Paediatric Blood and Marrow Transplant Overview

Indications and Long-term Follow-up

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Learning Objectives

• Physiological and developmental differences in children
• Types of diseases transplanted in paediatrics
• Graft sources & their challenges
• Veno-Occlusive Disease (VOD)
• Challenges of BMT
• Long Term Follow-up
Paediatric Blood and Marrow Transplant

- First successful BMT in children performed in 1968 using a matched sibling donor (MSD)
- First successful cord blood transplant was in 1988, in France using a matched sibling cord blood unit
- Approx. 130 allogeneic transplants performed throughout Australia annually
- Sydney Children’s Hospital Network – approx. 60 - 70 per year
Physiological and Developments Difference in Children
Children are not little adults

- Immature blood/brain barrier
- Higher respiratory rates
- Larger body surface area
- Thinner skin
- Rapidly dividing cells
- Higher metabolic rate
- Immature immune system
Airway and Breathing

- Babies are ‘obligatory nose breathers’
- Marked airway differences
- Inflammation can significantly decrease their airway
- Babies utilise oxygen more quickly than adults, their reserve is reduced
- Significantly higher respiratory rates
- Highly compliant chests
- Immature respiratory system until about the age of 8yrs
Circulation

- Lower total blood volume – amount of blood pumped through a single heart beat is lower
  - Causing an increased cardiac output - heart rate is quicker.
- Smaller size of heart
- BP is lower due to smaller body size
- Children compensate well and are more likely to go into respiratory arrest than cardiac arrest (cardiac arrest uncommon unless primary cardiac problem, or end result of progressive respiratory failure or shock)
Disability & Exposure

• Babies have large heads, big frontal lobes, open fontanel

• Immature blood brain barrier and enhanced CNS receptivity (can become a dangerous problem with exposure of chemicals)

• Temperature regulation – immature hypothalamus and large BSA leads to impaired temperature control until about 5yrs of age

• Children have a larger BSA to adults, thinner skin and higher metabolic activity – this can create excessive loss of heat and fluids

• Infants have greater fluid loss to that of adults
Disability and Exposure continued...

- Children eliminate drugs more rapidly than adults:
  - They have less GI absorption
  - More water versus fat
  - Immature enzymes
  - e.g. vincristine clearance is more rapid in younger children, alemtuzemab has higher renal clearance - higher dose recommended for better outcome, cyclosporine is ‘less active’ in younger children

- Children generally tolerate high doses of chemotherapy very well

- Chemotherapy doses often based on M² or /kg and occasionally age

- Because of they have such rapidly dividing cells, they are more susceptible to the effects of radiation than adults
Between the Flags

- Calling criteria for the early recognition of the deteriorating child was standardised across NSW for different age groups.
- Blue, yellow and red zones set criteria for calling clinical reviews or rapid responses and are based upon the child’s age and projected ‘norm’.

![Standard Paediatric Observation Chart (SPOC)](chart.png)
Psycho/Social Differences

- Emotional
- Social
- Adolescence
- Cognitive development
- Image
- Parents
- Peers
- School
- Hospital
Indications for BMT
# Indications for BMT

## Malignant / Allogeneic BMT

### Liquids
- ALL
- High risk AML
- NHL

## Malignant / Autologous

### Solid Tumours
- Stage IV Neuroblastoma
- Ewings Sarcoma
- Wilms tumour

## Non-Malignant / Allogeneic BMT

### Haematological
- Beta-Thal major
- Sickle cell disease
- Diamond Blackfan Anaemia

### Bone Marrow Failures
- Fanconi Anaemia
- Dyskeratosis Congenita
- Severe Aplastic Anaemia

### Immunodeficienes
- Severe Combined Immunodeficiency
- Haemophagocytic Lymphohisitocystosis
- Wiskott-Aldrich Syndrome (WAS)

### Metabolic
- Mucopolysaccharide Disease/Hurler Syndrome (MPS)
- Adreoleukodystropy (ALD)
Bone Marrow Failure

- **Dyskeratosis Congenita**
  - Rare progressive congenital disorder
  - Triad of abnormal skin pigmentation, nail dystrophy, lung disease, leukoplakia of oral mucosa
  - Characterised by short telomeres
  - Progressive BM failure in over 80%, causing early mortality
  - Often diagnosed at 5-15yrs of age
  - BMT cures BM failure but not tissues already damaged by DC such as lung disease
  - Prone to long oesophageal cancer in later life, skin cancers must avoid smoking
Primary Immunodeficiencies

Severe Combined Immunodeficiency (SCID)

• Rare genetic disorder, characterised by disturbed function or nil function of T and B cell
• Defective antibody response of B lymphocytes due to non-functional T-helper cells
• SCID is the most severe form of the primary immunodeficiency syndromes (PIDs)
• Can now be picked up with neonatal testing, though this is not available everywhere and the infant usually presents unwell, with frequent chest infections
• Fatal if not transplanted
Metabolic Disorders

Adreoleukodystrophy (ALD)

- X-linked recessive
- Fatty acid build up causes enzymes not to function properly, causing damage to the myelin sheath of the nerves
- Causes neurological deficit. Normal development in early childhood followed by rapid degeneration to a vegetative state leading to death
- Low fat diet can help with Lorenzo's oil administration
- BMT only cure
Graft sources & their challenges
**Graft Sources**

**Autologous**

**Allogeneic:**

- Matched unrelated donor (MUD)
  - Bone marrow preferred source to reduce GvH
  - PBSC asked for if CD34 selection required – malignant diseases

- MUD
  - Unrelated cord blood

- Matched sibling
  - Saviour siblings

- Haplo
  - CD34 selection & post transplant Cy
  - TCR a/b CD19+ selection
Cord Blood

• Good outcomes in the paediatric setting

• Children cope far better than adults with UCB transplants
  • Are better with coping with a more prolonged neutropenic phase than adults

• Used mainly for children with malignancies – good for immunotherapy i.e. GvL

• More immature immune system
  • Can be used with lesser degree of match i.e. 6/8
  • Mismatches far better tolerated

• Because children are generally smaller than adults, we can get better cell doses (TNC & CD34)
  • Better cell doses = quicker engraftment

• Easily accessible
  • Quick to get hold of
  • Know what we’re getting
  • Ideal for timing into transplant
Matched Sibling Donors (MSD) <16yrs.

• Certain risks need to be assessed as there is no medical benefit for the MSD going through this procedure:
  • Social
  • Psychological
  • Physical

• Require consent from parents and assent from the child
• Seen by independent paediatrician & haem/onc team
• General anaesthetic for procedure
• GCSF if MSD is smaller than recipient
• All siblings regardless of age require BMT donor questionnaire. Blood tests IDMs/NAT etc.

• Practical implications – which parent stays with which sibling for admission etc. Can create a lot of stress on the day
Saviour Siblings

• A child who is born specifically to provide their cells to an affected sibling with a fatal disease

• IVF techniques are used to select an embryo using a pre-implantation genetic diagnosis and HLA typing of embryo to match the recipient

• The ethical debate continues about the merits v’s demerits of this approach continue
Haploidentical

- Can use parents or siblings that are not a full match
- Easily available ‘on tap’
- Cells need to be heavily processed
  - CD34 selection and post transplant cyclophosphamide
  - TCR a/b CD19+ selection
  - Relatively new
  - Quick engraftment
  - Little or no GvH
  - Good for non-malignant children with no MUD available
Veno-Occlusive Disease

- Metabolites of chemotherapy cause damage to the endothelial cell lining.
- Obstruction of the veins (sinusoids) in the liver by the debris of damaged cells, causes obstruction to blood flow.
- Infants at greater risk.
- Associated with alkylating chemotherapy agents. TBI also increases the risk.
- Children with previous liver damage, lots of prior chemotherapy agents, MUD BMT, second BMT, certain diseases such as ALD, thalassaemia are at greater risk.
- Ranges from mild to severe.
- Can be life threatening.
Red blood cells  Toxic metabolites  Sinusoidal endothelial cells  Platelets

← Normal

VOD →
Veno-Occlusive Disease continued

**Signs & Symptoms**

- Rapid weight gain, puffy, fluid overloaded, large tummy, increased girth, pain
- Causes increased LFTs, coagulopathy and bilirubin

**Diagnosis**

- 5% weight gain from base line admission weight, bilirubin > 35, hepatomegaly, pain
- Ultrasound scan to show blood flow of the liver. Reverse blood flow indicating VOD
- Liver biopsy – rarely performed
Veno-Occlusive Disease continued

**Treatment**

- Largely supportive treatment – at least BD weights, BD girths, fluid restriction, diuretics, accurate fluid balance
- Monitoring of busulphan levels during conditioning
- Prophylaxis – ursodeoxycholic acid
- Treatment – defibrotide (antithrombotic, anti-inflammatory, anti-schaemic), monitor platelets and BP whilst on defibrotide
- Pain relief – vital!
- Child Life Therapy – distraction techniques
- Support to family and carers
Challenges of Paediatric Blood and Marrow Transplant
Challenges of Paediatric BMT

- Children are ‘not meant’ to be ill
  - Fed up with being in hospital
  - Little understanding as to why they are having a BMT
- Adolescence – don’t want to be in hospital
  - Away from peers, experimentation, relationships, normal activities, image changes
  - Always with parents

- Added challenges of terrible tasking medications and lots of tablets
  - Difficult to explain to children why we have to give them drugs with such awful side effects

- Parental Stress
  - Looking after their sick child
  - Not being there for their other children
  - Financial worries
  - Relationships
Long-term Follow-up
Long-term Follow-up

- Followed up for life, commencing 2 yrs. Post BMT
- Children’s Oncology Group (COG) guidelines are followed for follow up focusing on the screening and management of late effects.
- Tests based on their therapy - ECHO, PFT’s, Blood works including TFT’s, Insulin, lipids, FBC.
- Fertility specialist follow-up
- Endocrinologist follow up – focusing on adrenal insufficiency, growth hormones
- Focus on keeping the child/adult ‘engaged’ on their own health care follow up and aware of potential late effects
- General and psychosocial support
- Transition to the adult team can be challenging