

West of Scotland Cancer Network

**Haemato-oncology
Managed Clinical Network**



Recommended Screening and Preventative Practices for Adult Long- Term Survivors after Allogeneic Haemopoietic Stem Cell Transplant (HCT) and Total Body Irradiation (TBI) Autografts

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1. Introduction

The purpose of Recommendations for Screening and Preventative Practices for Long-term survivors after Haemopoietic Stem Cell Transplant (HCT) is to ensure consistency of practice and appropriate follow up care. Due to expanding indications for HCT and improvements in supportive care leading to decreased mortality, the use of HCT for treating various malignant and non-malignant diseases is increasing. ¹

Advances in transplantation techniques and supportive care practices have led to progressive improvements in survival for HCT recipients. As patients survive long-term after transplantation, they are at risk of developing late complications. These complications can cause substantial morbidity, impair quality of life and can contribute to late mortality in HCT recipients. ²

It is recognised that the life expectancy of HCT survivors is lower than expected at 10 to 30 years post-transplantation: secondary cancers, infection and organ dysfunction are common causes of late deaths in this population. Recognising the need for guidance about appropriate systematic long-term follow up of HCT survivors, the Centre for International Blood and Marrow Transplant Research (CIBMTR), the European Group for Blood and Marrow Transplantation (EBMT), and the American Society of Blood and Marrow Transplantation (ASBMT) convened a group of experts in 2006 and provided consensus recommendations for screening and preventative practices for autologous and allogeneic HCT survivors. These guidelines were revised in 2012.

The West of Scotland Haemato-oncology Managed Clinical Network (MCN) recommendations are adapted from these Guidelines. These recommendations are not intended to be mandatory for all patients. Good medical practice and judgment dictates that certain recommendations may not be applicable.

2. Recommendations

2.1 Immunity and Infections

Patients with chronic GVHD should receive antibiotic prophylaxis targeting encapsulated organisms given for at least as long as immunosuppressive therapy is administered.

Antiviral and antifungal prophylaxis should be considered in patients at high risk for viral and fungal infections (e.g., patients with chronic GVHD) according to published guidelines. Screening for CMV reactivation should be based on risk factors, including intensity of immunosuppression.

Allogeneic HCT recipients should receive PCP prophylaxis from engraftment until at least 6 months after transplantation or as long as immunosuppressive therapy is given (e.g. for the treatment or prevention of chronic GVHD). PCP prophylaxis for 3 to 6 months post-transplantation should be considered for autologous HCT recipients with substantial immunosuppression (e.g. patients with lymphoma, leukaemia or myeloma, especially when pre-transplant treatments or conditioning regimens have included purine analogues or high dose corticosteroids).

Immunisation with inactivated vaccines for all patients according to published guidelines. Since patients with chronic GVHD can mount responses to vaccines and are at risk for infections, postponing vaccination in patients with GVHD is not recommended with the exception of live vaccines. When vaccinating patients with active GVHD, it may be prudent to measure specific antibody levels before and after vaccination, to determine their level of protection and need for booster immunisations.

See NHS Greater Glasgow & Clyde, Haemopoietic Stem Cell Transplantation Services, Vaccination Policy. ³

2.2 Ocular Complications

Routine clinical evaluation of visual history and symptoms, with attention to sicca syndrome, is recommended at 6 months, 1 year and yearly thereafter for all HCT recipients.

Referral to an expert in optometry for routine ocular examination with measurement of visual acuity and fundus examination at 1 year after transplant is recommended for all HCT recipients. Patients with chronic GVHD may be referred for ophthalmologic exam sooner than 1 year post-transplant. Subsequent frequency of routine screening should be individualised according to recognised defects, ocular symptoms or the presence of chronic GVHD.

(Free) appointment with optician 2 yearly.

Patients experiencing visual symptoms should arrange to see GP or optician.

2.3 Oral Complications

All HCT recipients should be educated about preventive oral health and routine dental maintenance. Patients should also be counselled to avoid smoking and chewing tobacco, decrease regular intake of sugar containing beverages, and avoid intraoral piercing.

Clinical oral evaluations should be performed at 6 months, 1 year and yearly thereafter. More frequent evaluations may be needed in patients at high-risk of oral complications (e.g. chronic GVHD, exposure to TBI). Monitoring of oral complications post-transplantation is facilitated by thorough pre-HCT baseline oral assessment.

Patients at high-risk for squamous cell cancers of the oral cavity (e.g. oral chronic GVHD, Fanconi's anaemia) should undergo clinical oral evaluations every 6 months and should be educated to maintain meticulous oral hygiene and taught oral self-inspection.

All HCT recipients should receive a thorough evaluation by a dentist or oral medicine specialist at 1 year after HCT and yearly thereafter. More frequent dental consultations may be considered in patients with oral GVHD or Fanconi's anaemia. At each visit it is important to check for a history of xerostomia and high-risk habits, to perform a thorough oral and dental examination.

2.4 Respiratory Complications

Routine clinical assessment by history and, if indicated, physical examination for pulmonary complications is recommended for all patients at 6 months, 1 year and yearly thereafter.

Some experts recommend earlier and more frequent clinical and functional assessments including PFTs in patients with chronic GVHD.

History of smoking should be assessed and patients who smoke or are at risk for passive smoking should be counselled regarding smoking cessation.

Clinical assessment by history and, if indicated, physical exam at 6 months, 1 year and yearly thereafter. In patients with symptoms or signs of lung compromise, PFTs and focused radiologic assessment should be performed as clinically indicated. Follow-up evaluations should be guided by clinical circumstances for patients with recognised defects.

2.5 Cardiac and Vascular Complications

Routine clinical assessment and cardiovascular risk factor evaluation for all HCT recipients at 1 year and yearly thereafter. More frequent assessments and if clinically appropriate, extended cardiac evaluations (e.g. electrocardiogram, echocardiogram) may be indicated in patients at high-risk for cardiac complications (e.g. patients with Hodgkin lymphoma who have received mediastinal radiation therapy, patients with amyloidosis, and patients with pre-existing cardiac and vascular abnormalities).

Education and counselling on healthy life style (regular exercise, maintaining healthy weight, no smoking, dietary counselling) for all HCT recipients (see section on General Screening and Preventive Health).

Clinical assessment and cardiovascular risk factor evaluation for all HCT recipients at 1 year and yearly thereafter. Appropriate treatment of cardiovascular risk factors such as diabetes, hypertension and dyslipidemia for all HCT recipients. Among patients started on drug therapy for dyslipidemia, follow-up assessments should be performed based on published guidelines.

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2.6 Liver Complications

Liver function tests (total bilirubin, alkaline phosphatase, and transaminases) should be performed every 3–6 months for the first year and then at least yearly until year 5. More frequent assessments may be needed based on an individual patient's medical status (e.g. patients with GVHD), and particularly in allogeneic transplant survivors.

Serum ferritin and transferrin saturation should be measured at 1 year post transplant in patients who received RBC infusions pre- or post-transplant. Subsequent monitoring with serum ferritin should be considered among patients with elevated levels, especially in the presence of abnormal liver function tests, continued RBC transfusions, or HCV infection. Additional diagnostic testing (e.g. liver biopsy or MRI) may be indicated if therapy is contemplated for suspected iron overload – see below

Patients with viral hepatitis should have viral load monitored by polymerase chain reaction (PCR) and consultation with liver and/or infectious disease specialists for antiviral therapy.

Venesection should be carried out locally to achieve normal ferritin and transferrin saturation.

- Ferritin > 1000ug/L and Transferrin Saturation > 75% - recommend venesection.
- Ferritin > 300ug/L and < 1000ug/L, Transferrin Saturation > 50% and < 75% and LFT's abnormal - recommend venesection.
- Ferritin < 1000ug/L and Transferrin Saturation < 75% and LFT's normal - monitor annually.

2.7 Renal and Genitourinary Complications

Blood pressure should be checked at every clinic visit, and hypertension should be investigated and managed appropriately in all HCT recipients (see section on General Screening and Preventive Health).

Renal function should be evaluated at 6 months, 1 year and at least yearly thereafter for all HCT recipients. Further workup (e.g. assessment by renal physicians, renal ultrasound, renal biopsy), as clinically indicated should be pursued in patients with late onset acute renal failure or CKD post-transplantation. More frequent assessments may be needed based on an individual patient's medical status (e.g. ongoing therapy with calcineurin inhibitors).

In patients with progressive CKD, avoid nephrotoxins and consider early referral to a nephrologist for evaluation and treatment.

2.8 Complications of Muscle and Connective Tissue

All HCT recipients should follow general population age-specific guidelines for physical activity.⁵

For patients on corticosteroids, frequent clinical evaluation is recommended for steroid-induced myopathy by manual muscle tests or by assessing patients' ability to go from a sitting to a standing position.

Patients with muscle weakness, myalgias, or arthralgias should be evaluated for possible chronic GVHD or steroid associated myositis, and other muscular disorders (e.g. myasthenia gravis).

2.9 Skeletal Complications

A screening dual photon densitometry should be performed at 1 year after transplantation in adult women and all allogeneic HCT recipients and patients who are at high risk for bone loss after transplantation (e.g. prolonged treatment with corticosteroids or calcineurin inhibitors). Repeat densitometry should be performed in those with osteoporosis, ongoing risk factors or to follow up response to therapy as recommended by Bone Densitometry Team. Physicians should evaluate gonadal and other related endocrine abnormalities in patients with decline in bone density.

Screening for AVN is not recommended; however, clinicians should maintain a high level of suspicion for patients with exposure to irradiation or prolonged corticosteroids and evaluate patients with joint symptoms promptly.

Patients should be counselled about preventive measures for bone loss and fractures such as physical exercise, fall prevention, vitamin D intake and calcium supplementation. Vitamin D levels to be checked annually from 1 year post transplant.

Hormone replacement therapy should be discussed with women who have oestrogen deficiency via Menopause/Gynaecology Clinics. Consider use of bisphosphonates for patients at high risk for bone loss.

2.10 Central and Peripheral Nervous System Complications

All HCT recipients should undergo clinical assessment for symptoms or if indicated, signs of neurologic dysfunction at 1 year after HCT and at least yearly thereafter.

Adult patients should be queried annually for changes in cognitive function, which may be subtle.

Further evaluation (e.g. MRI, nerve conduction studies, electromyography, neuropsychiatry testing) may be warranted in recipients with symptoms or signs of neurologic or cognitive dysfunction.

2.11 Endocrine Complications

Thyroid: Thyroid function tests (TSH and free T4) should be performed at 1 year and yearly thereafter in all transplant recipients and additionally if relevant symptoms develop.

Gonadal: Clinical and endocrinologic gonadal assessment at 1 year after HCT is recommended for all women who were post-pubertal at the time of transplantation. Referral to Menopause Clinic, if appropriate, at Day 100 follow-up. Frequency of subsequent assessments should be guided by clinical need (e.g. menopausal status). Women should have regular gynaecology evaluation as part of general health screening, e.g. cervical screening. Hormone replacement therapy should be considered for those who are post-menopausal.

In men, FSH, LH, and testosterone, should be assessed if symptoms warrant (lack of libido or erectile dysfunction). Consider referral to an endocrinologist for men who may need testosterone replacement therapy.

2.12 Muco-cutaneous Complications

Patients should perform routine self examination of the skin and avoid excessive exposure of sunlight without adequate protection. The aim is healthy sun exposure without burning.

Discuss with all women recipients of allogeneic HCT symptoms of genital GVHD. Women who have established chronic GVHD should have gynaecological exam to screen for genital involvement.

Patients should be counselled about self examination of the vaginal area, general hygiene measures, and early recognition of local symptoms. Application of topical vaginal immunosuppressive agents, such as ultrahigh potency corticosteroids or calcineurin inhibitors, prescription of systemic hormonal replacement therapy if indicated, and the use of vaginal dilators should be initiated early in the course of genital cGVHD.

2.13 Secondary Cancers

Exposure to radiation, and photosensitising effects of many commonly used transplantation-related medications increases the risk of skin cancers among HCT recipients. All HCT recipients should be encouraged to reduce UV skin exposure through use of high SPF sunscreens or skin coverage.

All patients should be advised of the risks of secondary malignancies annually and encouraged to routinely perform recommended screening self-examination such as genital/testicular and skin examination. Women should discuss breast self-examination with their physicians. All patients should be encouraged to avoid high-risk behaviours as recommended under General Health and Preventive Screening section, including avoidance of tobacco, passive tobacco exposure or excessive unprotected skin UV exposure.

Screening clinical assessment should be performed yearly, and should include symptom review for secondary malignancies. Clinical examination and screening for secondary

malignancies should follow the recommendations outlined under the General Health and Preventive Screening section. In women with radiation exposure (e.g. TBI or radiation to the chest region), initiation of screening mammography should occur at age 25 or 8 years after radiation, whichever occurs later, but no later than age 40 years. Particular attention to oral malignancies should be paid to patients with previous severe chronic GVHD of the oral and pharyngeal mucosa.

2.14 Psychosocial Adjustment and Sexual Complications

A high level of vigilance for psychological symptoms should be maintained. Clinical assessment is recommended throughout the recovery period, at 6 months, at 1 year, and at least yearly thereafter, with mental health professional assessment recommended for those with recognised deficits.

Inquiry as to the level of spousal/caregiver psychological adjustment and family functioning should be performed at regular intervals.

In adults, sexual function should be queried at 6 months, at 1 year and yearly thereafter (also see section on Muco-Cutaneous complications).

2.15 Fertility

Consider referral to appropriate specialists for patients who are contemplating a pregnancy or are having difficulty conceiving.

Although infertility is common, patients should nevertheless be counselled regarding birth control post-transplantation.

2.16 General Screening and Preventive Health

Hypertension: Blood pressure should be checked at least every 2 years. Non-pharmacologic treatments may also be tried for mild hypertension and include moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise.

Hypercholesterolemia: Cholesterol and HDL levels should be checked every five years starting at age 35 for men and 45 for women. Screening should start at age 20 for anyone who smokes, has diabetes, hypertension, obesity (body mass index ≥ 30 kg/m²), or a family history of heart disease before age 50 for male relatives or before age 60 for female relatives. Fasting is not required for accurate measurement of cholesterol and HDL, but is required for LDL and triglycerides. As a rough guideline, total cholesterol levels >5.0 mmol/l or HDL levels <1 mmol/l should be followed up by a full fasting lipid panel. Treatment goals are based on overall risk of heart disease (e.g. greater than a 10% chance of coronary heart disease in 10 years as per ASSIGN score). Overall risk assessment will include the following risk factors: age, sex, diabetes, clinical atherosclerotic disease, hypertension, family history, low HDL (<1.0 mmol/l).

Colorectal cancer: Screening should start at age 50 in the absence of a family history (first degree relative diagnosed with colorectal cancer before age 60).

Diabetes: Screening for type 2 diabetes is indicated for people every three years after age 45 or in those with sustained higher blood pressure (>135/80) because blood pressure targets are lower for diabetics. A fasting plasma glucose >7 mmol/l, confirmed by testing on another day, is diagnostic for diabetes.

Depression: Asking two simple questions about mood and anxiety ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?") is probably as effective as longer screening tools. It is reasonable to screen at 6 months then every 12 months post-transplantation or as clinically indicated, using a Holistic Needs Assessment Tool.

Fatigue: Using an appropriate screening tool, such as the Holistic Needs Assessment, will identify individuals experiencing fatigue.

Sexually transmitted diseases: Chlamydia screening is recommended for women under the age of 25 who are sexually active. Screening and appropriate treatment decrease the incidence of pelvic inflammatory disease and pregnancy-related complications, although most women will be infertile after myeloablative transplantation. Male and female survivors should be reminded that protection against sexually transmitted disease is important even when pregnancy is unlikely.

Chlamydia Screening should be discussed with patients if appropriate and referrals made to Genito-Urinary Medicine if indicated.

Sex-specific recommendations

Recommended screening for men:

- Prostate cancer: There is **no** consensus about the use of prostate-specific antigen or digital rectal examination for prostate cancer screening.

Recommended screening for women:

- Breast cancer: Screening with mammograms should start at age 40 and occur every 1–2 years. Breast self-examination is recommended. In women exposed to > 800 cGy radiation, screening should start at age 25 or 8 years after radiation exposure, whichever is later but no later than age 40, (based on the data from Hodgkin lymphoma survivors).
- Cervical cancer: Screening with pap smears should be performed every 1–3 years in women aged 25 years or over.

Healthy lifestyle recommendations for all patients

Eat a healthy diet with a wide variety of foods.

Don't smoke (passive or active exposure), chew tobacco or use illegal drugs.

Use alcohol in moderation, generally less than 2 units per day. Recommend 2 alcohol free days per week.

Avoid excessive sun exposure and wear sunscreen protection for anticipated periods of long exposure.

Follow general population age specific guidelines for physical activity.⁵

3. References

1. Majhail NS et al. Recommended Screening and Preventative Practices for Long-term Survivors after Hematopoietic Cell Transplantation. *Bone Marrow Transplant* 2012 Mar 47(3): 337-341
2. Lost in Transition: The Essential Need for Long-Term Follow-Up Clinic for Blood and Marrow Transplantation Survivors. *Biology of Blood and Marrow Transplantation* 21 (2015) 225-232
3. NHS Greater Glasgow & Clyde Haemopoietic Stem Cell Transplantation Services Vaccination Policy. Access at <http://www.scothaem.org/>
4. SIGN Guideline 97: Risk estimation and prevention of cardiovascular disease. Scottish Intercollegiate Guidelines Network
5. UK Physical Activity Guidelines, Department of Health, 2011. Guidance from the Chief Medical Officer (CMO)

4. Appendix 1: Summary recommendations for screening and prevention of late complications in Adult long-term HCT survivors organised by time after transplantation.

Recommended Screening/Prevention	6 mo	1yr	Annually
IMMUNITY			
Encapsulated organism prophylaxis	2	2	2
PCP prophylaxis	2	2	
CMV testing	2	2	2
Immunizations	1	1	1
OCULAR			
Ocular clinical symptom evaluation	1	1	1
Ocular fundus exam	+	1	+
ORAL COMPLICATIONS			
Clinical assessment	1	1	1
Dental assessment	+	1	1

Recommended Screening/Prevention	6 mo	1yr	Annually
RESPIRATORY			
Clinical pulmonary assessment	1	1	1
Smoking tobacco avoidance	1	1	1
Pulmonary function testing	+	+	+
Chest radiography	+	+	+
CARDIAC AND VASCULAR			
Cardiovascular risk-factor assessment	+	1	1
LIVER			
Liver function testing	1	1	+
Serum ferritin testing		1	+
RENAL			

Recommended Screening/Prevention	6 mo	1yr	Annually
Urea &Electolyte testing	1	1	1
Blood pressure screening	1	1	1
MUSCLE AND CONNECTIVE TISSUE			
Evaluation for muscle weakness	2	2	2
Physical activity counselling	1	1	1
SKELETAL			
Bone density testing (adult women, all allogeneic transplant recipients and patients at high risk for bone loss)		1	+
NERVOUS SYSTEM			
Neurologic clinical evaluation	+	1	1
Evaluate for cognitive development		1	1
ENDOCRINE			
Thyroid function testing		1	1

Recommended Screening/Prevention	6 mo	1yr	Annually
Gonadal function assessment(postpubertal women)		1	+
Gonadal function assessment (postpubertal men)		+	+
MUCO-CUTANEOUS			
Skin self-exam and sun exposure counseling	1	1	1
Gynecologic exam in women	+	1	1
SECOND CANCERS			
Second cancer vigilance counselling		1	1
Screening for second cancers		1	1
PSYCHOSOCIAL			
Psychosocial/QOL clinical assessment	1	1	1
Sexual function assessment	1	1	1

1 = recommended for all transplant recipients

2 = recommended for any patient with ongoing chronic GVHD or immunosuppression

+ = reassessment recommended for abnormal testing in a previous time period or for new signs/symptoms