



# PREDICTING RENAL DYSFUNCTION FOLLOWING PAEDIATRIC LIVER TRANSPLANTATION

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## Elective Summary

After months of preparation and careful organisation of our elective placement, on the 13<sup>th</sup> of January 2014 we joined the paediatric renal team in Starship Children's Hospital, Auckland, New Zealand. Our choice of this placement was based upon developing interests within the fields of paediatrics and renal medicine, and we saw the elective as a good opportunity to experience working in a highly specialised tertiary centre, related to these interests. Time was divided equally between clinical activities and carrying out a research project. Our clinical experience included participating in ward rounds and carrying out ward jobs, clerking in patients for admission to the unit, observing clinics with the consultants, watching renal operations in theatre, and attending both teaching sessions and multi-disciplinary meetings.

The other half of our time was working with Dr. Tonya Kara, a Paediatric Nephrologist, to collect data for a research project investigating risk factors that influenced the renal outcomes of paediatric liver transplant patients. This involved looking at patient data from 43 children who received liver transplants due to biliary atresia between 2003 and 2012 and evaluating a range of different parameters from birth up to the transplant, to investigate whether any of these factors were correlated with adverse renal outcomes subsequent to the transplant itself. Having recently returned from New Zealand we are yet to complete the analysis of our results, but we hope that our study will contribute to a reduction in morbidity for liver transplant placements, in particular by recognising which patients are more likely to suffer from kidney injury.

## Introduction

In the 21<sup>st</sup> Century, vast improvements have been made in the management of paediatric liver transplants, such that mortality is now low in this group of patients (10 year survival 88-93%)<sup>1</sup>. Despite this, children receiving liver transplants subsequently develop morbidities that affect quality of life, including chronic kidney disease. The first study to explore the relationship between liver transplant and renal dysfunction investigated the 5-year risk of chronic renal failure after a non-renal transplant<sup>2</sup>. Since this article numerous studies have scrutinized the relationship further, focusing on intra-operative renal dysfunction and post-transplant renal outcomes of children undergoing liver transplantation<sup>3,4,5</sup>. Peri-transplant and post-transplant care is of great importance with regard to organ transplantation, especially once adverse events have occurred and interventions are required.

These studies have produced a wealth of information regarding intraoperative and post-operative management recommendations. However, a lack of literature exists between pre-operative renal function and its contribution to post-transplant renal outcomes. It is known that renal dysfunction can be sustained without a detectable change in typical biomarkers such as creatinine, serum albumin and proteinuria. Therefore by investigating a range of quantitative clinical measures there is potential to uncover relationships between certain drugs, demographics or medical history and the patient's renal function that may assist in the prediction of adverse renal events. These potential correlations could then be used to formulate a specific reno-protective management plan that is tailored for high-risk patients undergoing organ transplantation.

Evidence from within the field of paediatric nephrology has suggested a range of biomarkers and demographics that have been associated in the development of chronic kidney disease. Carmody and

Charlton identified low birth weight, prematurity and particularly episodes of acute kidney injury as being risk-factors in the development of chronic kidney disease later in life <sup>6</sup>. Exposure to certain drugs have also been found to play an important role in transplant outcomes, which is important when one considers the nephrotoxic nature of many of the immunosuppressive agents used in the prevention of organ rejection, for example cyclosporine and tacrolimus <sup>7</sup>.

The New Zealand paediatric liver transplant programme has been running since 2002 in Auckland's specialist Starship paediatric hospital, and has witnessed over 100 successful transplants to date. All patients are screened pre and post-transplant for adverse renal function and in 2009 a renal sparing protocol using delayed reduced dose tacrolimus was introduced for children with a glomerular filtration rate of  $< 60\text{mls/min/1.3m}^2$  following recommendations from the ReSpECT study <sup>7</sup>.

## Aims

The aim of this study is to identify risk factors that liver transplant recipients are exposed to prior to transplant, and assess whether these contribute to the development of adverse renal function following transplant. If any of the factors described below are found to contribute to, or indicate potential adverse outcomes then there is a potential to include these in the assessment of renal function at the time of initial presentation, and in the renal-protective liver transplantation protocol.

## Methodology

This study consisted of a retrospective analysis of electronic patient data from 43 paediatric liver transplant recipients between 2003 and 2012. All patients used in the study were diagnosed with congenital biliary atresia, a condition where the extra-hepatic biliary ducts are either absent or blocked due to fibrosis during embryological development. The initial treatment for this disease is hepatopertoenterostomy (Kasai procedure) where the small intestine is attached to the porta hepatis as a method of improving bile drainage <sup>8</sup>. However, this procedure often fails, as children generally develop worsening liver function over a period of months to years. The rationale behind the procedure is to allow more time to plan the definitive treatment of biliary atresia, liver transplantation <sup>7</sup>. Transplant is heavily reliant on the availability of organs from either living or deceased donors, therefore the time from diagnosis to the procedure itself can be lengthy. All children included in this study were operated on at Starship Children's Hospital, by the same team of transplant surgeons. Ethical approval was given by the Auckland District Health Board (ADHB) for this research project (ref: A+6033).

The electronic data was collected by reviewing inpatient notes, drug charts, discharge summaries and outpatient letters using Concerto® and 3M® software by Michael Webb and William Jenner. The following risk factors were investigated:

Demographics:

1. *Name*
2. *Current Age*
3. *Date of transplant*
4. *Age at transplant*

## 5. *Known renal disease*

Potential risk factors occurring between birth and transplantation included:

1. *Birth weight*
2. *Gestational age*
3. *Acute kidney injury episodes pre transplant (defined as a doubling of creatinine)*
4. *Episodes of sepsis*
5. *Aminoglycoside exposure (including gentamycin and amikacin)*
6. *Elevated aminoglycoside levels*
7. *Exposure to other known nephrotoxic medication e.g. amphotericin, ibuprofen, IV contrast*
8. *Hypotension requiring fluid or inotropic support*
9. *Cardiac or non-cardiac surgery*
10. *Renal replacement therapy requirement peri-transplant*

These data were tabulated, and matched with results previously acquired that documented the renal outcomes following liver transplant, including creatinine and GFR at one year post transplant, in addition to more general findings such as weight and height gain at one year.

## Results

Results were collated for 38 patients, and are presented as mean  $\pm$  standard deviation. Detailed results were missing in two patients. The average age at transplant was  $28.1 \pm 30.2$  months. Acute kidney injury prior to transplant was identified in 8/36 patients (22%), and 31/36 patients (86%) were exposed to aminoglycosides at some point prior to transplant. Whilst cholangitis was seen in 23/36 patients (64%), sepsis only occurred in 3/36 patients (8%). 35/36 patients (97%) underwent other surgical procedures prior to transplantation, including hepatopertoenterostomy (Kasai procedure), liver biopsy, and upper gastrointestinal endoscopy  $\pm$  variceal ligation.

Unfortunately given our recent return from New Zealand, it has not yet been possible to complete the statistical analysis to match pre-transplant risk factors with post-transplant renal outcomes. Final analysis of the data is planned for shortly after MBBS finals in May.

## Discussion

The initial results from the study show that a large number of these children suffer from infection, undergo numerous surgical procedures, and receive antibiotics prior to transplant, all of which have the potential to cause kidney injury. Despite this, only 8% of patients were observed to suffer a clinically diagnosable acute kidney injury (AKI), although it cannot be excluded that some instances of AKI may have been missed due to the timings of blood taking, and that a subclinical injury may not have caused a sufficient rise in urea or creatinine to be diagnostic.

A number of challenges arose during data acquisition. In some instances the discharge summaries lacked sufficient detail, or the inefficient coding system may have missed certain conditions such as sepsis. Furthermore the handwritten notes on 3M® were difficult to read at times, and it is possible

some incidents may have been missed. To determine exposure to aminoglycosides it was possible to use the blood test database for records of gentamycin and amikacin levels, however levels were not always taken at the recommended intervals (pre-dose trough for assessing toxicity). This therefore made some of the results difficult to interpret. Accounting for these challenges of data acquisition required considerable time. However this allowed us to develop our organisational skills as the project progressed, and taught us to manage the delicate balance between clinical and research responsibilities.

Furthermore, this data was acquired from a group of homogeneous patients with biliary atresia, and it remains uncertain whether conclusions drawn from these patients are also applicable to other paediatric patients receiving liver transplants for alternative causes. Other conditions may have greater renal involvement than those seen with biliary atresia. A future aim is to expand this work to the other recipients of liver transplants at Starship hospital.

The aim of this study was to determine whether any of the documented parameters and risk factors are of value when assessing pre-transplant renal function and in predicting patients who are at an increased risk of future transplant related renal events. Renal dysfunction will be determined by evidence of worsening biomarkers or clinical manifestation as described in the patients' notes. The cumulative aim is to improve pre-transplant renal risk assessment and reduce occurrences of post-transplant renal dysfunction and morbidity in paediatric liver transplant recipients.

This project has enhanced our understanding of monitoring renal function, teaching us factors that can contribute to adverse renal events, and how to overcome challenges of retrospective data analysis. We look forward to completing data analysis and developing a better understanding of medical risk stratification that will benefit our clinical and research acumen as we enter the foundation program in August 2014. We also aim to present our findings at local and international research conferences upon project completion.

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