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Paediatric Haematopoietic Stem Cell Transplant - Presenting hope as curative treatment for patients with Primary Immunodeficiencies

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Haematopoietic stem cell transplant (HSCT) is the leading curative treatment for the majority of severe primary immunodeficiencies (PID). PID are inherited disorders of the immune system comprising 330 distinct disorders and 320 genetic defects (IUIS 2017). These are classified phenotypically according to disorders of adaptive and innate immunity, immune dysregulation and auto-inflammation, which may overlap. Conditions that are common indications are Severe Combined Immunodeficiency (SCID), Familial Haemophagocytic Lymphohistiocytosis (HLH), Wiskott-Aldrich Syndrome (WAS) and Chronic Granulomatous Disease. But increasingly there is a recognition of severe or undefined autoinflammatory disorders that are part of the spectrum of PID for which HSCT is curative.

The first KKH PID transplant was in 2005 for an infant with SCID using umbilical cord transplant. Since then, 22 PID transplants have been performed in KKH from 2005 to 2020. Of these, 4 were matched related donors, 3 matched unrelated donors, 9 cord blood transplants, 6 haploidentical transplants. Our PID transplant programme sees an overall survival of 70% which is comparable to best international experience. KKH started the haploidentical transplant programme in 2017 for acute leukaemia and thalassaemias, and this expanded to include primary immunodeficiencies in 2018. This ensures that every

single PID patient will have a donor. In addition, the newborn screening for SCID by T-cell receptor excision circle (TREC) assay was officially rolled out in 2020 for all newborns in Singapore. SCID can be devastating if unrecognized until the first severe presentation and, if diagnosed and transplanted prior to 3 months of age, have close to a 100% overall survival. Haploidentical transplants would be a life-saving and immediate option for SCIDs that are diagnosed at birth.

A testimonial case of a life-saving haploidentical transplant was exemplified by a young boy aged 4 who arrived from a neighbouring country in extremis, with WAS, severe inflammatory bowel disease and malnutrition, complicated by Pneumocystis jirovecii pneumonitis with multiple air leaks as a result of chronic steroid use around Christmas 2019. He had no matched donors in his country and was given a palliative diagnosis. This led his parents to Singapore seeking a haploidentical transplant. He was counselled to expect the worst. With excellent ICU supportive care and nutritional rehabilitation, he finally underwent a high-risk haploidentical stem cell transplant from his father in June 2020, and is now a healthy child returning to his home country in Christmas 2020.

A Webinar on “Ethics and Transplantation” with Adj Prof Christy Simpson, held on 9 Dec 2020.

Adj Prof Christy is currently Head of the Department of Ethics at Dalhousie University.



Brief History

An organ transplant is usually one of the best options for patients with end stage organ failure. Patients are put on a waitlist and contacted as soon as a suitable organ from a cadaveric donor becomes available.

Transplants have been carried out in Singapore for more than 40 years, with the first kidney transplant performed in 1970. Organ donation rates continue to remain low with over 400 patients waiting for organ transplant according to figures from the Ministry of Health in 2019.

Pearls of wisdom from Adj Prof Christy Simpson

Why is it hard to have conversations about Organ Donation?

Conversations about organ donation are intrinsically difficult. Where they occur in the hospital, it is mostly during a time where the family is grieving and coming to terms with the loss of a loved one. Being there with the family when they are processing the information and news is ever-important to provide a supportive presence. In normal day-to-day interactions, talking about organ donation and death may be taboo and sensitive in certain cultures and societies.

When interacting with the families of donors, these exchanges take time and should be paced appropriately so that the family of the donor does not feel rushed. This situation is highly nuanced as there is a window period where organ donation can actualize and this may add pressure in discussing the opportunity of donation with the family.

Healthcare professionals need to manage their expectations arising from the conversations about Organ Donation and allow for space as to how the exchanges and interactions may pan out. This includes allowing the families to consider their options or letting individuals explore how their decision may impact the lives of others and their loved ones.

When considering the aspects above, we gather a holistic view as to why conversations about Organ Donation should occur as early as possible. By providing psychological support and information to families and individuals, the tension and difficulty of the process could be reduced.

HCPs perspective

Challenges faced in organ donation in Singapore



Unfamiliarity with legislation and process



Communication challenges between medical staff and families



Cultural and religious factors

You shared that “one of the biggest dilemmas in Organ Donation is juggling the scarcity of organs and tissues and knowing that patients with end-stage diseases are suffering until a transplant is available.” In light of an opt-out system, what can be done to improve Organ Donation awareness?

- 1 Increasing public education on Organ Donation and Transplantation so that resources on these topics are readily available and accessible
- 2 Reach out to schools and tertiary institutions to engage youths and young adults
- 3 Share more about what is to be expected in Organ Donation and its processes
- 4 Address misconceptions and myths surrounding Organ Donation and Transplantation

- 5 Champion how Organ Donation can benefit patients through successful person stories and also address the suffering of patients with end-stage diseases
- 6 Help people embrace Organ Donation as part of end-of-life conversations
- 7 Allay any mistrust and misinformation by ensuring that there is clarity in the key roles (coordinators, medical team etc.) of the Organ Donation process so that it is carried out efficiently and with due care and respect



Fellowship in Multivisceral and Intestinal Transplantation at the Cambridge Transplant Unit at Addenbrooke's Hospital

By, Dr Koh Ye Xin, Consultant, Hepato-pancreato-biliary and Transplant Surgery, Singapore General Hospital

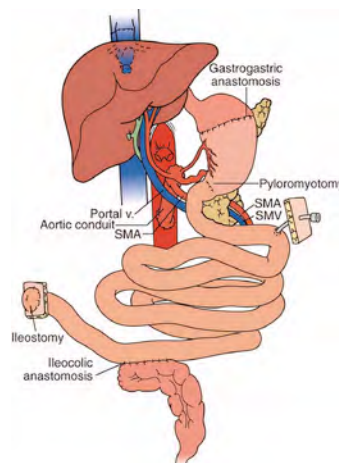
I had the exceptional opportunity to pursue a clinical fellowship in multivisceral and intestinal transplantation at the Cambridge transplant unit at Addenbrooke's Hospital, Cambridge, United Kingdom, in 2019. The experience greatly broadened my horizons. It was the first liver transplant unit in Europe and currently the largest multivisceral and intestinal program in the region.

When multivisceral and intestinal transplant first started 30 years ago, it was considered experimental and received with skepticism. Today, it has undeniably changed many lives for the better and is widely regarded as the standard of care for patients with intestinal failure who suffer from life-threatening complications of parenteral nutrition.

Patients with end-stage intestinal failure face grim prospects without transplantation. One patient described, "it was not a life, it was a mere existence". They are shackled to their parenteral nutrition (PN) bags forever. The inevitable complications of life-threatening sepsis, liver failure from chronic parenteral nutrition, and loss of central venous access loom ominously over them and many pass on after prolonged

suffering. It is heartbreaking for the patients, their families and their medical teams.

Fortunately, intestinal transplantation resolves most these problems and offers them a new lease of life. The patients are transformed after transplantation and go on to reintegrate into society, leading healthy and productive lives. Perhaps in the not-so-distant future, we can give new hope to our patients and their loved ones in Singapore with this life-changing transplant.



A multivisceral transplant involves the resection of the recipient's distal stomach, duodenum, pancreas, liver, and remaining small bowel.

Source: <https://clinicalgate.com/intestinal-and-multivisceral-transplantation/>

Pushing On Through a Pandemic – A journey to being a specialist in thoracic surgery and lung transplantation in Toronto General Hospital

By, Dr Chua Yang Chong, Consultant, Department of Cardiothoracic Surgery, National Heart Centre Singapore



Implanting donor lungs during lung transplant surgery in TGH. Operating with me is Dr Wei Huang, a lung transplant surgical fellow from Shanghai.

The Beginning of a Special Journey

My journey to become a consultant thoracic and lung transplant surgeon had many challenging and memorable moments. I undertook a clinical fellowship in thoracic surgery at the Toronto General Hospital (TGH) under sponsorship from SingHealth-MOH HMDP from 2018-2019. I stayed on for a second fellowship in lung transplant surgery under TGH's sponsorship from 2019-2020.



December 2019 – February 2020

In 2019, 212 lung transplants were carried out in total at TGH and, simultaneously, it remained the largest lung transplant programme in the world. I was performing lung retrievals independently and starting to perform pneumonectomies' (surgical procedure to remove one of your lungs) and vascular anastomoses (surgical procedures to connect vessels to each other) for the implant surgery. Bronchial anastomosis had always been the Achilles heel in lung transplant and was reserved for later. The team went into 2020 with much optimism and expectation, maybe 250 lung transplants next year? Anything seemed possible then.

Over a Chinese New Year dinner in February, a colleague from Shanghai grew worried about the COVID-19 situation and developments in China, especially at his own hospital, the Shanghai Pulmonary Hospital. Thus, the beginning of my challenging period.

A pediatric donor lung I retrieved from Nova Scotia, and implanted at Toronto's SickKids Foundation successfully.

March 2020

The 24-bedded Medical-Surgical ICU of TGH is always bustling with activities regardless if it is 3am or 3pm. One weekend in late March, during my usual transplant rounds, I suddenly walked into an empty 'corridor'. Although TGH was not designated as a 'COVID Hospital' (in view of the large volume of immune-compromised transplant and cancer patients), we were prepared for spill-overs as it was the center for Extra-Corporeal Life Support (ECLS) with equipment such as the Extra-Corporeal Membrane Oxygenator (ECMO) for Ontario and the surrounding province.



The 'Toronto thoracic and lung transplant family' during a summer barbeque 2019; standing from my immediate left to right, Dr Yasufuku, Dr Keshavjee and Dr Waddell- all my mentors.

All elective cases were halted and many operating room (ORs) were converted to potential ICU beds. This was a hospital that one almost never saw an empty ICU bed ever, and every OR slot was accounted for so carefully. It finally dawned on me, that the epidemic has arrived in TGH.

At this point, the Ministry of Health and SingHealth made provisions to repatriate all Singaporeans and PRs overseas to return, in particular those in healthcare. I recall the many phone calls from our Surgical Chair, Dr Tan Hiang Khoon, asking if I was alright. Though there were fear and uncertainties, I felt I was not ready to leave yet. I stand strong to the camaraderie and sense of duty at TGH.

Each week, in the Toronto's lung transplant surgical team, a fellow would take turn to be 'on call' and will, thus, be the de facto chief. On the week the programme was put on hold, I was the fellow in-charge and had already assigned my colleague on a trip to Montreal. Fortunately, he was not yet on the jet. We had to cancel the private jet and had him turn back while he was in the taxi.

During the combined ward round in the morning, the medical director of Toronto Lung Transplant, Dr Lianne G Singer, informed us the programme had been suspended. Thoracic and lung transplant fellows were expected to be at the frontline to provide service for ECLS for COVID patients. And just like that, what seemed impossible just a few weeks ago came to be; the world's largest lung transplant programme had been closed till further notice.

Measures were taken to safeguard the staff, our immune-suppressed lung transplant patients in the wards, community/rehabilitation hospitals and the community at large. Our transplant patients were followed up very attentively and they would come for the slightest hint of a cough or a cold. However, this model of care was no longer sustainable in COVID. Access to bronchoscopy or any aerosol generating procedures like a simple spirometry in the clinic had to be reviewed. The world we knew seemed to have altered forever.



As 'Black Lives Matter' protesters march on, so does the lung transplant fellow marching to the hospital- the work is never done.

April 2020

We started our first few veno-venous-ECMO cannulations. Fellows were 'paired' with other surgical staff with 6 lung transplant fellows and 9 staff surgeons divided into 3 teams. Residents, general thoracic fellows and nurse practitioners were a part of the effort too. A cardiac surgical fellow and cardiac surgeons volunteered to join the thoracic team in this exceptional situation (in Toronto, there were 2 ECLS teams, cardiac and thoracic). For COVID cases, the thoracic fellows would lead the team.

We covered most of Ontario; for in-house as well as remote cannulations. Our coverage was only limited by the geographical spread of Canada, and no jets were able or willing to transport COVID patients with ECMO by air. We could only cover areas accessible by ambulance, bearing in mind that we had to travel with the patients when they return to TGH. The initial guidelines for ECLS for COVID patients were very strict in terms of age. Apart from respiratory failure, patients with all types co-morbidities and organ failures must be excluded. Over time, when the team was not overwhelmed, some of the criteria became more adjusted.

May 2020

Many of our lung transplant patients on the waiting list were deteriorating, and the COVID numbers in Ontario seemed to be in control. The lung transplant programme reopened carefully and gradually. Every case had to be discussed in the multidisciplinary board prior to listing and only urgent cases could proceed. Initially, donor retrievals were limited from within Ontario and later, extended to the rest of Canada except Quebec. At one time, Quebec had one of the highest numbers of COVID cases. Subsequently, we opened the programme to the whole of Canada but not USA (which we went to before the pandemic).



Passing the baton to the current and new lung transplant surgical fellows, future lung transplant surgeons of the world- standing from left to right- Vancouver, Japan, Switzerland, Germany, Australia, and Chicago.

The 3 teams were now divided into a 'dirty' COVID team, a 'resting' (monitored for symptoms) team and a 'clean' transplant team to manage the lung transplant and COVID ECMO patients. The teams alternated weekly and each had only 2 fellows, hence, it could get busy. In the dirty team, 2 fellows had to perform all cannulations as well as all the rounds and procedures in the ICU. COVID patients had complicated clotting and bleeding problems, often occurring simultaneously. The circuit had to change intermittently, or there would be heavy bleeding. For the transplant team, the same 2 fellows had to manage both the donor and implant surgeries and often before completing the implant, another donor would be on the horizon.

June 2020

We reached the peak of what now appeared to be the first wave of COVID ECMO patients. We had cannulated more than 30 COVID patients, with more than 10 ECMOs in the ICU at one time at the worst. The survival data on decannulation in Toronto was over 60% for that cohort. Longer term survival was yet to be seen.

The surgical fellows managed many of the COVID cases complications including cavitating/cystic lung lesions, which could progress into necrotizing pneumonitis with superimposed secondary infections. Erosions into blood vessels resulted in hemoptysis and hemothoraces. There were many pneumatoceles and pneumothoraces. This resulted in many regular bronchoscopies, multiple chest drains - blocking and unblocking. Initially, we avoided tracheostomies and any potential aerosol-generating procedures. As patients survived longer, we had no option but to perform percutaneous tracheostomies on them bedside (while heparinized, as they clotted easily if off heparin while on ECLS) to avoid contamination of the ORs.

I was involved in several assessments of COVID cases for lung transplant. Unfortunately, in many cases, the decision to consider transplant came too late and the potential recipients were severely deconditioned or succumbed to complex resistant secondary infections. The programme and fellows were nevertheless involved in the design of international guidelines for lung transplantation. As we approached summer, COVID numbers seemed under control and, ultimately, we decannulated our last COVID ECMO patient.

July - August 2020

Time flew by as the programme resumed in full swing in these two months and more donor retrievals were performed. I returned to performing re-do lung transplants. The training in Toronto was so exceptional and the fellows 'rose to the occasion' as the situation required them to. Looking back, I did not know how I managed to handle some of the situations. Often, there was little time to worry but to just do it!

I continued my duties and performed lung transplants till the very last week of August and was glad to be able to catch the last regular flight from Toronto to Singapore. I felt like I left a part of me in Toronto, or perhaps a part of Toronto remained in me. The experience has thoroughly enriched my growth and experience as a surgeon, and many strong bonds were formed in such time of crisis. It was bittersweet to have had personal accomplishments in the backdrop of many lives lost, yet many lives saved too.

How could I describe the feeling and experience there? Going to work in knee-deep snow, not knowing when you will see your bed again, flying on a jet as a snowstorm raged, braving a street protest to get to the hospital and braving the trip at the back of ambulance with a 120kg COVID patient. There were joys of seeing a 9-year-old on the waiting list for years suddenly running again, working together with fellows from different countries and finally seeing oneself as an equal amongst the world's best. Given a chance, I would do it all again within a heartbeat and without batting an eyelid!

The Ongoing Pandemic

By November 2020, I returned safely to Singapore. I heard news of the second wave in Toronto. Knowing how amazing the team in Toronto is, I have every confidence they will rise to the occasion yet again, and hopefully, so will I when the time comes.

IN THE SPOTLIGHT

Outcomes of Randomised Clinical Trials of Interventions to Enhance Social, Emotional, and Spiritual Components of Wisdom: A Systematic Review and Meta-analysis

EE Lee, KJ Bangen, JA Avanzino - 2020

Key takeaways:

- Wisdom is a human trait with specific components such as prosocial behaviour, emotional regulation, spirituality, self-reflection, social decision-making, acceptance of uncertainty and decisiveness. Studies show that wisdom is associated with positive outcomes such as improved physical and mental health, happiness and lower level of loneliness.
- The idea that wisdom is adaptive, and could increase with age and personal experience allows for interventions that could potentially modify wisdom-type traits and improve wisdom-relevant brain function.
- Through effective psychosocial interventions aimed to enhance wisdom, individuals and societies may benefit from the improved well-being and health. These could include healthy stress-coping mechanisms and reduced destructive behaviour such as eating disorders and bullying.
- Wisdom components appear to share similar brain regions specifically the prefrontal cortex and limbic striatum. Damage to these areas led to a loss of function in components of wisdom without impairing cognitive abilities.



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Our Transplantation Journey

The **SD Transplant Centre Commemorative Book "Gift of Life, Gift of Hope"** includes stories of strength and resilience from our transplant patients. It also features sharings from healthcare professionals who are instrumental to the progress of transplant in SingHealth. Through the accounts and stories, we hope that they serve as an inspiration and testament to the transformative gift of hope in transplant!

Scan the QR code to read this book

