Renal toxicity	2A
30	Methotrexate	Neurocognitive deficits	1
31	Methotrexate	Leukoencephalopathy	1
32	Anthracycline	Acute myeloid leukemia / myelodysplasia	1
33	Anthracycline	Cardiac toxicity (male)	1
34	Anthracycline	Cardiac toxicity (female)	1
35	Bleomycin	Pulmonary toxicity	1
37	Corticosteroid	Low bone mineral density	2B
38	Corticosteroid	Avascular necrosis	1
39	Corticosteroid	Cataract	1
43	Epipodophyllotoxin	Acute myeloid leukemia / myelodysplasia	1
44	Radiotherapy-any	Second cancer, any	1
45	Radiotherapy-any	Dysplastic nevi, skin cancer	1
45	Radiotherapy-any	Skin cancer	1

Section number	Treatment exposure	Late effect	Evidence score
46	Radiotherapy-any (excluding TBI)	Skin changes	1
48	Radiotherapy-head/TBI	Brain tumor	1
49	Radiotherapy-head/TBI	Neurocognitive deficits	1
50	Radiotherapy-head/TBI	Leukoencephalopathy	1
51	Radiotherapy-head/TBI	Cerebrovascular disease	1
52	Radiotherapy-head	Craniofacial abnormalities	1
54	Radiotherapy-head	Overweight/obesity	1
55	Radiotherapy- head/TBI	Growth hormone deficiency	1
56	Radiotherapy-head	Precocious puberty (male)	1
57	Radiotherapy-head	Precocious puberty (female)	1
64	Radiotherapy-head/TBI	Cataract	1
65	Radiotherapy-head/TBI	Ocular toxicity	1
66	Radiotherapy-head/TBI	Ototoxicity	1
67	Radiotherapy-head/TBI	Ototoxicity	1
68	Radiotherapy-head/neck/spine/mantle/TLI	Xerostomia	1
69	Radiotherapy-head/neck/spine/mantle/TLI/TBI	Dental abnormalities	1
71	Radiotherapy-head/neck/spine/mantle/TLI/TBI	Thyroid nodules	1
72	Radiotherapy-head/neck/spine/mantle/TLI/TBI	Thyroid cancer	1
73	Radiotherapy-head/neck/spine/mantle/TLI/TBI	Hypothyroidism	1
77	Radiotherapy-axilla/chest/TLI/TBI	Breast cancer	1
78	Radiotherapy-axilla/chest/TLI/TBI	Breast tissue hypoplasia	1
79	Radiotherapy-axilla/chest/TLI/TBI	Pulmonary toxicity	1
80	Radiotherapy-chest/abdomen/spine/TLI/TBI	Cardiac toxicity (male)	1
81	Radiotherapy-chest/abdomen/spine/TLI/TBI	Cardiac toxicity (female)	1
84	Radiotherapy-abdomen/extended mantle/ TLI/TBI	Diabetes	1
85	Radiotherapy-TBI	Dyslipidemia	1
91	Radiotherapy-abdomen/extended mantle/ TLI/TBI	Renal toxicity	1
94	Radiotherapy-abdomen/pelvis/spine/TLI	Bladder cancer	2A
95	Radiotherapy-abdomen/pelvis/spine/TLI/TBI	Uterine vascular insufficiency	2B
96	Radiotherapy-abdomen/pelvis/spine/TLI/TBI	Ovarian dysfunction	1
97	Radiotherapy-abdomen/pelvis/TLI	Vaginal changes	2A
98	Radiotherapy-abdomen/pelvis/testes/ TLI/TBI	Testicular dysfunction	1
99	Radiotherapy--abdomen/pelvis/testes/ TLI/TBI	Testosterone deficiency/insufficiency	1
100	Radiotherapy-all fields	Musculoskeletal growth problems	1
101	Radiotherapy-chest/abdomen/spine/TLI	Scoliosis/kyphosis	1
103	HCT	Acute myeloid leukemia / myelodysplasia	1
104	HCT (male)	Solid tumor, any	1
105	HCT (female)	Solid tumor, any	
106	HCT	Lymphoma	1
107	HCT	Hepatitic toxicity	1
108	HCT	Avascular necrosis	1
109	HCT	Low bone mineral density	2B

Section number	Treatment exposure	Late effect	Evidence score
110	HCT	Renal toxicity	1
111	GVHD	Skin changes	1
112	GVHD	Xerophthalmia	1
113	GVHD	Xerostomia, dental problems, oral cancer	1
114	GVHD	Pulmonary toxicity	1
115	GVHD	Immune deficiency, dysfunction	1
116	GVHD	Functional asplenia	1
117	GVHD	Esophageal stricture	1
118	GVHD	Vaginal changes	1
119	GVHD	Joint contracture	1
157	All survivors (female)	Breast cancer screening	USPHSTF
158	All survivors (female)	Cervical cancer screening	USPHSTF
159	All survivors	Colorectal cancer screening	USPHSTF
160	All survivors (female)	Endometrial cancer screening	USPHSTF
161	All survivors	Lung cancer screening	USPHSTF
162	All survivors	Oral cancer screening	USPHSTF
163	All survivors (male)	Prostate cancer screening	USPHSTF
164	All survivors	Skin cancer screening	USPHSTF
165	All survivors (male)	Testicular cancer screening	USPHSTF
166	All survivors	General health screening	USPHSTF

GVHD, graft versus host disease; HCT, hematopoietic cell transplant; TBI, total body irradiation; TLI, total lymphoid irradiation; USPHSTF, US Preventative Health Services Taskforce