ACI NSW Agency for Clinical Innovation

CLINICAL GUIDELINES

Blood and marrow transplant long-term follow-up

Blood and Marrow Transplant Network

Collaboration. Innovation. Better Healthcare.

The Agency for Clinical Innovation (ACI) works with clinicians, consumers and managers to design and promote better healthcare for NSW. It does this through:

- *service redesign and evaluation* – applying redesign methodology to assist healthcare providers and consumers to review and improve the quality, effectiveness and efficiency of services.
- *specialist advice on healthcare innovation* – advising on the development, evaluation and adoption of healthcare innovations from optimal use through to disinvestment.
- *initiatives including Guidelines and Models of Care* – developing a range of evidence-based healthcare improvement initiatives to benefit the NSW health system.
- *implementation support* – working with ACI Networks, consumers and healthcare providers to assist delivery of healthcare innovations into practice across metropolitan and rural NSW.
- *knowledge sharing* – partnering with healthcare providers to support collaboration, learning capability and knowledge sharing on healthcare innovation and improvement.
- *continuous capability building* – working with healthcare providers to build capability in redesign, project management and change management through the Centre for Healthcare Redesign

ACI Clinical Networks, Taskforces and Institutes provide a unique forum for people to collaborate across clinical specialties and regional and service boundaries to develop successful healthcare innovations.

A key priority for the ACI is identifying unwarranted variation in clinical practice. ACI teams work in partnership with healthcare providers to develop mechanisms aimed at reducing unwarranted variation and improving clinical practice and patient care.

www.aci.health.nsw.gov.au

AGENCY FOR CLINICAL INNOVATION

Level 4, Sage Building
67 Albert Avenue
Chatswood NSW 2067

PO Box 699 Chatswood NSW 2057
T +61 2 9464 4666 | F +61 2 9464 4728
E aci-info@health.nsw.gov.au | www.aci.health.nsw.gov.au

SHPN (ACI) 160340, ISBN 978-1-76000-489-7 (print); 978-1-76000- 490-3(online).

Produced by: Jody Gough, Blood and Marrow Transplant Network

Further copies of this publication can be obtained from
the Agency for Clinical Innovation website at *www.aci.health.nsw.gov.au*

Trim: ACI/D18/3261

Version: V1.1

Date Amended: 08/11/2016

Review date: 2023

Acknowledgements

The Agency for Clinical Innovation (ACI) gratefully acknowledges the important contributions and guidance provided by the following members of the Blood and Marrow Transplant (BMT) Network Long-Term Follow-Up (LTFU) working group.

Prof Ian Kerridge (Co-Chair)
BMT Physician
Royal North Shore Hospital

Prof Peter Shaw (Co-Chair)
BMT Physician
The Children's Hospital Westmead

Jody Gough
BMT Network Clinical Nurse Consultant
NSW Agency for Clinical Innovation

Louisa Brown
BMT Clinical Nurse Consultant
Calvary Mater Hospital Newcastle

A/Prof Richard Cohn
Head, Clinical Oncology and LTFU Program
Sydney Children's Hospital Randwick

Gemma Dyer
Content Author (BMT and Cancer Genetics)
eviQ, Cancer Institute NSW

Dr Melissa Gabriel
Paediatric Oncologist
The Children's Hospital Westmead

Dr Matthew Greenwood
BMT Physician and Director, BMT Program
Royal North Shore Hospital

Megan Hogg
LTFU Clinical Nurse Specialist
Westmead Hospital

Annabel Horne
BMT Clinical Nurse Consultant
St Vincent's Hospital Sydney

Karen Johnston
LTFU Clinical Nurse Consultant
Sydney Children's Hospital Randwick

Dr John Kwan
BMT Physician
Westmead Hospital

A/Prof Stephen Larsen
BMT Physician
Royal Prince Alfred Hospital

Prof David Ma
BMT Physician
St Vincent's Hospital Sydney

Alana Paterson
LTFU Clinical Nurse Specialist
Liverpool Hospital

John Stubbs
Consumer Representative

Steven Tran
Data Analyst/Statistician
Australasian Bone Marrow Transplant
Recipient Registry (ABMTRR)

Ida Twist
Nurse Practitioner BMT Follow-Up
The Children's Hospital Westmead

Leonie Wilcox
Manager
ABMTRR

Katrina Wilczek
LTFU Clinical Nurse Consultant
Royal Prince Alfred Hospital

Additional reviewers and contributors include all members of the BMT Network Council, as well as:

- Dr Nicole Gilroy, Infectious Diseases Physician, BMT Network, ACI/Westmead Hospital
- Dr Jennifer Bradford, Obstetrician and Gynaecologist
- Dr Mark Schifter, Specialist Oral Pathologist, Westmead Hospital
- Professor Peter McCluskey, Professor of Ophthalmology, Save Sight Institute, University of Sydney
- Dr Lisa Brice, Clinical Psychologist, Asperger Services Australia
- A/Prof Peter Middleton, Respiratory and Sleep Medicine Physician, Westmead Hospital
- Dr Tim Furlong, Senior Staff Specialist, Nephrology, St Vincent's Hospital
- A/Prof Andrew Jabbour, Cardiologist, St Vincent's Hospital, Sydney
- Dr Lyndal Tacon, Staff Specialist, Endocrinology, Royal North Shore Hospital
- A/Prof Rory Clifton-Bligh, Senior Staff Specialist, Endocrinology, Royal North Shore Hospital
- Dr Brett Jones, Senior Staff Specialist in Hepatology, Royal North Shore Hospital
- Dr Sylvia Lim-Tio, Endocrinologist, Westmead Hospital
- Kate Lloyd, Program Manager Acute Care, ACI
- Michelle Frawley, BMT Network Manager, ACI
- ACI Respiratory, Cardiac, Musculoskeletal, Gynaecological Oncology, Ophthalmology, Gastroenterology, Endocrine, Renal and Mental Health Networks.

Glossary

Abbreviation	Description
ABMTRR	Australasian Bone Marrow Transplant Recipient Registry
ACI	Agency for Clinical Innovation
ASBMT	The American Society of Blood and Marrow Transplant
APBMT	The Asia Pacific Blood and Marrow Transplant Group
AVN	Avascular necrosis
BMD	Bone mineral density
BMI	Body mass index
BMT	Blood and marrow transplant
BMTSANZ	The Bone Marrow Transplant Society of Australia and New Zealand
CIBMTR	Centre for International Blood and Marrow Transplant Research
CKD	Chronic kidney disease
cGVHD	Chronic graft-versus-host disease
DLCO	Diffusing capacity of the lungs for carbon monoxide test
DXA	Dual-energy X-ray absorptiometry
EBMT	European Group for Blood and Marrow Transplantation
FACT	Functional assessment of cancer therapy
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HPV	Human papillomavirus
LHD	Local health district
LTFU	Long-term follow-up
MRI	Magnetic resonance imaging
PFT	Pulmonary function test
SCC	Squamous cell carcinoma
SOS/VOD	Sinusoidal obstructive syndrome/veno-occlusive disease
SQUID	Superconducting quantum interference device
TBI	Total body irradiation

Contents

Section 1

Introduction

Blood and marrow transplant (BMT) has an established role in the treatment of a range of haematological, immunological and metabolic conditions and for many patients provides the only possibility of long-term survival. At the same time, BMT may cause significant morbidity and mortality and is associated with a series of serious late effects – many of which may impact upon the transplant survivor's life expectancy and quality of life. For survivors of BMT therefore, it is crucial that they have access to high quality, expert, integrated healthcare in the years following transplantation.

The Agency for Clinical Innovation (ACI) BMT Network long-term follow-up (LTFU) working group brings together expert clinicians, consumers and partners to advise on the design and delivery of BMT LTFU to optimise the health and wellbeing of survivors of BMT. A priority of this group was to develop clinical guidelines for the long-term care of BMT recipients in the anticipation that these would enable the standardisation and delivery of high quality long-term care across NSW to improve patient outcomes, ensure sustainable healthcare and provide optimum quality of life for survivors of BMT.

The clinical guidelines combine international recommendations with evidence from BMT survivors both internationally and in NSW to support provision of high quality life-long care for survivors of BMT and ensure better health outcomes following BMT.

These prevention and screening guidelines for clinical care aim to support local health districts (LHDs) and health professionals to provide safe and effective care. The guidelines are an essential requirement to developing an integrated state-wide approach to the ongoing clinical care that ensures that all NSW patients have access to services, expertise and resources consistent with their needs, values and preferences.

Section 2

Background

During the past 30 years advances in BMT technology and techniques have resulted in an increase in both the number of people undergoing the procedure and the number becoming long-term survivors. In NSW there are over 1600 survivors of allogeneic BMT – with approximately 200 children and adults undergoing allogeneic transplants each year. With improvements in donor selection, conditioning therapies and supportive care 35–80% of allogeneic BMT recipients can now be expected to become long-term survivors and be cured of their underlying disease.[1, 2] These survivors will be at increased risk of late complications resulting from their disease, its treatment and from BMT itself. These complications may impair not only physical functioning but may also have significant impacts upon a survivor's psychosocial and emotional function – causing unemployment, relationship difficulties, financial hardship and social isolation. The collective impact of these complications is profound, with allogeneic BMT survivors experiencing a 30% lower life expectancy compared with someone who has not been transplanted[3], 66% reporting at least one chronic complication of BMT and 18% reporting a life threatening health consequence of BMT.[4]

In addition to patients undergoing allogeneic BMT, there are large numbers of patients who have undergone autologous BMT. Although mortality and morbidity (both short and long-term) are much greater in survivors of allogeneic BMT, international guidelines for post-BMT follow-up currently recommend that follow-up and management of survivors of autologous BMT are the same as for survivors of allogeneic BMT.

Table 1: NSW transplant activity 2009–2014[5]

NSW TRANSPLANT ACTIVITY						
	2009	**2010**	**2011**	**2012**	**2013**	**2014**
Allogeneic related	75	91	96	94	81	83
Allogeneic unrelated	70	75	95	119	101	117
Allogeneic total	145	166	191	213	182	200
Autologous (single and staged)	258	248	265	287	345	335

Currently there is wide variation in the organisation, delivery, quality and extent of LTFU of BMT consumers in NSW. Post-BMT care is also compromised by the fact that there is, in general, limited institutional support for BMT LTFU across NSW allogeneic transplant centres. All BMT LTFU services have also reported experiencing limitations in terms of dedicated staffing, data management and resources. Consequently, the BMT LTFU system relies heavily on individual clinicians, is often inconsistent with current best practice, and is largely unable to provide for the diverse, complex and changing needs of BMT survivors across NSW, both within BMT units and as patients transition between health services.

Section 3

BMT LTFU clinical guidelines: purpose and methodology

Purpose

In 2010 the ACI convened a working group of BMT clinicians who had expertise in the care of patients requiring long-term follow-up. This group was tasked with:

- reviewing the experience of survival and care following BMT in NSW
- describing international best practice in LTFU following BMT
- reviewing the evidence to support LTFU in reducing the adverse impact of late effects on the health and quality of life of BMT survivors
- developing resources to support improvements for the long-term care of BMT recipients
- standardising high quality long-term care across NSW
- improving patient outcomes and quality of life for survivors of BMT.

A priority of this group was therefore to develop clinical guidelines for the long-term care of BMT recipients in the anticipation that these would enable the standardisation and delivery of high quality long-term care across NSW to meaningfully improve patient outcomes. More specifically, the anticipation of the ACI and the LTFU working group was that implementation of these guidelines may facilitate best practice to improve the care of survivors of BMT across NSW with the expectation that this will result in:

- reduced morbidity and mortality resulting from late effects of BMT
- decreased admissions or readmissions
- increased efficiency of service delivery.

These clinical guidelines, which are not mandatory, reflect the consensus recommendations of the ACI BMT Network LTFU working group. They are based on clinical expertise, expert opinion and available evidence, including international guidelines on BMT LTFU, published evidence regarding the prevention and management of late effects of BMT, and contemporary data regarding the experience of survivors of BMT in NSW.

While their absolute number of cases makes up a small percentage of transplant survivors, Aboriginal people are more likely to experience additional challenges related to access to culturally safe care. Providers therefore need to reflect on the specific needs of Aboriginal consumers and health services in relation to each of the recommended preventive and screening strategies.

In practical terms, this requires a focus on:

- ensuring there are clear opportunities for Aboriginal people to be identified
- the development of trust
- screening and assessment processes that recognise the holistic approach to health that is shared by most Aboriginal people and communities
- education processes that will build the literacy, engagement and empowerment of Aboriginal people
- referral processes to appropriate agencies with a particular focus on the unique role of Aboriginal medical services
- follow-up to ensure that Aboriginal people are receiving the services required and supported to effectively manage their health.

The development of culturally competent and safe services is described in greater detail in the *Chronic Care for Aboriginal People Model of Care.*

Methodology

Specifically, the steps in the development of these guidelines were as follows:

1. Thirteen 'risk areas' were identified and classified under clinical domains for prevention and screening of survivors of BMT following review of existing international guidelines for BMT LTFU.
2. These clinical domains were then allocated to two members of the LTFU working group – each of whom were tasked with drafting and reviewing guidelines for prevention and screening for late effects based upon:
    a. review of published evidence regarding the prevalence, prevention and treatment of the late effects of BMT
    b. guidelines produced by international working groups [6, 7]
    c. the results of the Sydney post-BMT survey [8] – a cross-sectional study of BMT survivors completed in 2015 which provided a comprehensive account of the experiences, needs and attitudes of long-term survivors of BMT in NSW.
3. The 13 clinical domain guidelines were then reviewed by the entire LTFU working group – who articulated an informal consensus position on each of the recommendations.
4. Each clinical domain was subsequently reviewed by clinical experts in each sub-specialty field.
5. Subsequent revisions of the draft guidelines were then reviewed by the LTFU working group – with a penultimate draft again agreed to by an informal consensus process.
6. The penultimate draft was then made available to the applicable ACI Networks for comment – with comments and suggested recommendations considered by the BMT LTFU working group.
7. The final draft was agreed by the BMT LTFU working group by an informal consensus process and then reviewed by the ACI Director, Acute Care prior to submission to the BMT Network Council for endorsement.
8. The BMT Network Council referred the endorsed document to the ACI Executive for approval for publication.

Section 4

Clinical guidelines

4.1 Bone disease

Osteoporosis

BMT patients have an increased risk of bone disease post-transplant, with osteopenia occurring in up to 50% of survivors, osteoporosis in up to 25% of survivors and 'fragility' fractures in 10–20% of survivors. The results of the Sydney post-BMT survey also demonstrate a high prevalence of bone disease in survivors of BMT with osteoporosis/osteopenia reported in 29.1% and vertebral or hip fractures in 4.3% of long-term survivors of BMT.[8]

Multiple risk factors contribute to bone loss including conditioning chemo-radiotherapy, graft-versus-host disease (GVHD), the use of glucocorticoids and calcineurin inhibitors (especially cyclosporine), gonadal failure, malabsorption, chronic renal dysfunction, malnutrition, vitamin D deficiency, weight loss and immobility. Glucocorticoid therapy, in particular, is associated with a markedly increased risk of bone loss, particularly in the first few months of use. Glucocorticoids also increase fracture risk, with fractures occurring at a higher bone mineral densitometry (BMD) than occurs in postmenopausal osteoporosis.

In each of these cases, impaired bone mineralisation occurs through a range of different physiological processes including through disturbances of calcium and vitamin D homeostasis, osteoblast and osteoclast dysfunction and deficiencies in growth or gonadal hormone secretion. Collectively these contribute to rapid bone loss post-BMT, which is maximal in the first 3–6 months following transplant.[9] While spine BMD may improve over time, femoral neck BMD often does not.

PREVENTION OF OSTEOPOROSIS

Prevention involves the following:

- All patients should receive education regarding smoking cessation, limiting alcohol consumption, early mobilisation post-BMT and fall prevention – all of which are beneficial for bone health.
- All patients should be encouraged to perform regular weight-bearing exercise (30 minutes, three times per week), for example walking, jogging or resistance training. Exercise may aid or help in the prevention and treatment of osteoporosis and muscle atrophy.[10]
- All patients at risk of bone disease should be referred to a dietitian and physiotherapist/exercise physiologist as appropriate.
- Prior to and following BMT, all patients should receive 800–1,000 iu/day of vitamin D through diet or supplements; or at a higher level if vitamin D deficiency is documented. While there is ongoing controversy regarding the optimal vitamin D targets, it would be reasonable to aim for vitamin D targets of 75–120 nmol/l in high-risk BMT survivors.
- Prior to and following BMT, all patients should maintain at least the recommended daily calcium intake – which for the general population is 1000 mg per day for adult men and women, and 1300 mg per day for women over 50 years and men over 70 years. Importantly, recent data suggests that an increased calcium supplement intake may be associated with an increased risk of cardiovascular events in older adults. In general therefore – and particularly for BMT survivors, who are at an increased risk of cardiovascular disease – it may be preferable to focus on dietary sources of calcium; limiting supplementation to 500–600 mg exogenous calcium per day up to the recommended daily intake if dietary intake appears inadequate.

- For patients receiving prednisone this should be reduced to the lowest dose compatible with chronic graft-versus-host disease (cGVHD) control. In addition, where possible, topical therapy should be used for control of oral, gastrointestinal, cutaneous or pulmonary cGVHD.
  Pharmacotherapy should be initiated in those with osteoporosis, defined by BMD T-score ≤ -2.5 SD, or previous fragility fracture. Pharmacotherapy should be strongly considered in those with osteopenia (T-score between -1.0 and -2.5 SD) who are receiving glucocorticoids at a dose equivalent of prednisone > 5 mg for ≥ 3 months, as well as in those without other risk factors for minimal trauma fracture who have a low T-score or who have documentation of accelerated bone loss on serial bone density studies. Fracture risk may be calculated using algorithms that take account of risk factors including BMD, age, weight and glucocorticoid exposure, one of the most extensively validated algorithms is the FRAX risk calculator. [11]
- Bisphosphonates are advised in many patients post-BMT as they have proven efficacy in reducing bone loss and fractures in BMT recipients [12] and in patients with glucocorticoid-induced osteoporosis.[13] Options include zoledronic acid 5 mg IV annually, oral alendronate 70 mg weekly or oral risedronate 35 mg weekly. [14, 15]
  The decision to initiate pharmacotherapy should generally be made in consultation with endocrinology/bone disease services. In view of the rare association of osteonecrosis of the jaw with bisphosphonate use, and association with glucocorticoid use and oral disease, it is advisable that an individual completes dental review and any necessary treatment prior to commencing bisphosphonate therapy.
- In male and female survivors of BMT, testosterone and oestrogen-progestin replacement, respectively, have been shown to slow bone loss. Blood and marrow transplant survivors should therefore be referred for endocrinology consultation regarding the risks and benefits of hormonal therapy for prevention or management of bone disease post-BMT. This is particularly relevant for:
  - premenopausal women who are hypogonadal as studies have shown that they will benefit (both in terms of reduced fracture risk and all-cause mortality) from oestrogen/progestin replacement (if not contraindicated)
  - symptomatic hypogonadal men as they may benefit from testosterone therapy (if not contraindicated)
- All patients should be referred for endocrinology/bone disease consultation as the duration of bisphosphonate therapy is uncertain, the assessment of response to therapy may be difficult and the necessity for alternative medical therapy for osteoporosis is complex.

SCREENING FOR OSTEOPOROSIS

Screening should involve the following:

- All patients should have:
  - clinical musculoskeletal assessment done annually; including assessment of falls risk
  - vitamin D levels measured annually
  - BMD using DXA (dual-energy X-ray absorptiometry) scan done prior to transplant and at 1 year post-BMT (refer to ACI's musculoskeletal resources).
- In premenopausal women:
  - menstrual history should be regularly assessed
  - gonadal hormones (testosterone, oestrogen, progesterone, luteinizing hormone [LH] and follicle stimulating hormone [FSH]) should be measured prior to transplant and then annually post-BMT in all not reporting regular menses.
- In men testosterone should be measured prior to transplant and then annually post-BMT as clinically indicated in all males.

- In pre-pubertal children gonadal hormones (testosterone, oestrogen, progesterone, LH and FSH) should be measured annually post-BMT to assist with monitoring growth and puberty.
- BMD assessment should be based upon assessment of the risk of bone disease. Patients who have evidence of osteoporosis/osteopenia or who require continued glucocorticoid therapy (prednisone at > 5mg/day) should have serial BMD done every 1–2 years as necessary. Patients with normal BMD, who have stable BMD or who are weaned from glucocorticoids should have BMD done less frequently (every 3–5 years).
- All patients found to have osteoporosis/osteopenia or a fragility fracture should be investigated for secondary causes of bone loss. When secondary causes, for example vitamin D deficiency or hypogonadism, are identified these should be treated.

Osteonecrosis (avascular necrosis of bone)

Avascular necrosis of bone (AVN) is a debilitating focal bone disease that occurs with increased frequency in survivors of allogeneic transplant. Most commonly affecting the hip, knees, ankles and shoulders, AVN occurs in 4–19% of survivors with a cumulative incidence of 3–10% at 5 years post-BMT.[16] These rates are consistent with the Sydney post-BMT survey, which reported rates of AVN of 3.6% in long-term survivors of BMT done in adulthood.[8]

A number of risk factors for AVN have been identified including: the use of glucocorticoids, a history of acute lymphoblastic leukaemia, transplant conditioning with total body irradiation (TBI), excessive alcohol intake, cGVHD and being female. In BMT patients the risk of osteonecrosis is dependent upon the duration and cumulative dose of glucocorticoids as well as the presence of cGVHD. The risk is low (< 3%) in patients treated with doses of prednisone less than 15–20mg/day.[17]

PREVENTION AND SCREENING OF AVN

There is no evidence to support screening for AVN. The most important aspects of prevention therefore involve:

- identification of patients with risk factors for AVN
- reduction of prednisone to the lowest dose compatible with cGVHD control and use of topical therapy where possible
- appropriate investigation (especially magnetic resonance imaging [MRI] where AVN is suspected to enable early diagnosis and management to prevent collapse)
- early referral to orthopaedic surgery for non-operative management, joint-preservation procedures and joint replacement.

4.2 Cardiac and circulatory disease

Late cardiac events may appear years and even decades after BMT. A clear relationship between post-transplant cardiovascular risk factors and late coronary and cardiovascular disease in long-term survivors has been demonstrated. [18, 19]

Any form of cardiac dysfunction may occur post-BMT including: cardiomyopathy, congestive heart failure, valvular dysfunction, ischaemic heart disease (AMI or angina), arrhythmia and pericarditis. [20] All forms of vascular disease, including cardiovascular, cerebrovascular and peripheral vascular disease occur with greater frequency in BMT survivors. [1]

The leading risk factors for cardiac toxicity following BMT are cumulative exposure to anthracyclines, TBI or chest irradiation as part of the treatment of the primary malignancy or conditioning regimen, and cardiac co-morbidity. Other contributors to cardiovascular risk post-BMT include gender, age at transplantation, presence of non-cardiac co-morbidities and standard cardiovascular risks. [3]

Established risk factors for cardiovascular disease, such as hypertension, dyslipidaemia, diabetes, smoking and physical inactivity are associated with higher risk of complications post-transplant due to the high prevalence of metabolic syndrome reported among BMT survivors [1]. In a cross sectional study, patients treated with allogeneic BMT showed a 2.2–fold increase of metabolic syndrome, compared to age and gender matched controls [21, 22], increasing the risk of cardiovascular disease. Prevalence of dyslipidaemia ranges from 8.9% to 39%, depending on the presence of comorbid conditions or other risk factors. [23]

In the Sydney post-BMT survey, 43.5% of survivors had cardiovascular risk factors (diabetes, hypertension or high cholesterol), 43.5% were taking an antihypertensive medication and 24.1% had been prescribed a lipid-lowering agent.

PREVENTION

Prevention should involve:

- education and counselling on a 'healthy heart' lifestyle (regular exercise, maintaining healthy weight, smoking cessation and dietary counselling) for all BMT patients
- referral of all high-risk patients to a dietitian and physiotherapist/exercise physiologist as appropriate
- early recognition and treatment of cardiovascular risk factors.

SCREENING

Screening should involve the following:

1. Annual assessment of cardiac risk factors is required, commencing 1 year post-BMT and yearly thereafter, including;
    - assessment of prior exposure to irradiation and anthracyclines
    - history and clinical examination (including measurement of blood pressure)
    - fasting lipid profile and fasting glucose.
2. Pre-transplant measurement of cardiac function with post-transplant cardiomyopathy surveillance should begin no later than 1 year post-BMT, and be repeated as clinically indicated if abnormal in high-risk patients (generally every 1–2 years for those who received anthracyclines and/or irradiation, especially in childhood) or otherwise repeated every 5 years thereafter. Electrocardiography (ECG) and echocardiogram are recommended as the primary surveillance modalities. Radionuclide angiography or cardiac MRI may be reasonable alternative modalities for assessing cardiac function where echocardiography is not optimal.
3. All abnormal tests and high-risk patients should be referred for cardiologist review.

4.3 Dental and oral disease

Late complications involving the oral cavity are common after BMT and have been reported internationally. [24, 25] The most important risk factors include oral cGVHD, irradiation to the head and neck region, long-term immunosuppressive therapy, diabetes mellitus, sicca syndrome, presence of chronic and latent infections, patient age at BMT and adequacy of post-BMT dental care. [6, 24]

Oral function is essential for many aspects of normal daily activities and any compromise can profoundly impact quality of life, overall health and psychosocial wellbeing. [25-27] Chronic graft-versus-host disease in particular, may cause a range of mucosal abnormalities including a marked risk of development of squamous cell carcinoma (SCC) of the oral mucosa and salivary hypofunction resulting in significant pain affecting alimentation, nutritional status and the maintenance of oral/dental health. [24, 27]

The Sydney post-BMT survey reported that the most frequent dental and oral health problems experienced by transplant recipients included dry mouth (45.1%), mouth ulcers (35.3%), tooth decay (36.7%) and oral GVHD (35.1%). Of the respondents 6% reported having had a dental abscess and 1.5% a diagnosis of oral cancer.

Osteonecrosis of the jaw (ONJ) following invasive dental procedures such as dental extractions is associated with the long-term use of anti-resorptive therapies used for the prevention of osteoporosis, whether this is age-related or iatrogenic from long-term and/or high dose glucocorticoid use or direct use of anti-absorptive agents in diseases such as multiple myeloma for the management and prevention of hypercalcaemia or lytic bone lesions.[28, 29] Long-term bisphosphonate use has the highest risk for ONJ, but there is published data demonstrating an association between the use of Denosumab and ONJ.[30] Excellent levels of oral hygiene and the prevention of caries with resulting pulpitis and periodontal disease and consequent odontogenic-related infections are proven to reduce the risk of ONJ in patients on long-term anti-resorptive therapy with bisphosphonates. [28, 31, 32]

PREVENTION

Prevention should involve:

- education and preventive oral health and routine dental care
- counselling to avoid smoking, moderate alcohol intake, decrease regular intake of sugar containing beverages and avoid intraoral piercings
- referral of patients at risk to a dietitian as appropriate
- early treatment and management of dental caries and oral infections.

SCREENING

Screening should involve the following:

- Standard oral and dental review should take place at 6 months, 1 year and then annually. Dental consultation should include specific advice regarding topical fluoride use and the necessity for sialogogues and antifungal therapies. More frequent evaluation is indicated for those at high-risk of oral complications – that is those with cGVHD, exposure to TBI or Fanconi's anaemia.
- More complex cases should be referred to specialised dental centres.
- All potentially malignant oral lesions should undergo monitoring and biopsy.

4.4 Ocular complications

There are three main ocular late effects after allogeneic BMT [1]; ocular cGVHD and keratoconjunctivitis sicca syndrome (KCS)/dry eye disease [6, 33-35]; cataract formation resulting from exposure to TBI and/or prolonged corticosteroid exposure (> 3 months)[1]; and ischaemic microvascular retinopathy related to TBI, cyclosporine and diabetes mellitus. [6, 36]

Ocular cGVHD is common – affecting between 25–50% of transplant survivors.[36, 37] Ocular manifestations of cGVHD, including reduced tear flow, KCS, sterile conjunctivitis, corneal epithelial defects and corneal ulceration can produce a range of symptoms, including dryness, burning, irritation, grittiness, pain, foreign body sensation, blurred vision, photophobia and excessive tearing, that profoundly impact upon survivor's quality of life. [1, 34, 35]

PREVENTION

Prevention should involve:

- education and counselling regarding the symptoms and signs of ocular GVHD, the need to avoid excessive ultra violet exposure and the benefits of wearing sunglasses
- use of regular ocular topical lubricants in patients with established ocular cGVHD
- assessment and management of diseases and risk-factors associated with post-transplant microvascular disease including diabetes mellitus, dyslipidaemia and hypertension.

SCREENING

Screening should involve:

- routine clinical evaluation of visual history and symptoms, with attention to sicca syndrome at 6 months, 1 year and then annually thereafter for all patients
- referral to an ophthalmologist for routine ocular examination with measurement of visual acuity and fundoscopy at 1 year for all patients – with earlier referral for patients with established ocular cGVHD – and subsequent frequency of routine screening as clinically indicated
- urgent ocular examination and expert referral for all patients experiencing visual symptoms.

4.5 Endocrine complications

Endocrine dysfunction occurs commonly post-BMT as a result of conditioning chemoradiotherapy prior to BMT, cumulative chemo/radiation exposure from previous treatment/relapse, cGVHD and prolonged corticosteroid exposure. [6, 38]

Endocrine complications of BMT, which are often more profound in patients transplanted in childhood or adolescence, include short stature (19%) [6], hypogonadism (25%), hypothyroidism, hyperthyroidism, hypoadrenalism, weight problems (both over- and underweight) and other metabolic risks including dyslipidaemia and diabetes mellitus. [3, 38, 39] Importantly, endocrine dysfunction may have profound psychological effects in addition to their physiological effects, potentially resulting in diminished quality of life.

Hypothalamic-pituitary dysfunction

Hypothalamic-pituitary dysfunction may result from cranial irradiation, as well as TBI, potentially resulting in secondary gonadal dysfunction, central hypothyroidism, secondary adrenal failure and growth hormone (GH) deficiency. Survivors who received doses greater than 18 Gray (Gy) are at greatest risk (> 18 Gy for GH deficiency; > 30 Gy for gonadotropin/adrenocorticotropic hormone (ACTH) dysfunction), but can occur even at lower doses.

Adrenal insufficiency is particularly important because unrecognised ACTH deficiency resulting in secondary adrenal insufficiency can be life-threatening and may be easily misdiagnosed or underdiagnosed because it often presents in a 'non-specific' fashion (for example, fatigue).

Children and adolescents who undergo BMT frequently have compromised growth and growth velocity – depending upon their pre-transplantation therapy and whether their transplant conditioning includes TBI. [6, 39] Growth failure may result from specific endocrine defects (for example, GH deficiency or hypothyroidism) as well as from general systemic factors and nutrition.

Gonadal dysfunction

Gonadal dysfunction, principally as a result of conditioning chemotherapy (particularly alkylating agents), TBI and cGVHD [36,37], is highly prevalent in BMT recipients – occurring in up to 92% of males and 99% of females. [6] Potential effects include pubertal failure, infertility, sexual dysfunction, osteoporosis, fragility fractures and a range of troublesome symptoms including menopausal symptoms (in women), hot flushes, night sweats, mood disorders, insomnia, lack of concentration, arthralgia, impaired sexual function and cognitive impairment. [40] In the Sydney post-BMT survey 26.2% of females and 5.6% males reported taking some form of hormonal therapy for gonadal dysfunction/failure.

Thyroid disease

Clinical hypothyroidism frequently complicates allogeneic transplant, occurring in up to 50% of patients whose conditioning includes TBI and up to 15% in those who receive myeloablative conditioning with busulfan and cyclophosphamide (BuCy).[1] Subclinical compensated hypothyroidism occurs in 7% to 15% of patients in the first year after transplantation. [6] Hyperthyroidism is less common after BMT, and generally occurs early in the transplant process. The incidence at 12–18 months post-BMT is 15%. [3, 38, 39]

The incidence of both thyroid nodules and thyroid cancer is increased in patients after head and neck irradiation and TBI. The risk of malignancy is higher for those individuals exposed to radiation at a younger age.

Metabolic disease

Obesity, diabetes mellitus and dyslipidaemia are also more common in BMT survivors. Diabetes mellitus, in particular, occurs in 3.3–15% of survivors, with studies demonstrating that BMT survivors have an odds ratio (OR) of 3.65 of developing diabetes mellitus compared to their siblings when controlled for age, sex, race and body mass index (BMI). [38, 39] Conditioning that includes TBI, cGVHD, prolonged corticosteroid exposure and/or weight gain (corticosteroids, mobility) all contribute to these metabolic risks. Late onset diabetes mellitus with pancreatic endocrine and exocrine insufficiency may also occur following abdominal irradiation. [65]

PREVENTION

Prevention should involve:

- education and counselling regarding the need for regular exercise, maintaining a healthy weight, smoking cessation, alcohol moderation and consumption of a healthy diet
- referral of patients at risk to a dietitian and exercise physiologist/physiotherapist as appropriate
- education regarding the signs and symptoms of common endocrinopathies (for example, gonadal failure).

SCREENING

Screening should involve:

- annual clinical assessment, including:
    - metabolic risk assessment (weight, BMI, waist circumference and blood pressure)
    - fracture history
    - thyroid palpation
    - assessment of libido and potency (in all adult patients)
    - pubertal status, linear growth and growth velocity (in children and adolescents)
    - menstrual history in premenopausal women

- annual laboratory assessment of endocrine function including:
    - thyroid function tests (fT4, TSH with or without fT3 – if TSH suppressed), fasting glucose, HbA1c, vitamin D, glomerular filtration rate (GFR), calcium, phosphate, cortisol, ACTH and fasting lipid profile
    - gonadal hormones (testosterone, prolactin, oestrogen, progesterone, LH and FSH) in all premenopausal women not reporting regular menses
    - testosterone, LH and FSH, which should be measured prior to transplant and then annually post-BMT as clinically indicated in all males
    - insulin (in children)
- thyroid assessment including:
    - annual thyroid ultrasound in all patients who received TBI or head and neck irradiation as a child, adolescent or young adult
    - annual clinical thyroid examination with ultrasound as clinically indicated in older individuals
- referral of all paediatric patients and all adult patients with gonadal failure or evidence of clinically relevant endocrinopathy or high-risk of endocrinopathy for expert endocrinology review
- bone density assessment (biennial) in all women with premature ovarian failure.

4.6 Genital complications and sexual function

Genital complications

Genital disorders, sexual dysfunction and infertility following BMT are some of the most common and confronting challenges facing long-term survivors of BMT. Collectively, these complications occur as a result of a range of interrelated factors including genital cGVHD, immunosuppression, human papillomavirus (HPV) infection, premature ovarian and testicular failure, interruption to the sexual response cycle and psychosocial issues. The impact of these complications is profound – compromising the quality of life, sexual function and relationships of many of those affected. [41]

Genital cGVHD

Genital cGVHD is commonly reported post-BMT, with international studies suggesting that up to 50% of women surviving BMT experiencing some degree of vaginal cGVHD. [42-44] This is consistent with Australian data, with 22% of women and 5% of men participating in the Sydney post-BMT survey reporting genital disease. [45] In women, genital cGVHD can affect the vulva and vagina and may present with lichen planus-like changes including erosions, leukokeratosis and vaginal scarring/stenosis. Vulvovaginal cGVHD may be asymptomatic (thus delaying diagnosis and treatment) or cause a range of symptoms including vaginal dryness, burning, itching, difficulty with urination, dyspareunia, cyclic pain and amenorrhea (due to haematocolpos/haematometra). [46] In men, penile cGVHD may cause balanoposthitis, phimosis, lichen sclerosis-like changes and Peyronie's disease and erectile dysfunction. [44]

Primary ovarian failure

Primary ovarian failure (POF) is almost ubiquitous following BMT – occurring in up to 90% of women who undergo BMT while in their reproductive years – principally as a consequence of conditioning chemotherapy, TBI and cGVHD. [36, 37] Post-transplant ovarian failure results in infertility in most-BMT survivors of reproductive age, increases the likelihood of osteoporosis and fragility fractures and cause a range of troublesome symptoms, including hot flushes, night sweats, mood disorders, insomnia, lack of concentration, arthralgia, impaired sexual function and cognitive impairment. [40]

Male gonadal failure and impaired spermatogenesis

The vast majority of men (approximately 90%) will develop azoospermia, oligospermia and sperm motility problems as a consequence of high-dose conditioning chemotherapy, TBI and cGVHD.[47] While some men (up to 25%) will show some evidence of recovery (particularly those who are aged < 30 at the time of transplant)[48] many men will remain hypogonadal and infertile.

Genital secondary cancers and HPV infection

As with other viral infections, HPV occurs with a greater frequency in BMT survivors than in the general population. In those infected, HPV can cause genital warts, cervical, vaginal, vulvar and anal intraepithelial neoplasia and anogenital SCC. The risk of cervical squamous cell cancer in female BMT survivors is reported to be 13 times greater than that of the general population.[49] Genital malignancy also occurs with much greater frequency in male BMT survivors with premalignant or malignant conditions reported in 8.4% of men with genital lichen sclerosis.[50]

PREVENTION OF GENITAL COMPLICATIONS

Prevention should involve:

- education of all patients regarding the importance of genital hygiene, the avoidance of muco-cutaneous irritants and the signs and symptoms of genital cGVHD
- education of women undergoing BMT regarding the signs and symptoms of medically-induced menopause and the measures that may be used to optimise sexual function and reduce genital symptoms
- referral of all patients with gonadal failure for specialist endocrinology, with or without gynaecology, review regarding the risks/benefits of hormonal therapy including:
    - women aged < 40 years with POF
    - men with hypogonadal symptoms and documented low testosterone levels
    - women with decreased libido attributable to oestrogen and androgen deficiency
- education of all patients regarding safe sex practice
- HPV vaccination.

SCREENING FOR GENITAL COMPLICATIONS

Early identification of genital complications can greatly reduce genital symptoms and improve quality of life. It is therefore recommended that patients undergo:[51]

- exploration of genital tract symptoms and sexual dysfunction at regular BMT follow-up appointments
- monitoring of all patients with genital lichen planus or sclerosis at least 6 monthly for evidence of pre-malignant or malignant transformations, with biopsy done wherever dysplasia or malignancy is suspected.

Recommendations for females include:

- gynaecology review and vaginal examination starting at 3-6 months post-BMT and then as clinically indicated
- referral for specialist gynaecology review in all patients with cGVHD and with new onset of genital symptoms
- early consideration of vaginal/vulval biopsy in patients who do not have other features of cGVHD to distinguish genital GVHD from hypo-oestrogenic states
- papanicolaou (Pap) smears from 18 years of age or within 2 years of commencement of sexual activity (whichever is later) – repeated every 2 years until 70 years of age.[52]

Sexual dysfunction

Up to 80% of long-term BMT survivors will experience some form of sexual dysfunction.[40, 53] A range of factors including: gonadal insufficiency, genital disease, altered body image, illness and debility, relationship dysfunction, anxiety and depression may impact upon all aspects of the sexual response cycle including desire/libido, arousal and orgasm.[44, 54] In the Sydney post-BMT survey, 66% of females and 51% of males reported sexual dysfunction.[45]

PREVENTION OF SEXUAL DYSFUNCTION

Prevention involves:

- education and counselling of all patients and their partners regarding the possibility of sexual dysfunction post-BMT and the availability of appropriate expert care where necessary
- early diagnosis and treatment of endocrine and medical complications of BMT that may contribute to sexual dysfunction
- referral to a clinical psychologist and/or relationship counsellor for individual or couple therapy as required
- use of vaginal oestrogen or lubricants in women experiencing dyspareunia as a result of atrophic vaginitis.

SCREENING FOR SEXUAL DYSFUNCTION

Screening should include:

- regular exploration of sexual function at regular BMT follow-up appointments, including questioning regarding dyspareunia, impotence, hypoactive sexual desire and dysfunction with arousal or orgasm
- gynaecology review and vaginal examination starting at 3–6 months post-BMT and then as clinically indicated
- clinical assessment of the BMT recipient's intimate partner's psychological adjustment and level of support and family functioning
- annual psychometric assessment of quality of life and sexual function utilising the FACT BMT.

4.7 Fertility and reproduction

Almost all patients will be infertile following BMT, with up to 90% of patients who undergo BMT while in their reproductive years developing primary ovarian or testicular failure as a consequence of high-dose conditioning chemotherapy, TBI, high dose steroids, severe infection, cGVHD, older age, long-term immunosuppression and pre-BMT therapy (particularly alkylating agents and pelvic irradiation). [46] Hypothalamic-pituitary dysfunction and secondary hypogonadism, thyroid dysfunction and effects on other reproductive organs (for example, the uterus) may also result in infertility.

While some patients – particularly those aged less than 26–30 years at the time of BMT and those who did not receive TBI as part of their conditioning therapy – will regain some gonadal function, the vast majority of women will enter premature menopause and the vast majority of men will have persistent azoospermia, oligospermia and sperm motility problems. [39, 55]

A small number of women (0.6% in international studies and 3.3% in the Sydney post-BMT survey) will successfully achieve a pregnancy and have a child following BMT. [45, 56, 57] While children born to survivors of BMT do not have higher than expected rates of cancer or genetic disorders, female survivors experience a range of adverse pregnancy outcomes including increased rate of intrauterine growth restriction (IUGR), low birth rate, preterm delivery, spontaneous abortion (due to decreased uterine volume), placental abruption, uterine rupture and caesarean section deliveries compared with the general population. [58-60]

PREVENTION

Prevention should involve the following:

- Before BMT, all patients should receive education and advice from expert fertility specialists with regard to fertility sparing options highlighting the individual risk of infertility post-BMT. Males should be advised to bank sperm and females, if time allows, should be referred for consideration of oocyte, ovarian tissue or embryo freezing.
- Post-BMT, patients should be advised to delay spontaneous or assisted pregnancy for at least 2 years, due to the high-risk of disease relapse during this period
- Patients wishing to conceive should be referred to an endocrinologist and reproductive medicine specialist
- Where appropriate, patients and their partners may also require referral to specialist psychological services for support and counselling regarding the impact of BMT on fertility and parenting.

SCREENING

Screening should involve:

- annual clinical assessment including menstrual history (in premenopausal women) and clinical symptoms of hypogonadism
- annual assessment of gonadal hormones (testosterone, prolactin, oestrogen, progesterone, LH and FSH) in all premenopausal women not reporting regular menses
- annual assessment of testosterone, LH and FSH as clinically indicated in all males
- annual assessment of prolactin and thyroid function studies in all patients
- assessment of anti-mullerian hormone – as a marker of ovarian reserve – in women desiring fertility
- semen analysis in men who have not stored sperm pre-BMT beginning at 12 months post-BMT.

4.8 Liver disease

Late liver complications of BMT are most commonly related to cGVHD, hepatitis B (HBV) and hepatitis C (HCV) infection, prior hepatic sinusoidal obstructive syndrome (SOS/VOD), iron overload from transfusions and/or ineffective erythropoiesis and/or hepatotoxic medications.[6] Hepatic cGVHD occurs commonly and may manifest with asymptomatic elevation of serum alanine aminotransferase (ALT), alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT), slowly progressive cholestatic jaundice or acute hepatocellular injury.[61]

Infection with HCV is also associated with greater morbidity and mortality in BMT survivors, with cirrhosis and end-stage liver disease related to chronic HCV infection occurring in approximately 35% of long-term survivors, and with a faster rate of progression in BMT survivors than in matched controls.[61]

PREVENTION

Prevention should involve:

- education and counselling of all patients regarding the moderation of alcohol consumption
- referral of all patients with pre-existing liver disease and/or chronic HBV or HCV infection to a hepatology service for comprehensive evaluation of hepatic fibrosis and liver function; and for consideration and planning of pre- and post-BMT antiviral therapy and monitoring of viral load
- adequate iron chelation pre-BMT where possible to improve survival and reduce the incidence of transplant-related hepatotoxicity[61]
- antiviral prophylaxis as indicated (under the care of a hepatology service) for patients with chronic HBV infection
- HFE gene studies in patients with consistently elevated ferritin to exclude hereditary haemochromatosis.

SCREENING

Screening should involve:

- liver function tests every 3–6 months for the first year, then yearly (at least) thereafter[1]
- ferritin level checks annually while elevated with referral of patients with significant hyperferritinaemia for venesection or iron chelation at 6–12 months post-BMT when clinically stable
- monitoring of viral load in patients with known HBV and HCV at the frequency recommended by the supervising hepatology service (typically 3–6 months)
- reviewing the need for liver biopsy in HCV positive patients with the hepatology service at 8–10 years post-transplant or as clinically indicated
- closer and more frequent monitoring of patients with established hepatic cGVHD, SOS/VOD, myelofibrosis, amyloidosis, hepatic fibrosis, cirrhosis or cholestasis due to higher rates of hepatic decompensation and mortality in these patient populations
- non-invasive liver iron quantification by MRI or SQUID-biosusceptometry or liver biopsy for those with persistently elevated serum ferritin
- regular surveillance of all patients with cirrhosis and selected patients with chronic HBV infection for hepatocellular carcinoma with 6-monthly liver ultrasounds.

4.9 Pulmonary disease

Pulmonary complications significantly contribute to late morbidity and mortality after BMT. [62] Predisposing factors can include pre-existing lung disease, smoking history, infection, the type, duration and intensity of pre-transplantation conditioning chemotherapy, radiation exposure – including TBI and pre-transplant thoracic radiotherapy, hypogammaglobulinaemia and cGVHD.[1]

Late onset non-infectious pulmonary complications among BMT recipients include bronchiolitis obliterans syndrome (BOS), cryptogenic organising pneumonia, idiopathic pneumonia syndrome and sinopulmonary infections – each of which is increased in patients with cGVHD. [6] Asthma has also been reported following BMT from atopic asthmatic donors. [63]

The Sydney post-BMT survey reported an incidence of chronic GVHD of 69.3% in the post-transplant population, with 18.2% developing pulmonary manifestations of GVHD. This is consistent with international studies of BOS (which is currently considered diagnostic of cGVHD) which have documented BOS as occurring in 14% of long-term survivors of BMT who develop cGVHD. [64]

PREVENTION

Prevention should involve:

- pre- and post-BMT assessment of the risk of pulmonary disease including smoking history, radiation exposure and history of sinopulmonary infection
- education and counselling regarding the need to avoid smoking, maintain a healthy weight and exercise regularly.

SCREENING

Screening should involve:

- clinical assessment including history, physical examination and spirometry at 6 months, 1 year, then annually
- formal pulmonary function tests (PFT) with measurement of 'diffusing capacity of the lungs for carbon monoxide test' (DLCO) pre-BMT and then at 12, 24 and 60 months post-BMT, with repeat testing then done every 5 years or more frequently as clinically indicated (particularly in patients with pulmonary cGVHD)
- imaging studies, for example high resolution computerised tomography (HRCT) where pulmonary disease is suspected, with referral to thoracic medicine units as required.

4.10 Renal disease

Chronic renal/kidney disease (CKD) occurs commonly after allogeneic BMT, with the cumulative incidence of CKD as high as 66% in adult survivors of BMT and 62% in paediatric survivors of BMT.[65]

Although survivors of BMT are prone to the same risk factors and causes that lead to CKD in the general population, there are a number of factors related to BMT that further increase their risk of CKD. These include: transplant-related renal toxicity resulting from SOS, haemorrhagic cystitis, endothelial damage from acute and/or chronic GVHD and infection, treatment-related renal toxicity resulting from chemotherapy exposure, TBI, calcineurin inhibitors and antimicrobial drugs (antibiotics, antiviral and antifungal drugs), and increased rates of chronic illness post-BMT including hypertension and diabetes mellitus.[66]

PREVENTION

Prevention should involve:

- education and counselling regarding the importance of blood pressure control and maintaining an adequate fluid intake
- caution with nephrotoxic agents post-BMT including antibiotics, bisphosphonates, anti-inflammatory medications and immunosuppression
- caution with calcium supplements in patients with known CKD.

SCREENING

Screening should involve:

- baseline electrolytes and GFR pre-BMT
- annual electrolytes and GFR
- annual blood pressure
- annual urinalysis.

4.11 Psychosocial functioning

Adult and child survivors of BMT are vulnerable to declines in cognitive and academic functioning over time and are at risk of developing psychological effects as a result of their treatment. While many survivors of BMT enjoy an acceptable quality of life post-BMT, many survivors also experience anxiety, depression, guilt, post-traumatic stress disorder, difficulties with self-image, insomnia, fatigue and low self-esteem; and report an overall decrease in their quality of life. As a consequence of these behavioural, psychological and cognitive alterations, survivors may have difficulty initiating and maintaining relationships, returning to work or school and socialising in their usual way. Up to 50% will not return to work post-BMT and most children require additional support with school and tertiary studies.[1,3] While adult patients may experience less direct neuropsychiatric effects of BMT than children, they may also experience profound psychosocial challenges – with high rates of unemployment, underemployment and relationship or marital difficulties. [22]

In addition to the neurocognitive adverse effects that may complicate post-BMT survival, survivors of BMT also experience high rates of mental illness, notably anxiety and depression, as a result of the intractable nature of survival with chronic illness, the complications of BMT, particularly chronic GVHD, and the medications used to prevent and treat these complications, including steroids and immunosuppressive therapies. The Sydney post-BMT survey found high rates of mood disorder post-BMT, with 28.8% of survivors experiencing clinically significant depression or anxiety post-BMT. [8]

Psychological status prior to transplant has been shown to predict both psychosocial and physical outcomes with patients with psychiatric morbidity pre-BMT experiencing an increased risk of anxiety and depression post-transplant. Studies also suggest that patients with poorer social support prior to BMT may experience poorer survival, while those with a high level of perceived social support may have improved survival and a higher quality of life. The direct correlation between psychosocial support and positive health outcomes highlights the importance of assessing social support prior to transplant, during transplant and for many years after transplant.

PREVENTION

Prevention should involve:

- patient/carer education and counselling regarding the psychosocial, emotional, occupational and financial impact of BMT
- provision of information to all patients/carers regarding community support and educational services for BMT patients, for example the Leukaemia Foundation, Myeloma Foundation, Cancer Council, CanTeen and school support services
- referral of all patients with pre-existing mental illness to mental health services and to expert BMT clinical psychology/psychiatry services
- assessment of the level of spousal/caregiver psychological adjustment and family functioning with referral of those patients experiencing distress to expert clinical psychology, psychiatry and/or social work services
- assistance with support in the workplace to prevent discrimination and enable ongoing employment
- specific support for paediatric survivors of BMT and for their families including:
    - provision of paediatric neuropsychological assessments to guide applications for educational support and accommodation
    - assistance with applications for educational assistance to address neurocognitive dysfunction, including changes in executive functioning and processing speed [133, 134]; and progressive decline of verbal and non-verbal reasoning and verbal memory
    - assistance with referral to vocation guidance
    - assistance with applications for additional support at school, including individual education plans, referral to learning support services for considerations for school assessments (including extra time, provision of a scribe or exams administered in smaller, quieter settings) and referrals to funded literacy and math programs.

SCREENING

Screening of adults patients should involve baseline (pre-BMT) assessment using FACT BMT quality of life questionnaire, repeated at 1, 2 and 5 years post-BMT and then every 5 years thereafter or more frequently as clinically indicated.

Screening of paediatric patients should involve:

- baseline (pre-BMT) assessment using PedsQL Paediatric Quality of Life Inventory, repeated annually for children aged 5–18 years
- baseline neuropsychometric testing, repeated at the beginning of each stage of the school curriculum (stages 1 to 6).

4.12 Second cancers

BMT recipients have a two to three-fold increased risk of developing a range of solid tumours, including brain, breast, thyroid, lymphoid and gastrointestinal malignancies post-BMT, compared with an age-, gender-, and region-adjusted population.[6] The impact of these is significant with registry studies analysing late causes of death consistently reporting that second cancers represent the fourth leading cause of non-relapse-related death in patients who survive more than 2–5 years post-transplantation – accounting for 5–10% of late deaths.[67, 68, 69] Australian data-linkage studies of cancer risk in Australian survivors of autologous and allogeneic transplant have also demonstrated an increased cancer risk following autologous (relative risk [RR] 1.4) and allogeneic (RR 2.1) transplant with increased risks of AML/myelodysplasia, melanoma, non-Hodgkin's lymphoma, lung cancer, oesophageal, lip and soft-tissue cancers relative to the Australian population.[70, 71] The Sydney post-BMT survey reported at least one cancer following BMT in 24% of patients surveyed.[8]

Risk factors for second cancers include radiation therapy including TBI, disease-directed pre-transplant radiotherapy and cranial irradiation (particularly in patients transplanted as children), the duration, type and intensity of immunosuppression and cGVHD. The risk of second cancers increases with time after transplantation, particularly for radiation-related malignancies. Recent analyses suggest that risk of radiation-related (sarcoma, breast and thyroid cancers) and non-radiation-related (SCC linked to cGVHD) solid tumours continues to increase beyond 10 years post transplantation. [6, 68, 72] Thyroid cancers, which are increased 3.3-fold following BMT, are related not only to radiation exposure, but age at transplant of < 10 years, female gender and cGVHD.[73]

As HPV infection occurs with a greater frequency in BMT survivors than in the general population, survivors are at risk of cervical, vaginal, vulvar and anal intraepithelial neoplasia and anogenital SCC. The risk of cervical squamous cell cancer in female BMT survivors is reported to be 13 times greater than that of the general population. [49] Genital malignancy also occurs with much greater frequency in male BMT survivors with premalignant or malignant conditions reported in 8.4% of men with genital lichen sclerosis.[50]

PREVENTION

Prevention should involve:

- education and counselling of all patients to:
    - avoid smoking, moderate alcohol intake, exercise regularly and maintain a healthy weight
    - maintain ongoing dental care
    - adopt 'sun smart' behaviours including the routine use of sunscreen, hats, sun protective attire, sunglasses and sun avoidance during the daily periods for peak exposure
- encouraging all patients to report any new or concerning symptoms or signs to their medical practitioner and BMT team
- HPV vaccination to reduce the risk of cervical cancer and HBV vaccination to reduce the risk of HBV infection and hepatocellular carcinoma (HCC).

SCREENING

The recommended screening schedule incorporates screening for:

- **skin cancer:** annual dermatology examination for BCC, SCC, melanoma and solar keratosis
- **breast cancer:** mammography every 2 years for patients aged > 40 (or at 5 years post-BMT) with annual mammogram or MRI (or both) to start at 25 years of age or 8 years (whichever comes last) in high-risk patients (exposure of ≥ 10 Gy radiation to chest, including TBI, particularly in childhood or adolescence)
- **cervical cancer:** Pap smear from 18 years or within 2 years of becoming sexually active (whichever is later), repeated every 2 years
- **bowel cancer:** faecal occult blood when > 50 years, repeated every 2 years
- **prostate cancer:** annual general practitioner review including history and digital rectal exam
- **testicular cancer:** annual examination optional in high-risk patients
- **oral cancer:** annual dental review with urgent review of intraoral lesions suspicious of malignancy
- **thyroid cancer:** annual thyroid palpation with or without thyroid ultrasound as appropriate.

4.13 Vaccine-preventable disease and re-immunisation post-BMT

Bone and marrow transplant recipients generally lose immunity to common childhood illnesses as a result of conditioning chemoradiotherapy and long-term immunosuppression.[26] B cell function typically returns to normal 3–12 months post-transplant while T cell recovery typically takes longer, taking 9 to 12 months. The speed and extent of immune reconstitution however, is determined by the patient's age, disease, post-transplant immunosuppression and morbidity – with patients experiencing cGVHD frequently taking over 2 years to recover.[8, 74]

Antibody titres to vaccine-preventable diseases, such as pneumococcus, tetanus, polio, measles, mumps and rubella decline immediately after transplantation and remain low unless the recipient is revaccinated. As a consequence, vaccine-preventable diseases, including pneumococcal infection, haemophilus influenza type b (Hib) infection, measles, varicella and influenza occur more commonly in the BMT population than in the general population and are associated with greater morbidity and mortality. For these reasons BMT recipients require antimicrobial prophylaxis in the first 3–24 months following transplantation and should be routinely revaccinated post-BMT to gain immunity to vaccine-preventable diseases.[74]

PREVENTION

Prevention should involve:

- education and counselling regarding vaccine preventable diseases and the necessity for post-BMT revaccination
- regular (annual) review of vaccination status and need for annual influenza vaccination
- documentation of vaccines received, including dates
- revaccination of the patient as per the *Australian Immunisation Handbook*
- vaccination of close household contacts, particularly for influenza
- antimicrobial prophylaxis post-BMT with consideration of extended prophylaxis in patients conditioned with TBI, in hyposplenic patients, and in those receiving ongoing immunosuppression for cGVHD
- advice on extended vaccination cover if planning overseas travel; and medical documentation of yellow fever vaccine exemption if required (that is, if travelling to a yellow fever endemic area and live-attenuated vaccination is contraindicated).

SCREENING

Screening should involve:

- routine clinical review of vaccination status
- annual assessment of serum immunoglobulin's, T cells and B cells.

Section 5

Summary of allogeneic BMT LTFU clinical guidelines

Annual clinical screening	Notes
1. Bone	
Vitamin D and calcium	Supplementation as required
Clinical musculoskeletal assessment	Including fracture history and falls risk
BMD assessment (at 1 year post-BMT)	Osteopenia/osteoporosis: repeat every 1–2 years Stable: repeat every 5 years
2. Cardiac	
Clinical examination including blood pressure	Assess cardiac risk factors and prior exposure to irradiation and anthracyclines
Fasting lipid profile	
Fasting glucose	
Cardiomyopathy surveillance (at 1 year post-BMT); ECG and ECHO recommended as primary surveillance	1–2 yearly in high-risk patients or 5 yearly thereafter
3. Dental	
Dental review	Including oral cancer review
4. Ocular	
Clinical evaluation of visual history and symptoms	
Optometrist or ophthalmologist for routine ocular examination	As clinically indicated
5. Endocrine	
Metabolic risk assessment	Including weight, BMI, waist circumference
Thyroid palpitation	Including thyroid cancer review
Thyroid function tests (fT4, TSH, with or without fT3)	
HbA1c	
Phosphate, cortisol, ACHT	
FSH,LH, prolactin	
In children: puberty status, linear growth, growth velocity	
In children: insulin	
6. Genital complications and sexual function	
Assessment for genital tract and sexual dysfunction symptoms	Questions and physical exam
Menstrual history (premenopausal women) and symptoms of hypogonadism	
Assessment of libido and potency (in men)	
Gynaecological referral and vaginal exam	As clinically indicated
7. Fertility and reproduction	
Female: testosterone, prolactin, oestradiol, progesterone	Repeat screen not required in post-menopausal women > 50 years
Males: testosterone and semen analysis (if required)	
8. Liver	
LFTs, ferritin	Consider non-invasive liver iron quantification with MRI or SQID or liver biopsy in patients with abnormal results with or without iron chelation
In patients with known HBV and HCV monitor viral load	

Annual clinical screening	Notes
9. Pulmonary	
Clinical assessment	History, physical exam, spirometry
Formal PFT with DLCO at 1 year and 2 years post-BMT	Normal PFT: 5 yearly review Abnormal PFT: 1–2 years (or as clinically indicated)
10. Renal	
Electrolytes, GFR	
Urinalysis	
11. Psychosocial function	
Adults: FACT BMT quality of life questionnaire	
Children: PedsQL quality of life inventory Neuropsychometric testing	Each stage of the school curriculum
12. Second cancers	
Skin cancer: primary preventive advice and examination of skin	
Breast cancer: • mammography 2 yearly • annual mammography or MRI in high-risk patients	 In patients aged > 40 years (or at 5 years post-BMT) At age 25 years or 8 years (whichever is latest)
Cervical cancer: Pap smear 2 yearly	From 18 years of age
Bowel cancer: faecal occult blood 2 yearly	From > 50 years of age If family history, 10 years prior to age of onset of affected family member
Testicular cancer	
13. Vaccine-preventable disease and re-immunisation	
Revaccination as per Australian Immunisation Handbook [75]	Live attenuated vaccines not to be administered in presence of cGVHD/immunosuppression
Clinical review of vaccination status	
Serum immunoglobulin's, T cells and B cells	

Section 6

References

1. Mohty B, Mohty M. Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. *Blood Cancer Journal* 2011;1(4):e16. Epub 2011 Apr 29.
2. Khouri IF, McLaughlin P, Saliba RM et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood* 2008;111(12):5530–6.
3. Martin PJ, Counts GW Jr, Appelbaum FR et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *Journal of Clinical Oncology* 2010;28(6):1011–6.
4. Sun CL, Francisco L, Kawashima T et al. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood* 2010;116(17):3129–39.
5. Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). *Australasian Bone Marrow Transplant Recipient Registry Annual Data Summary*. Darlinghurst, NSW: ABMTRR.
6. Majhail NS, Rizzo JD, Lee SJ et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. *Biology of Blood and Marrow Transplantation* 2012;18(3):348–71.
7. Children's Oncology Group. Long term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer, Version 4.0 [Internet]. Monrovia CA: Children's Oncology Group; 2013. Available from: www.survivorshipguidelines.org.
8. Gilroy N, Dyer G, Kerridge I et al. The Sydney Post-BMT Survey. ACI/BMT Network, 2016.
9. Tauchmanova L, Colao A, Lombardi G et al. Bone loss and its management in long-term survivors from allogeneic stem cell transplantation. *Journal of Clinical Endocrinology and Metabolism* 2007;92(12):4536–45.
10. Howe TE, Shea B, Dawson LJ et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database of Systematic Reviews* 2011; 6(7): Art No. CD000333.
11. The World Health Organization Collaborating Centre for Metabolic Bone Diseases. FRAX® WHO Fracture Risk Assessment Tool [Internet]. Sheffield, UK; 2011. Available from: https://www.shef.ac.uk/FRAX/tool.aspx?country=31.
12. Kananen K, Volin L, Laitinen K et al. Prevention of Bone Loss after Allogeneic Stem Cell Transplantation by Calcium, Vitamin D, and Sex Hormone Replacement with or without Pamidronate. *The Journal of Clinical Endocrinology and Metabolism* 2005;90(7):3877–55.
13. Homik J, Cranney A, Shea B et al. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database of Systematic Reviews* 2000;(2): Art No. CD001347.
14. Reid DM, Devogelaer JP, Saag K et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *The Lancet* 2000;373(9671):1253–63.
15. Boonen S, Reginster JY, Kaufman JM et al. Fracture risk and zoledronic acid therapy in men with osteoporosis. *New England Journal of Medicine* 2012;367(18):1714–23.
16. McClune B, Majhail NS, Flowers ME. Bone loss and avascular necrosis of bone after hematopoietic cell transplantation. *Seminars in Hematology* 2012;49(1):59–65.
17. Schulte CM, Beelen DW. Avascular osteonecrosis after allogeneic hematopoietic stem-cell transplantation: diagnosis and gender matter. *Transplantation* 2004;78(7):1055–63.
18. Tichelli A, Bucher C, Rovo A et al. Premature cardiovascular disease after allogeneic hematopoietic stem-cell transplantation. *Blood* 2007;110(9):3463–71.

19. Tichelli A, Passweq J, Wojcik D et al.Late cardiovascular events after allogeneic hematopoietic stem cell transplantation: a retrospective multicenter study of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica* 2008;93(8):1203–10.

20. Savani BN. How can we improve life expectancy and quality of life in long-term survivors after allogeneic stem cell transplantation? *Seminars in Hematology* 2012;49(1):1–3.

21. Majhail NS, Flowers ME, Ness KK et al. High prevalence of metabolic syndrome after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplantation* 2009;43(1):49–54.

22. Rovo A, Tichelli A, Late Effects Working Party of the European Group for Blood and Marrow Transplantation. Cardiovascular complications in long-term survivors after allogeneic hematopoietic stem cell transplantation. *Seminars in Hematology* 2012;49(1):25–34.

23. Gunasekaran U, Agarwal N, Jagasia MH et al. Endocrine complications in long-term survivors after allogeneic stem cell transplant. *Seminars in Hematology* 2012;49(1): 66–72.

24. Hull KM, Kerridge I, Schifter M. Long-term complications of allogenic haematopoietic SCT. *Bone Marrow Transplantation* 2010;47(2):265–70.

25. Nappalli D, Lingappa A. Oral manifestations in transplant patients. *Dental Research Journal* 2015;12(3):199–208.

26. Savani BN, editor. *Blood and Marrow Transplantation Long-Term Management, Prevention and Complications*. Chichester, UK: John Wiley and Sons; 2013.

27. Treister N, Duncan C, Cutler C et al. How we treat oral chronic graft-versus-host disease. *Blood* 2012;120(17):3407–18.

28. Atsuta Y, Suzuki R, Yamashita T et al. Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease. *Annals of Oncology* 2014;25(2):435–41.

29. Kruse AL, Grätz KW. Oral carcinoma after hematopoietic stem cell transplantation – a new classification based on a literature review over 30 years. *Head and Neck Oncology* 2009;1:29. doi: 10.1186/1758-3284-1-29.

30. Epstein MS, Ephros HD, Epstein JB. Review of current literature and implications of RANKL inhibitors for oral health care providers. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 2013;116(6):e437–42.

31. Sim IeW, Sanders KM, Borromeo GL et al. Declining Incidence of Medication-Related Osteonecrosis of the Jaw in Patients With Cancer. *The Journal of Clinical Endocrinology and Metabolism* 2015;100(10):3887–93.

32. Hinchy NV, Jayaprakash V, Rossitto RA et al. Osteonecrosis of the jaw – prevention and treatment strategies for oral health professionals. *Oral Oncology* 2013;49(9):878–86.

33. Ogawa Y, Kim SK, Dana R et al. International Chronic Ocular Graft-vs-Host-Disease (GVHD) Consensus Group: Proposed Diagnostic Criteria for Chronic GVHD (Part I). *Scientific Reports* 2013;3:3419. doi: 10.1038/srep03419.

34. Nassar A, Tabbara KF, Aljurf M. Ocular manifestations of graft-versus-host disease. *Saudi Journal of Ophthalmology* 2013;27(3):215–22.

35. Balasubramaniam SC, Raja H, Jau CB et al. Ocular Graft-Versus-Host Disease: A Review. *Eye and Contact Lens* 2015;41(5):256–61.

36. Jeppesen H, et al. Ocular Chronic Graft Versus Host Disease after Bone Marrow Transplantation. *Acta Ophthalmologica* 2015;93.

37. Na KS, Yoo YS, Mok JW et al. Incidence and risk factors for ocular GVHD after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2015;50(11):1459–64.

38. Brennan BM, Shalet SM. Endocrine late effects after bone marrow transplant *British Journal of Haematology* 2002;118(1):58–66.

39. Ranke MB, Schwarze CP, Dopfer R et al. Late effects after stem cell transplantation (SCT) in children – growth and hormones. *Bone Marrow Transplantation* 2005;35(1):S77–81.

40. Thygesen KH, Schjodt I, Jarden M. The impact of hematopoietic stem cell transplantation on sexuality: a systematic review of the literature. *Bone Marrow Transplantation* 2012;47(5):716–24.

41. 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):1265–9.

42. Zantomio D, Grigg AP, MacGregor L et al. Female genital tract graft-versus-host disease: incidence, risk factors and recommendations for management. *Bone Marrow Transplantation* 2006;38(8):567–72.

43. Riera CY, Deroover Y, Marechal M. Severe vaginal chronic graft-versus-host disease (GVHD): two cases with late onset and literature review. *European Journal of Gynaecological Oncology* 2010;31(6):703–4.

44. Mueller SM, Haeusemann P, Robo A et al. Genital chronic GVHD in men after hematopoietic stem cell transplantation: a single-center cross-sectional analysis of 155 patients. *Biology of Blood and Marrow Transplantation* 2013;19(11):1574–80.

45. Dyer G, Gilroy N, Bradford J et al. A survey of fertility and sexual health following allogeneic haematopoietic stem cell transplantation in New South Wales, Australia. *British Journal of Haematology* 2016;172(4):592–601.

46. Shanis D, Merideth M, Pulanic TK et al. Female long-term survivors after allogeneic hematopoietic stem cell transplantation: evaluation and management. *Seminars in Hematology* 2012;49(1):83–93.

47. Howell SJ, Shalet SM. Testicular function following chemotherapy. *Human Reproduction Update* 2001;7(4):363–69.

48. Savani BN, Kozanas E, Shenoy A et al. Recovery of spermatogenesis after total-body irradiation. *Blood* 2006;108(13):4292–3.

49. Bhatia S, Louie AD, Bhatia R et al. Solid cancers after bone marrow transplantation. *Journal of Clinical Oncology* 2001;19(2):464–71.

50. Barbagli G, Palminteri E, Mirri F et al. Penile carcinoma in patients with genital lichen sclerosus: a multicenter survey. *The Journal of Urology* 2006;175(4):1359–63.

51. Dignan FL, Scarisbrick JJ, Cornish J et al. Organ-specific management and supportive care in chronic graft-versus-host disease. *British Journal of Haematology* 2012;158(1):62–78.

52. Australian Government Department of Health. National Cervical Screening Program [Internet]. Canberra: Australian Government Department of Health; 2015 [cited 18 May 2016]. Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/content/cervical-screening-1.

53. Syrjala KL, Kurland BF, Abrams JR et al. Sexual function changes during the 5 years after high-dose treatment and hematopoietic cell transplantation for malignancy, with case-matched controls at 5 years. *Blood* 2008;111(3):989–96.

54. Tierney KD, Facione N, Padilla G et al. Altered sexual health and quality of life in women prior to hematopoietic cell transplantation. *European Journal of Oncology Nursing* 2007;11(4):298–308.

55. Sanders JE, Buckner CD, Amos D et al. Ovarian function following marrow transplantation for aplastic anemia or leukemia. *Journal of Clinical Oncology* 1988;6(5):813–8.

56. Salooja N, Szydlo RM, Socie G et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: a retrospective survey. *The Lancet* 2001;358(9278):271–6.

57. Loren AW, Chow E, Jacobsohn DA et al. Pregnancy after hematopoietic cell transplantation: a report from the late effects working committee of the Center for International Blood and Marrow Transplant Research (CIBMTR). *Biology of Blood and Marrow Transplantation* 2011;17(2):157–66.

58. Hammer RA, Umes PD, Lurain JR. Unanticipated pregnancy with intrauterine growth retardation after radiation-induced ovarian failure. A case report. *The Journal of Reproductive Medicine* 1996;41(5):372–4.

59. Norwitz ER, Stern HM, Grier H et al. Placenta percreta and uterine rupture associated with prior whole body radiation therapy. *Obstetrics and Gynecology* 2001;98(5):929–31.

60. Critchley HO, Wallace WH. Impact of cancer treatment on uterine function. Journal of the National Cancer Institute. *Monographs* 2005;34:64–8.

61. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. *Hepatology* 2010;51(4):1450–60.

62. Hildebrandt GC, Fazekas T, Lawitschka A et al. Diagnosis and treatment of pulmonary chronic GVHD: report from the consensus conference on clinical practice in chronic GVHD. *Bone Marrow Transplantation* 2011;46(10):1283–95.

63. Rietz H, Plummer AL, Gal AA. Asthma as a consequence of bone marrow transplantation. *Chest* 2002;122(1):369–70.

64. Bacigalupo A, Chien J, Barisione G et al. Late pulmonary complications after allogeneic hematopoietic stem cell transplantation: diagnosis, monitoring, prevention, and treatment. *Seminars in Hematology* 2012;49(1):15–24.

65. Abboud I, Peraldi MN, Hingorani S. Chronic kidney diseases in long-term survivors after allogeneic hematopoietic stem cell transplantation: monitoring and management guidelines. *Seminars in Hematology* 2012;49(1):73–82.

66. Singh N, McNeely J, Parikh S et al. Kidney Complications of Hematopoietic Stem Cell Transplantation. *American Journal of Kidney Diseases* 2013;61(5):809–21.

67. Socie G, Rizzo JD. Second solid tumors: screening and management guidelines in long-term survivors after allogeneic stem cell transplantation. *Seminars in Hematology* 2012;49(1):4–9.

68. Rizzo JD, Curtis RE, Socie G et al. Solid cancers after allogeneic hematopoietic cell transplantation. *Blood* 2009;113(5):1175–83.

69. Majhail NS. Secondary cancers following allogeneic haematopoietic cell transplantation in adults. *British Journal of Haematology* 2011;154(3):301–10.

70. Vajdic CM, Mayson E, Dodds AJ et al. Second Cancer Risk and Late Mortality in Adult Australians Recieving Allogeneic Hematopoietic Stem Cell Transplantation: A Population Based Cohort Study. *Biology of Blood and Marrow Transplantation* 2016;22(5):949–56.

71. Bilmon IA, Ashton LJ, LeMarnsey RE et al. Second cancer risk in adults recieving autologous haemopoietic sct for cancer: a population based cohort study. *Bone Marrow Transplantation* 2014;49(5):691–8.

72. 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):3802–11.

73. Cohen A, rovelli A, Merlo DF et al. Risk for secondary thyroid carcinoma after hematopoietic stem-cell transplantation: an EBMT Late Effects Working Party Study. *Journal of Clinical Oncology* 2007;25(17):2449–54.

74. Tomblyn M, Chiller T, Einsele H et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biology of Blood Marrow Transplantation* 2009;15(10):1143–238.

75. Australian Technical Advisory Group on Immunisation (ATAGI). *The Australian immunisation handbook 10th edition* (2015 update). Canberra: Australian Government Department of Health, 2015.

Section 7

Appendix 1

Table 3.3.3: Recommendations for revaccination following haematopoietic stem cell transplant (HSCT) in children and adults, irrespective of previous immunisation history [107, 108, 115-119]

Vaccine	Months after HSCT				Comments
	6	8	12	24	
Streptococcus pneumoniae (pneumococcal disease)					
13-valent pneumococcal conjugate vaccine (13vPCV)	Yes	Yes	Yes	Not needed	Refer to 4.13 *Pneumococcal disease*
23-valent pneumococcal polysaccharide vaccine (23vPPV)	No	No	No	Yes (after 13vPCV)	Refer to 4.13 *Pneumococcal disease*
***Haemophilus influenzae* type b**					
Hib	Yes	Yes	Yes	Not needed	
Diphtheria, tetanus, pertussis					
DTPa-containing vaccine for children < 10 years of age dTpa for those ≥ 10 years of age	Yes	Yes	Yes	Not needed	For recipients < 10 years of age, give all three doses as DTPa-containing vaccine. For recipients ≥ 10 years of age, give the first dose as dTpa, followed by two doses of dT. If dT is unavailable, complete vaccination course with dTpa.
Poliomyelitis					
IPV	Yes	Yes	Yes	Not needed	A three-dose course of inactivated poliomyelitis vaccine is recommended. This can be given as DTPa-IPV or dTpa-IPV; refer to 'Diphtheria, tetanus, pertussis' above.
Hepatitis B					
Hepatitis B vaccine	Yes	Yes	Yes	Not needed	A high-dose formulation (H-B-Vax II dialysis formulation) is preferred. Alternatively, give single strength Hep B vaccine in each arm at each dosing interval OR administer a standard vaccination course, then check HBsAb titres 4–8 weeks following the last vaccine dose. If titres are < 10 mIU/mL, repeat the vaccination course.
Influenza					
Two doses of influenza vaccine at least 4 weeks apart are recommended for all HSCT recipients receiving influenza vaccine for the first time (irrespective of age), with the first dose given as early as 6 months after transplant (refer also to the introduction of 3.3.3 *Vaccination of immunocompromised persons* above), then a single dose annually thereafter.					

Vaccine	Months after HSCT				Comments
	6	8	12	24	
***Neisseria meningitidis* (meningococcal disease)**					
Meningococcal B vaccine (MenBV)	Yes	Yes	Not needed (refer to comments)	Not needed (refer to comments)	Two doses of MenBV are recommended for persons ≥ 6 months of age. Additional doses are required if the vaccine course was commenced before 6 months of age (refer to 4.10 *Meningococcal disease*, Table 4.10.1). The co-administration of MenBV and 4vMenCV in persons who are at increased risk of meningococcal disease is acceptable based on first principles. (Refer also to 4.10 *Meningococcal disease*.)
Quadrivalent meningococcal conjugate vaccine (4vMenCV)*	Yes	Yes†	Not needed (refer to comments)	Not needed (refer to comments)	Two doses of 4vMenCV are recommended for persons ≥ 6 months of age. Additional doses are required if the vaccine course was commenced before 6 months of age (refer to 4.10 *Meningococcal disease*, Table 4.10.2). The co-administration of MenBV and 4vMenCV in persons who are at increased risk of meningococcal disease is acceptable based on first principles. (Refer also to 4.10 *Meningococcal disease*.)
Human papillomavirus					
HPV vaccine	A three-dose course of 4vHPV is recommended at intervals of 0, 2 and 6 months. Specific immunogenicity data in this group are not available; better immune responses may be expected at >12 months post transplantation when a greater level of immune reconstitution has been achieved.				Individual recommendations for HPV vaccination in those > 9 years of age should be determined by an individual risk assessment (refer to 4.6 *Human papillomavirus*).
Measles, mumps and rubella					
MMR vaccine	No	No	No	Yes, one or two doses separated by a minimum interval of 4 weeks (refer to comments)	Give only if the person is off immunosuppressive therapy, with no cGVHD and with reconstituted cell-mediated immunity. Check serology 4 weeks after first vaccine dose. If there is no seroconversion, repeat the dose.
Varicella					
Varicella vaccine	No	No	No	Yes, two doses separated by a minimum interval of 4 weeks (refer to comments)	Give to a seronegative recipient only if the person is off immunosuppressive therapy, with no cGVHD and with reconstituted cell-mediated immunity.

* Any transplant recipient who anticipates travelling may require additional vaccination, such as for meningococcal and hepatitis A disease (refer also to 3.2 *Vaccination for international travel*).

† The recommended interval between doses is 12 weeks for children who commenced their 4vMenCV course between 7 and 23 months of age as outlined in Table 4.10.2 in 4.10 *Meningococcal disease*.

HIV-infected persons [120]

Vaccination schedules for HIV-infected persons should be determined by the person's age, degree of immunocompromise (CD4+ count) and the risk of infection (refer to Table 3.3.4 below). Children with perinatally acquired HIV differ substantially from adults, as immunisation and first exposure to vaccine antigens occurs after HIV infection, whereas in adults, most vaccines are inducing a secondary 'boosted' immune response. HIV-infected persons of any age whose disease is well controlled on combination antiretroviral therapy (undetected or low viral load with good preservation of CD4+lymphocyte count) are likely to respond satisfactorily to vaccines.