Long-term Follow-up in an adult setting

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Todays session

- Why LTFU?
- Causes of late effects
- Body systems
- Carers
- Summary
BMT survivorship

- Increasing numbers of survivors
- Increasing indications (autoimmune, non-malignant haematology, immune disorders, malignant)
- Advances in histocompatibility testing, conditioning regimens, supportive care, management of GVHD
- Increasing amount of survivors requiring lifelong surveillance for complications
Cause of late effects

- Poor baseline health
- cGVHD
- CT, TBI, IST toxicities

LATE EFFECTS increased mortality and decreased QOL
Timelines for post HCT late effects

(courtesy - Dr. John Barrett)

Years

1  3  5  10  15  20

A-GVHD

C-GVHD

Endocrine complications

Gonadal/ sexual issues

Quality of life and psycho-social issues

Viral reactivation

Relapse

Ocular and dental issues

Bone loss / premature ageing
Cardiovascular / Pulmonary/
renal/ GI- liver issues

Early TRM

Second cancers
Late effects

- Acute and chronic infections
- Cutaneous
- Oral cavity
- Hepatic
- GI
- Genital
- Renal
- Sexual
- Secondary malignancies

- Ocular
- Endocrine
- Hypogonadism, infertility
- Dental
- Musculoskeletal
- Pulmonary
- Neurologic
- Cardiovascular
- Psychological/social
Chronic GVHD

- Immune mediated disease caused by interaction between donor and recipient, mainly caused by donor T cells
- Acute is distinctive syndrome of dermatitis, hepatitis and enteritis
- Chronic is diverse syndrome involving ocular, oral, GI, pulmonary, neuromuscular, genital, cutaneous...
- Occurs in 30-65% of recipients
- 5 year mortality rate of 30-50% (due to immune dysregulation, opportunistic infections)
- Primary cause of transplant related mortality later after transplant
- Contributes to most late complications
- Slows rebuilding of immunity – prolonged immunosuppression and ↑risk of infection
Chronic GVHD

Figure 2: Cutaneous manifestations of chronic GVHD to illustrate the importance of complete skin examination (i.e., color changes, shape of lesion, surface, thickness and mobility). Example of a case difficult to rate with various skin manifestations in each affected area.
Cutaneous GVHD

- Most frequent manifestation of cGVHD (75%)
- Significant morbidity, functional impairment, ↓QOL
- Prolonged IST = ↑risk of potentially lethal infections, complications
- Affects skin, mucous membranes, genitals
- Often associated with multi-organ involvement
- Joints and fascia often affected – contractures, range of movement limitation
The spectrum of cutaneous findings in ScGVHD.

Cutaneous GVHD

- Topical steroids, systemic steroids (standard primary treatment), IST

- Extracorporeal Photopheresis (ECP) – collecting leucocytes from peripheral blood, exposing to a photosensitising agent, then treated with UV radiation and reinfused

25 treatments over 12 weeks, review then 2 per month if require maintenance ($2000 per treatment)
Infection/immunity

- Immune system recovery – B cell 3-12 mths, T cell 9-12 mths, cGVHD 2yrs
- Discharged on antiviral, PJP prophylaxis, immunosuppression
- Should continue infection prevention at home (food, pets, avoiding sick people)
- Lost immunity to childhood diseases – schedule 6mths – 2yrs, lifelong seasonal viral immunisation
**A) Vaccinations during first 12 months post HPCT**

<table>
<thead>
<tr>
<th>Disease &amp; vaccine preparations</th>
<th>Months post HPCT</th>
<th>Additional considerations</th>
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</thead>
<tbody>
<tr>
<td><strong>Influenza</strong> Per recommended annual seasonal formulation</td>
<td>6</td>
<td>2 doses at least 4 weeks apart required in first year. Annual single dose influenza vaccination after first year post HPCT.</td>
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<tr>
<td><strong>S. pneumoniae</strong> (pneumococcal disease) – 13v PCV 13-valent conjugate vaccine</td>
<td>7</td>
<td>Requires further vaccination with 23-valent polysaccharide (23vPPV) vaccine at 24 months &amp; beyond – see Section B</td>
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<tr>
<td>e.g. Prevenar 13 ® IM</td>
<td>8</td>
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<tr>
<td><strong>Haemophilus influenzae type b</strong> (Hib)</td>
<td>12</td>
<td>The same brand of Hib vaccine should be used for all primary doses. If different Hib-containing vaccines (i.e. a mix of PRP-OMP &amp; PRP-T vaccines) are used in the primary series, then give a Hib booster dose at 24 months post-transplant.</td>
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<td>e.g. ACT-HIB ® IM</td>
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<tr>
<td>Hiberna ® IM</td>
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<tr>
<td>Liquid Pedvax Hib ® IM</td>
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<tr>
<td><strong>Neisseria meningitidis</strong> (meningococcal disease) Quadivalent meningococcal conjugate vaccine (4vMenCV)</td>
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<td>Requires ongoing 5 yearly boosters for life – see Section B</td>
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<td>e.g. Menactra ® IM, Mencevax ® IM</td>
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<td>Nimenrix ® IM</td>
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<tr>
<td><strong>Meningococcal B</strong> (MenB)</td>
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<td>e.g. Bexsero ® IM</td>
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<tr>
<td><strong>Diphtheria, Tetanus &amp; Pertussis</strong> t</td>
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<td>dT is preferred for booster doses at 8 and 12 months.</td>
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<td>e.g. Adacel ® IM, Boostrix ® IM</td>
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<tr>
<td>dT</td>
<td></td>
<td>If dT unavailable, complete the vaccination course with dTpa.</td>
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<tr>
<td>e.g. ADT Booster ® IM</td>
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<tr>
<td><strong>Polio</strong> I</td>
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<td>Please note IPOL® is given subcutaneously.</td>
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<td>e.g. IPOL (inactivated polio vaccine) SC</td>
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<tr>
<td><strong>Hepatitis B</strong></td>
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<td>High-dose formulation (H-B-Vax II dialysis formulation) preferred. Alternatives: Give single strength Hep B vaccine in each arm at each dosing interval.</td>
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<td>10 to &lt; 20 yrs</td>
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<td>Standard vaccination course</td>
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<td>e.g. H-B-Vax II ® (dialysis formulation)</td>
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<tr>
<td>H-B-Vax II ® (pediatric formulation)</td>
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<td>Engerix B ® (pediatric formulation)</td>
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<tr>
<td>≥ 20 yrs</td>
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<tr>
<td>e.g. H-B-Vax II ® (dialysis formulation)</td>
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<tr>
<td>H-B-Vax II ® (adult formulation)</td>
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<tr>
<td>Engerix B ® (adult formulation)</td>
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**B) Vaccinations beyond 12 months post HPCT**

<table>
<thead>
<tr>
<th>Vaccine &amp; preparations</th>
<th>Dose No.</th>
<th>Timing</th>
<th>Additional considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human Papilloma Virus (4vHPV)</strong> e.g. Gardasil ®</td>
<td>Dose 1: At least 12 months post-transplant (optimal timing is between 11-13 years old.)</td>
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<tr>
<td>Dose 2: 2 months after last dose</td>
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<td>Dose 3: 4 months after last dose</td>
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<tr>
<td><strong>Streptococcus pneumoniae</strong> (pneumococcal disease) – 23vPPV e.g. Pneumovax 23 ®</td>
<td>Dose 1: 24 months</td>
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<tr>
<td>Dose 2: 5 years after last dose</td>
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<tr>
<td>Dose 3: 65 yo (non-indigenous) / 50 yo (indigenous) OR 5 years after last dose whichever is later</td>
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<tr>
<td><strong>Neisseria meningitidis</strong> (meningococcal disease) – 4vMenCV e.g. Menactra ® IM</td>
<td>Indefinite Booster every 5 years</td>
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<td>Note: No booster dose is currently recommended for MenBV.</td>
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<tr>
<td>Mencevax ® IM</td>
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<tr>
<td>Nimenrix ® IM</td>
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<td></td>
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</tr>
<tr>
<td><strong>Influenza</strong> Per recommended annual seasonal formulation</td>
<td>Indefinite</td>
<td>Annual vaccination</td>
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</tbody>
</table>

**LIVE ATTENUATED VACCINES – Consider at 24 months post-transplant**

Can only be given if:
- Off immunosuppression
- No cGVHD
- Cell-mediated immunity has reconstituted

**Measles, Mumps & Rubella (MMR)**

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<tr>
<td>e.g. M-M-R ®</td>
<td>Priorix ®</td>
<td>≥24 months post-transplant</td>
<td>Check serology 4 weeks after first dose. Repeat dose if no seroconversion.</td>
</tr>
<tr>
<td><strong>Varicella zoster</strong> (VZV) e.g. Varilrix ®</td>
<td>Varivax®</td>
<td>Dose 1: Check serology prior to administration. If seropositive, no need for vaccination.</td>
<td>DO NOT USE Herpes zoster vaccine (e.g. Zostavax®) which contains 14x the amount of live attenuated virus.</td>
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<tr>
<td>Dose 2: At least 4 weeks after dose 1</td>
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</table>

IVIG and other transfusion products can interfere with immune response to live vaccines. Therefore a dose interval should be therefore allowed between administration of the two product types to optimise the response to vaccination. Recommended waiting intervals varies, e.g.:
- IVG – dose dependent, ranges from 8-11 months
- Blood, plasma, platelets – ranges from 3-7 months
Please refer to Table 3 for more detailed information on recommended intervals between the administration of live attenuated vaccines and transfusion products.
Cardiovascular effects

- Can appear decades after transplant
- Any form – cardiomyopathy, CHF, valve dysfunction, IHD, arrhythmia, pericarditis
- Vascular disease – CVD, PVD, cerebrovascular disease
- Cumulative exposure to anthracyclines, TBI, standard risks (HT, dyslipidaemia, diabetes, smoking, inactivity)
- 2 fold increase in metabolic syndrome – HT, ↑BGL, ↑waist circumference, abnormal cholesterol and triglycerides
- Healthy heart lifestyle counselling – exercise, weight maintenance, smoking cessation, healthy diet advice
- Early recognition and treatment of risk factors – annual fasting lipids and glucose
- Echo at 1 year then as required
Endocrine effects

- **Thyroid dysfunction**
  - hypothyroid (TBI 50%, BuCy 15%)

- **Metabolic disease**

- **Gonadal dysfunction** – 92% males, 99% females
  - infertility, sexual dysfunction, osteoporosis, menopausal symptoms

- **Annual thyroid, Vitamin D, FSH, LH, testosterone, oestriadiol levels**
Sexual health/fertility - women

- Vaginal GVHD - ¼ of long term female survivors, up to 49% in literature
  - vulval or vaginal irritation, discharge, ulceration, vaginal stenosis
- Premature ovarian failure/oestrogen deficiency (<5% recover ovarian function then enter early menopause)
  - genital atrophy
  - menopausal symptoms (hot flushes, low libido, night sweats, mood disorders, sleep disorders, low BMD)
  - infertility (often too late for fertility preservation)
- HPV /secondary SCC or dysplasia – vaccination post transplant
- ↑ risk of breast cancer in TBI – early mammography
- Gynae review/exam in the first 3-6 months then as required
- Dilators, lubricants, oestrogen replacement, surgery
- Large impact on quality of life, relationships
Sexual health/fertility - men

- Low testosterone - low libido, low BMD, fatigue, depression, erectile dysfunction
- Penile GVHD (5%)
- Infertility – sperm donation
- Annual testosterone, LH, FSH levels
- Sexual function assessment
- Referral to endocrine/andrology/psychology
Hepatic dysfunction

- GVHD - difficulty assessing, combination of LFTs, physical examination and history
- Hepatitis – monitor viral load, prophylactic treatment
- Iron overload – monitor serum ferritin, venesection
Musculoskeletal effects

- Avascular necrosis – focal bone disease, death of bone tissue due to lack of blood supply, (4-19%), attributed to glucocorticoids
  - No screening, awareness

- Osteopaenia (50%), osteoporosis (25%), fragility fractures (10-20%) – cyclosporin, GVHD, conditioning therapy, glucocorticoids, gonadal failure, vitamin D deficiency, immobility
  - Vitamin D levels – supplements, sun discouraged due to IST, Bactrim and ↑risk of skin cancers
  - BMD at one year, then as required (2yrs for low BMD)
  - Calcium (dietary sources, esp. for older adults)
  - Weight bearing exercise
Ocular effects

- **Cataracts**
  - TBI and corticosteroids (80% of TBI at 10yrs)
- **cGVHD and keratoconjunctivitis sicca syndrome** (dry eye disease)
  - 40-60% of transplant patients
  - Reduced tear flow, KCS, sterile conjunctivitis, corneal defects and ulceration
  - Symptoms – dryness, reduced tears, burning, blurred vision, foreign body sensation
- **Ischaemic microvascular retinopathy** – TBI, cyclosporine, diabetes mellitus
- Ophthamologist at 1yr then follow up as required
- Autologous eye drops – loss of tear production, natural tears made from patients serum and saline
- Punctal plugs – biocompatible device inserted into tear ducts, blocks drainage and ↑ tear film and surface moisture
Oral effects

- cGVHD – common, ulceration, alteration in taste
- Oral mucosal infection – candidiasis, herpes simplex virus (HSV)
- Salivary gland complications – dryness, difficulty swallowing, dental decay, gingivitis
- Malignancy
  - oral SCC’s (mostly in combination with cGVHD)
  - 50% of solid tumours post transplant are oral SCCs
- Annual dental review
Pulmonary effects

- Pre-existing factors – lung disease, smoking history, infection, conditioning therapy, radiation and cGVHD
- Bronchiolitis Obliterans Syndrome (BOS) – airflow obstruction, poor prognosis,
- Bronchiolitis obliterans organising pneumonia (BOOP) – inflammatory proliferative bronchiolitis, responsive and good prognosis
- sino-pulmonary infections
- All ↑ in cGVHD
- PFT pre and post transplant
- Regular chest assessment and examination
Secondary malignancies

- Two to three-fold ↑ risk of solid tumours
- **Solid tumours**
  - related to previous chemotherapy, TBI, immunosuppression, GVHD, viral infection
  - brain, breast, thyroid, lymphoid, GI, skin, sarcoma, cervical, anogenital,
  - risk ↑ over time and DOESNT PLATEAU
- **Myeloid malignancies**
  - usually 12-40 months post-transplant, more common in autologous
  - AML/MDS
  - therapy related

- **Post-transplant lymphoproliferative disorders (PTLD)**
  - usually within 1st year
  - mostly associated with Epstein Barr virus (EBV)
  - B-symptoms, lymphadenopathy, extranodal involvement (GIT, CNS)
Surveillance

○ Mammograms – TBI over 25, over 50 as per population

○ Skin cancer screen annually

○ Annual thyroid function/palpitation

○ Pap smears -1-2 yearly

○ FOBT over 50 as per population

○ cGVHD – oral cancer screening

Prevention

○ Education

○ Screening

○ Monitoring
Psychosocial effects

- Anxiety, depression, guilt, PTSD, self image issues, insomnia, fatigue, low self esteem
- Overall decrease in QOL
- Difficulty maintaining relationships, returning to work or school (up to 50% will not return to work)
- Fear of relapse
- “people forget and expect you to get on with it”
- Psychology referral
Adaptation and modification of lifestyle

- Loss of work
- Loss of study
- Change in relationships
- Financial implications
- Sleep disturbance, pain, appointments with various specialties, vaccinations, social isolation, symptoms of GVHD, side effects of medications
- Rural and regional patients
Family/carers

- Patients with low social support prior to BMT may experience poorer survival
- Direct correlation between psychosocial support and positive health outcomes
- Length of time of recovery is daunting for carers
- Frequently experience distress, burnout, diminished QOL – reported higher than the patient themselves
- Uncertainty, adverse health outcomes
- Carers program, BMT rehab
- Education, Psychology referrals
Jason Bowers
Multiple Myeloma

“Having been a regular exerciser, my post transplant challenge was to want to get back to doing exercise ‘can I do it’... It didn’t take long to feel the benefits, both physically and mentally. The part I initially enjoyed was setting very achievable daily goals... as they say little steps! These little steps then became kilometres and it was too long after that I had registered to run the City2Surf fun run. Having the goal of running and raising awareness and donations for Myeloma this also fuelled my reason to continue exercising. 6 years on and numerous fun runs, triathlons and obstacle events completed, I believe the benefits of those ‘first little steps of exercise’ not only made me feel stronger but also happier!

This program is made possible thanks to the kind support of the Danks Trust and Marian and EH Flack Trust

How to register

1. Discuss with your transplant specialist
2. For further information or to make an appointment, you can phone or email the LivingRoom:

email: livingroom@lh.org.au
ph: (02) 8514 0028

Living Well BMT Rehabilitation Program

Post blood and marrow transplant (BMT) a combination of physical changes, medication, bed rest and sleep problems can lead to a sense of fatigue, loss of strength and reduced quality of life.

To help manage such issues the ‘Living Well BMT Rehabilitation Program’ is now being offered at Chris O’Brien Lifehouse. The program will run 4 times per year for 8 sessions over 8 weeks, with before and after assessments to track your progress.

The management team includes the following health practitioners:

• **BMT Specialist**
  (Dr Stephen Larsen)
• **Dietitian**
• **Exercise Physiologist**
  (Michael Marthick)
• **Clinical Psychologist**
  (Toni Lindsay)
• **Clinical Nurse Consultants**
  (Sally Taylor, Katrina Wilczek)

These experienced health practitioners provide support and evidence based advice, within their respective fields, to assist you throughout the program.

The following is a list of some of the topics that may be covered over the 8 weeks:

• Dealing with fatigue
• Cancer treatment side effects
• Activity pacing
• Research around lifestyle intervention for cancer recovery
• Increasing lost muscle mass with diet and exercise changes
• Stress management
• Food supplements and myths
• Practical meal preparation
• Returning to work and social activities
• Sleep
• Healthy Eating Guidelines
• Developing a home exercise program
• Reading food labels
• Benefits of resistance training
Role of CNC

- Co-ordinate, assess, plan care for adult allogeneic patients

- Improve health outcomes
  - Health promotion
  - Illness prevention
  - Monitoring for late effects
  - Education
  - Referral pathways
  - Clinical assessment

- Improve communication between specialists, GPs and patients

- Transition paediatric patients to adult services
Summary

• Care doesn’t end at discharge

• Treatments cause lifelong complications and need for monitoring and prevention strategies

• Awareness about late effects is crucial

• Education and support for carers

• Continuing to support and assist patients post discharge helps them have some form of normality