Triumphs & Tribulations:
The first 50 paediatric liver transplants in New Zealand

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Triumphs & Tribulations

- Background
- Results
- Triumphs – things we’ve done well
- Tribulations – problems we’ve faced
- Future challenges
- Acknowledgements
Liver transplantation (LT) in children

- Children have very good outcomes following LT
- Most childhood liver diseases are non-recurrent
  - LT potentially curative
- Established programmes publish 5 yr survival rates > 85%
Innovations breeding success

- **Immunosuppression**
  - Cyclosporin & tacrolimus
  - Mycophenolate mofetil, sirolimus, induction antibodies

- **Preservation solutions**

- **Antimicrobials**

- **Ability to reduce liver in size for use in children**
  - Surgical reduction
  - Splitting the liver for use in 2 recipients
  - Live donation
In the good old days

 Liver transplantation in Queensland

- 1990-2002: New Zealand children were referred to Brisbane for LT
- Average stay in Australia = 6 months (range 3 – 17 months)
- 5 yr graft survival = 64%
- 5 yr patient survival = 73%
Liver transplantation in Auckland

- Adult LT programme began in 1998
- Contract awarded in 2001 for 6-7 paediatric cases per year
- 1\textsuperscript{st} paediatric transplant in Feb 2002
- 50\textsuperscript{th} paediatric transplant in Oct 2009
### Patient demographics

- 22 Male; 28 Female
- Median age 26 months
  - Range 4 months – 16 years
- Median weight 12.5 kg
  - Range 5.8 – 75 kg
- Combined liver & kidney transplant in 2

### Indications for liver transplantation

- Biliary atresia
- Re-transplant
- A1AT def
- Metabolic
- Acute
- Alagille
- Cryptogenic
- PSC
- PFIC 2

Metabolic = Wilson (1), Maple syrup urine (1), Oxalosis (1), Protein C deficiency (1)
Indications for liver transplantation

- BA commonest diagnosis
  - 29/46 primary transplants + 2/4 re-transplants
  - 62% of total transplants
  - 13/14 Maori patients
  - 2 children presented too late for Kasai

- Re-transplants of 4 children transplanted in Australia
  - 2 chronic rejection
  - 1 acute graft failure
  - 1 recurrent cirrhosis

Ethnicity of LT recipients
Origin of recipients within NZ

** Central Auckland (3); Counties Manukau (13); Waitemata (5)

Reduced size liver transplantation

- LT for children commonly uses segments II-III of the adult donor liver
- Segments V-VIII can then be used for an adult
Type of liver transplant

For 50 patients (51 transplants):

- **32 deceased donors:**
  - 11 reduced size grafts
  - 11 split grafts
  - 10 whole grafts

- **19 live donors:**
  - 7 Fathers
  - 4 Mothers
  - 3 Family friends
  - 3 Aunts/Uncles
  - 2 Grandparents
  - 2 live donors used for acute liver failure
  - 1 live liver/kidney donor

Triumphs

- Excellent graft & patient survival
- Shorter length of stay
- Responsive to change & evolving problems
  - EBV surveillance
  - Hepatitis B immune status monitoring
  - Protocol biopsy surveillance
  - Renal function monitoring
  - Establishment for live donor programme
  - Live immunisations following LT
  - *De novo* food allergies
- Multidisciplinary team with motivated nurses
- Collaboration with shared care centres
Graft & patient survival

- Compares favourably with overseas benchmarks
  - ANZLTR 2005-2008: 1 yr patient survival 95%; 5 yr 93%
- Overall survival = 96% patient; 94% graft
  - 1 patient re-transplanted for non-function day 2
  - 2 patients died
- 1 yr survival (n=43) = 98% patient; 95% graft
- 5 yr survival (n=16) = 94% patient; 88% graft

Psychosocial outcomes

- Good psychosocial outcomes
  - Difficult to measure
- All school age children at school
- Some mild concentration problems
- Some non-adherence in adolescents
- Live donor outcome excellent
How long did the patients stay?

- Median time in PICU = 2 days (range 1 – 8)
- Median time in Starship = 19 days (range 6 – 109)
- Median time in Ronald McDonald House = 18 weeks (9 – 34)
- Median time in Australia 1990-2002 = 24 weeks

Epstein-Barr virus (EBV)

- In most cases there is EBV mismatch between donor and recipient

Bad news:
- Difficult virus to treat
- No vaccine
- Can lead to PTLD

Good news:
- Good monitoring tests
- Usually responds to reducing immune suppression
Post transplant lymphoproliferative disease

- Unrestricted EBV replication can lead to lymphoproliferation & malignancy
- Occurs in up to 5 – 10% of LT recipients
- Initial treatment is reduction of immunosuppression
- Can also use anti-CD20 antibodies (Rituximab) or chemotherapy

Post transplant lymphoproliferative disease

- Monthly EBV load monitoring for 1st year
- 1 biopsy-proven Burkitts lymphoma (patient died)
- 1 likely PTLD of lung (responded to Rituximab)
- Several children have stable high loads
  - Largely managed by keeping IS as low as possible
- 5 children have received Rituximab
Hepatitis B infection

- 2 donors had past hepatitis B infection
- Recipients felt to be immune
- Loss of protective antibody in both
  - One spontaneous
  - One following Rituximab for high EBV loads
- Both developed hepatitis B
  - More difficult to manage in immunosuppressed
  - Often leads to recurrent cirrhosis

Hepatitis B monitoring

- Recognition of loss of immune status by 1 year post LT
  - Not previously reported
  - Almost universal
- More rigorous attention to pre-transplant immunisation
- Regular monitoring of antibodies
- Re-immunisation if antibody lost

Evans et al. IPTA meeting 2009
Protocol biopsy monitoring

- Growing recognition of chronic hepatitis on biopsy despite normal liver function
- May be immune phenomenon
- Post LT biopsy at 1, 5, 10 years
- Biopsy at 1 yr prior to steroid withdrawal


Renal dysfunction following LT

- Renal dysfunction common following LT
  - Nephrotoxic drugs esp tacrolimus
  - Multi-system disease
  - Hepatorenal syndrome
- Initially may be reversible
- Can respond to immunosuppression adjustment
Renal function monitoring

- Established links with renal team
- Pre-transplant assessment introduced
  - Awareness that function is not normal prior to LT
- Regular Cystatin C measurements
  - Non-invasive marker of renal function
  - Can use to calculate GFR
- Low threshold for biopsy
- Treatment of hypertension
- Early IS adjustment if needed

Kara et al. IPTA meeting 2009

Deceased donor numbers are decreasing

- Shortage of donors continues to be a big challenge in New Zealand
Live immunisations following LT

- Accelerated immunisations for children with chronic liver disease
  - Includes hepatitis A & varicella vaccine
- Often children transplanted before vaccines complete
- Exposure to measles & VZV a problem later
- Increasing international experience of live vaccines following LT
- Some VZV vaccines given with success
**MMR immunisation following LT**

- Measles outbreak in Auckland 2009
- All LT patients tested for measles immunity
- Those immunised pre-LT mainly still immune
- Non-immune patients offered MMR if:
  - Tacrolimus monotherapy
  - Stable liver function
- Some accepted
  - Good response to single dose
  - No clinical measles

**De novo food allergies**

- Increasing awareness internationally
- New food allergies after transplant
- Mechanism not understood
- Several children with new allergies noted
- Immunology input in all cases
Multidisciplinary teamwork

- Contributions from allied health professionals can not be underestimated
  - Dietitians ensure adequate nutrition pre-LT
  - Pharmacist ensures medication compatibility & educates families pre-discharge
  - Social worker used frequently
  - Ward staff & educator receptive to innovation
  - Charge nurse studied family stressors for Masters thesis
  - Specialist nurses support families pre & post LT and have ensured consistent long-term follow-up

Malnutrition in chronic liver disease

Patient with BA and his twin (same birth weight) – prior to enteral feeding
Malnutrition in chronic liver disease

Patient with BA and his twin (same birth weight) – after 3/12 enteral feeding

Patient support & education

- Liver transplant manual
- Support via Kids Foundation
- Focus on adolescent health
Collaboration

- Guidelines for shared care established
- Outreach clinics:
  - Christchurch/South Island
  - Hawkes Bay
  - Wellington
  - Palmerston North
  - Whangarei

Collaboration

- Regular liaison with South Island gastroenterologist (Andrew Day)
- Joint liver & renal paediatric transplant meetings since 2007
- Study days for shared care paediatricians
- Auckland Transplant meetings
- Paediatric Society – Gastroenterology SIG
- Data contributed to ANZLTR
- PLANZ meetings with Australian teams
- TSANZ & IPTA representation
Tribulations

- Long wait times and low deceased donor rates
- Wait list mortality
- Technical complications
  - Especially biliary complications
- Patients becoming more complex
- Small numbers mean inability to partake in much research

Wait times

- All: Median 99 days (range 0 – 702 days)

- Live donors: Median 96 days (range 6 – 313 days)

- Deceased donors: Median 110 days (range 0 – 702 days)
Wait times

- All:
  - Median 99 days (range 0 – 702 days)

- Blood group A (n = 26)
  - Median 89 days (range 8 – 599 days)

- Blood group O (n = 21)
  - Median 136 days (range 0 – 702 day)

Waiting list deaths

- 8/63 (13%) of children died on the waiting list for LT
  - Sudden death at home in sick neonate 1
  - Variceal bleeding 2
  - Other bleeding 1
  - Acute liver failure 2
  - Hepatopulmonary syndrome 1
  - RSV infection 1

- Those who died did not wait longer nor have higher PELD score

Wilde et al. NZMJ 2007
Strategies to shorten wait time
- Live donation
  - Need to make families aware of option without coercion
- Donation after cardiac death
- ABO incompatible transplantation
  - Done with some success in Japan
- Paired donor exchange
- Hepatocyte transplantation for metabolic disease

Technical complications
- Primary non-function 1 (2%)*
- Bile duct complications 18 (36%)**
  - Re-operations in 9 (18%)
- Vascular complications 11 (22%)*
- Intestinal ischaemia 1 (2%)*
  - Patient died
- Allograft ischaemia 3 (6%)*
  - Gram negative sepsis 2
  - Hepatic artery dissection 1

*Comparable to or lower than international series
**Higher than international series
Biliary complications

- Small patients
- Reliance on technical variant grafts
  - Fewer complications in whole liver recipients
  - Incidence may be increasing in other centres
- Initial learning curve issue
- Aggressive management with biliary stenting +/- re-operation
- Some later strictures identified recently

Increasingly complex patients

- Combined liver-kidney transplants
  - Oxalosis
  - Protein C deficiency
- High risk hepatoblastoma patients
- PFIC type 2 with malignancy
- Acute liver failure following lymphoma
- Unusual metabolic disorders
- Sclerosing cholangitis, ulcerative colitis & spherocytosis
- Children with significant social problems

Gunawansa. *In press* 2010
The Balancing Act after transplant

- PTLD
- Recurrence
- Infection
- Kidney damage
- Poor growth
- Graft loss
- Rejection
- Kidney damage
- Graft loss
- PTLD

Cumulative Risk of Diagnosis of Cancer Following Liver Transplant 1985-2008

Patients at Risk (3066)

- Red: Any Ca
- Skin: Non skin (includes recurrent primary and secondary liver cancer)
- De Novo Non skin
- Age-Matched Gen. Pop

Years Post Tx

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

0 20 40 60 80 100
Future challenges

- Excellent survival means focus of follow-up is minimisation of morbidity
  - How can we safely minimise immunosuppression?
  - Will our patients ever come off immunosuppression?
  - Is 100% survival achievable

- As programme has progressed patients are older & young persons clinic is required

- Good outcomes mean indications for LT are likely to become extended
  - E.g. metabolic diseases
  - But this needs to be balanced by availability of donor organs
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- Pathology
- Pharmacy
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