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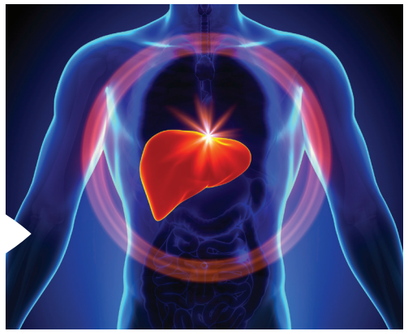

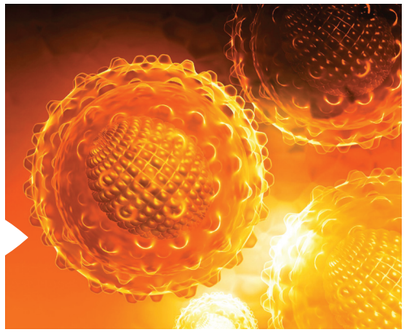

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NUCOT OVERVIEW

The National University Centre for Organ Transplantation (NUCOT) is a one stop Centre dedicated to the care of patients undergoing kidney, liver and pancreas transplants. Established in 2008, NUCOT brings together an expert team of doctors from various departments at the National University Hospital (NUH) including transplant physicians, surgeons and intensivists, nurses and allied healthcare professionals, all working together to provide expert care for organ transplant recipients and donors. Helmed by Co-Directors, Prof KK Madhavan and Prof A Vathsala, together with the Medical and Surgical Directors, NUCOT has grown from strength to strength to become today the leading transplant centre performing the highest number of solid organ transplants in Singapore.

KIDNEY TRANSPLANT: To put the history of solid organ transplant into perspective, a little more than two years after NUH opened its doors for patient care in 1985, the first kidney

1st Live Donor Kidney Transplant at NUH 1st Pediatric Kidney Transplant in Singapore 1st Deceased Donor Kidney Transplant at NUH	1987 1990	 1st Deceased - Donor Liver Transplant in Singapore 1st Paediatric Liver Transplant in Singapore
1st Deceased Donor Paediatric Kidney Transplant in Singapore	1995	1st Reduced Liver Graft 1st Live Donor Liver Transplant in Singapore 1st Split Liver Transplant in Singapore
	2000	1st Right Lobe graft from a Live Donor
1st Combined Bone-marrow and Kidney Transplant in Singapore	2005	
1st Live Donor Kidney Transplant across ABO and HLA incompatibility in Singapore	2010	
1st Altruistic Non-directed Donor Kidney Transplant in Singapore 1st Live Donor Paired Exchange Kidney Transplant in Singapore	2015 2017	1st Simultaneous Pancreas and Kidney transplant performed in Singapore 1st Altruistic Non-directed Donor Liver Transplant in Singapore

Solid Organ Transplants performed in Singapore are kidney (live and deceased), liver (live and deceased), pancreas, heart and lung.

transplant was performed at NUH on 5th October 1987. The patient, under the care of Prof Evan Lee, then Head of Nephrology at NUH, underwent a live-donor kidney transplant from his sister. The surgeries for donor and recipient were performed by Prof Foong Weng Cheong and Prof Abu Rauff. Over the years, kidney transplantation at NUH has grown in numbers, scope and complexity. The first paediatric kidney transplant in Singapore was performed at NUH in 1989. As the only centre for kidney transplants for children in Singapore, the programme has grown under the able leadership of paediatric nephrologist of Prof Yap Hui Kim. Other notable firsts in kidney transplantation for Singapore at NUH were the first combined bone marrow and kidney transplant in 2005, the first HLA and Blood group incompatible kidney transplant in 2009 and the first Paired Live Donor Kidney Exchange in 2015. Today, the multidisciplinary kidney transplant team at NUCOT manages over 100 new referrals for kidney transplant and performs over 40 new kidney transplants annually with outcomes surpassing international standards.

LIVER TRANSPLANT: On 29th September 1990, a pioneering team at NUH made history with the first deceased donor liver transplant performed in Singapore. This patient is still alive 27 years later with a functioning liver transplant. This milestone was soon followed by the first pediatric liver transplant performed on 8th March 1991 by Prof Prabhakaran. He, together with Prof Quak Seng Hock went on to establish the only paediatric liver transplant programme in Singapore in the ensuing years. In addition, the liver transplant teams at NUCOT have scored many firsts in Singapore, including the first live donor liver transplant in 1996, the first split liver transplant in 1997 and the first altruistic non-directed live-donor liver transplant performed in 2016. With these milestones, the liver transplant team has gained the prestige of being the highest volume liver transplant centre in Singapore, performing over 80% of the liver transplants nationally. Moreover the success rates rank among the best from international registries.

Pancreas transplant is yet another pioneering transplant for Singapore, on 13th September 2012, the first simultaneous pancreas and kidney transplant was performed at NUCOT for a young patient with Type I diabetes mellitus and kidney failure on dialysis. With this surgery, the patient was cured of both diabetes and kidney failure overnight and has remained insulin and diabetes free subsequently. This achievement is yet another testament to the success of solid organ transplantation and the efforts of the multidisciplinary transplant team at NUCOT to give a new lease of life to patients with organ failure.

Currently, more than half of all solid organ transplants performed at restructured hospitals in Singapore are performed at NUCOT. NUCOT is also a major referral centre for complex tertiary care, with patients being referred from all hospitals in Singapore and from overseas centres including those from Brunei, India, Indonesia, Malaysia, Myanmar, Sri Lanka, United Arab Emirates and Vietnam, to name a few. NUCOT is the only transplant centre in Singapore which hosts both paediatric and adult organ transplant services under one roof.

In addition to its clinical services, NUCOT is a key driver for training and research in transplantation. It is accredited by the International Society of Nephrology for training in kidney transplantation and hosts fellows from Singapore and throughout Asia for specialty training in both kidney and liver transplantation. Given the excellent long-term survival after transplantation in its clinical programme, research in transplantation at NUCOT is centered on the signature of chronic allograft survival, with interest focused on antibodies that mediate chronic alloantibody mediated rejection in kidney transplants and Cytokines and Immune Cellular profiles that mediate immunological quiescence in the presence of Anti HLA antibodies.

With the clinical, educational and research efforts in organ transplantation, NUCOT is in the forefront of advancing the care of organ failure patients in Singapore and beyond.

TNP PICTURE: **BENJAMIN SEETOR**

SUCCESS: **Transplant patient Shawn Huang (in grey) with (clockwise, from top left) Dr Tiong Ho Yee, Dr Victor Lee, Assoc Prof Krishnakumar Madhavan, transplant coordinator Manjit Kaur and Prof A Vathsala.**

‘I have been given my life back’

MR SHAWN Huang, 29, is the first person in Singapore to receive a new kidney and pancreas in a simultaneous 5½ hour transplant here on Sept 13.

Mr Huang suffered from Type 1 diabetes since he was 14. His kidneys failed in April and he had to go on dialysis.

“I was thirsty all the time and was drinking a lot of water then,” he said. It was finally diagnosed when he went for a medical check-up.

“Every night I had to rush home to do dialysis. This was on top of injecting myself with insulin every morning and evening,” he said.

Mr Huang was using peritoneal dialysis, where a special sterile fluid is introduced into the abdomen through a permanent tube in his peritoneal cavity.

This fluid circulates to draw impurities from surrounding blood vessels in the peritoneum, and drains them from the body.

Feeling tired all the time because of his condition, and the fact that he had to reach home at a certain time at night to do the dialysis, Mr Huang quit his job in sales and became a student at a private school.

It was his youth, the type of diabetes and his kidneys failing that made him the perfect candidate for the first kidney-pancreas transplant.

He said: “I was sleeping when I got the call that they had found a donor and I was to be the first to receive both kidney and pancreas. I thought I was dreaming.”

It has been 35 days since his landmark surgery and Mr Huang said apart from taking his three types of medication, he no longer needs insulin shots or dialysis.

“It’s like a rebirth. I have been given my life back and I have the donor, his family and the doctors to thank,” he said.

Prof Krishnakumar MADHAVAN

MBBS, MS, FRCSEd, FRCS (Gen), FCPS (Hon)
Co-Director, Liver and Pancreas Transplantation, National University Centre for Organ Transplantation, National University Hospital
Senior Consultant, Division of Hepatobiliary and Pancreatic Surgery , University Surgical Cluster, National University Hospital
Professor, Yong Loo Lin School of Medicine, National University of Singapore

Prof Krishnakumar Madhavan joined the University Surgical Cluster as an Associate Professor in University Surgical Cluster, National University of Singapore. He is also Head and Senior Consultant of Division of Hepatobiliary and Pancreatic Surgery and Director, Liver Transplant Programme, National University Hospital.

After initial schooling and undergraduate medical education in India, Prof Madhavan did his MS in General Surgery at the Post-Graduate Institute of Medical Education & Research. After doing the FRCS from the Royal College of Surgeons of Edinburgh, he went for further Higher Surgical Training in the UK and after successfully completing this training, was appointed in 1996, a Consultant General and Transplant Surgeon at the Royal Infirmary of Edinburgh. After 11 years in that post, he joined the NUS/NUH.

In addition to all aspects of liver transplantation, he has extensive experience in kidney and pancreatic transplantation and also the whole spectrum of benign and malignant hepatobiliary and pancreatic surgery. He was also deeply involved in surgical training over the years and till 2007 was the Deputy chair of the surgical training committee for the South east of Scotland and tutor and convener for the Basic Surgical skills course of the RCSEd. He has also been an examiner for the FRCS, AFRCS and MRCS exams and is also on the panel of examiners for the exit FRCS examination (intercollegiate).

His current research interests include the role of chemoembolisation in the management of hepatocellular carcinoma, management of cholangiocarcinoma, role of portocaval shunting in Piggy-back liver transplants, various aspects of live donor liver transplantation and saphenovenous peritoneal shunting in intractable ascites due to cirrhosis of liver. He is a co-author of many papers pertaining to his field of interest.

Prof A. VATHSALA

BS (USA), MD (USA), FRCP (Edinburgh), FAMS (Singapore)
Co-Director, Renal Transplantation, National University Centre for Organ Transplantation, National University Hospital
Head and Senior Consultant, Division of Nephrology, University Medicine Cluster, National University Hospital
Professor, Yong Loo Lin School of Medicine, National University of Singapore

Prof A Vathsala is a Co-Director and Senior Consultant at the National University for Organ Transplantation at the National University Hospital. She is also a Professor of Medicine at the National University of Singapore.

She graduated with a Bachelors of Science in the Premedical Curriculum from Auburn University, Auburn, Alabama, studied Medicine at Vanderbilt University School of Medicine, Nashville, Tennessee, USA and completed her training in Internal Medicine in Singapore. She obtained her Membership in the Royal College of Physicians (United Kingdom) followed by additional training in renal medicine at the Singapore General Hospital and kidney Transplantation at the University of Houston, Texas and the Cornell University School of medicine, USA. She is a Fellow of the Royal College of Physicians of Edinburgh and a Fellow, Academy of Medicine, Singapore.

She was the founding President of the Society of Transplantation (Singapore) and Current President of the Asian Society of Transplantation. She is also a member of the Board of Directors of the National Kidney Foundation, Singapore. She was the recipient of the National Outstanding Clinician Award for her contributions to transplantation in Singapore in 2010. She also led the team that garnered the National Outstanding Team Award for their work on prevention of progression in diabetic kidney disease in primary care in 2016. She has research interests in many areas in the field of transplantation including cellular and molecular signatures of chronic allograft survival, immunosuppression, pharmacokinetics and pharmacogenomics and has a special interest in preventive nephrology, lupus nephritis and glomerulonephritis.

LIVER TRANSPLANTATION AT NATIONAL UNIVERSITY CENTRE FOR ORGAN TRANSPLANTATION

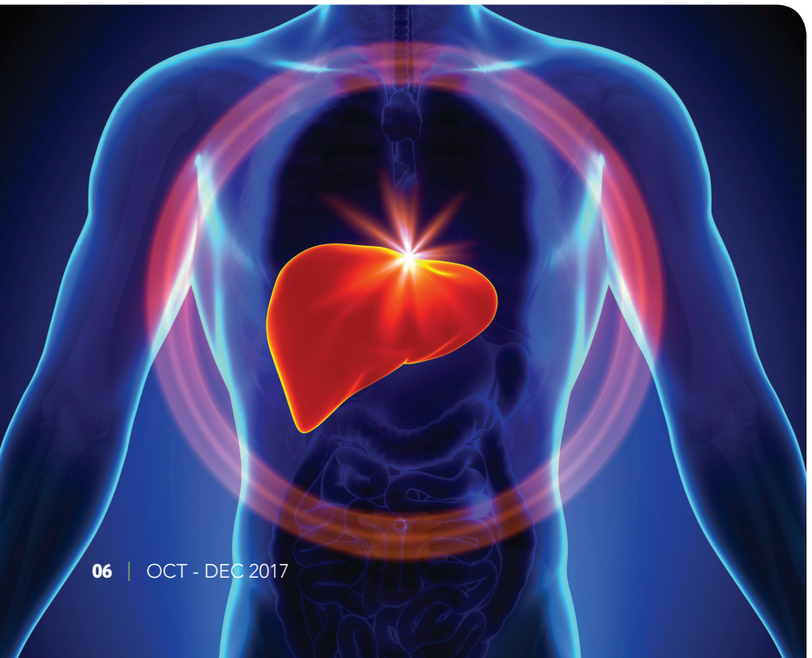
WHO NEEDS A LIVER TRANSPLANT?

Chronic liver disease (CLD) and liver cancer are the most common indications for a liver transplant in adults in Singapore. In children, the common indications are biliary atresia and metabolic diseases (Table 1). Liver transplantation is aimed at restoring health and improving survival, but unlike other operations, limited organ availability restricts the number of people who receive transplants.

The Model for End-stage Liver Disease (MELD) score (score based on measurements of bilirubin, creatinine, and International normalised ratio — www.unos.org/resources/MeldPeldCalculator. asp) statistically quantifies the risk of death in adult patients with advanced liver disease. In Singapore, the allocation policy is through the MELD score, which is an 'urgency' based model that allocates livers to the patients with the highest pre-transplant mortality. Likewise, Paediatric End-stage Liver Disease (PELD) is used in children. Although there are no strict age restrictions for liver transplants, the risks are higher in infants less than 10kg and adults over age of 70. The national cut off for listing for deceased donor liver transplant (DDLT) is 70 years. HIV is no longer a contraindication for patients with controlled viral count. In patients with alcohol-related liver disease a six-month abstinence rule applies to reduce risk of recidivism and allow improvement in liver function.

THE NEED FOR LIVER TRANSPLANTATION IN SINGAPORE

It is estimated that the average worldwide need for liver transplant is 10 - 11 per million population (pmp). It is likely to be higher in Singapore due to the higher prevalence of Hepatitis B infections, and the universal surveillance program resulting in the detection of Hepatitis B and C carriers, and liver cancers. Liver cancer is the 5th most common cancer in males in Singapore. The current 5 pmp rate of deceased donor referral does not meet the national requirement for liver transplants.



INDICATIONS FOR LIVER TRANSPLANTATION

ACUTE/SUBACUTE

Drug induced:

- Direct toxicity (for example, from paracetamol or herbal remedies)
- Idiosyncratic (for example, from isoniazid or nitrofurantoin)
- Viral hepatitis
- Acute fulminant autoimmune hepatitis
- Acute Budd-Chiari syndrome not amenable to radiological treatment
- Metabolic disease (such as Wilson's disease or neonatal haemochromatosis)

CHRONIC (usually with cirrhosis and liver decompensation)

- Chronic hepatitis B or C virus infection
- Alcohol related liver disease
- Malignancy (such as hepatocellular carcinoma, haemangioendothelioma, or, rarely, neuroendocrine tumour)
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Biliary cirrhosis, usually primary
- Primary Sclerosing cholangitis
- Biliary atresia
- Alagille's syndrome
- Haemochromatosis, Wilson's disease, or α-1 antitrypsin deficiency
- Gaucher's disease, glycogen storage disease, Crigler-Najjar type 1, familial intrahepatic cholestasis
- Chronic Budd-Chiari syndrome
- Cryptogenic cirrhosis
- Familial amyloidosis

MISCELLANEOUS

- Polycystic liver disease, Caroli's disease, congenital hepatic fibrosis
- Portopulmonary hypertension, hepatopulmonary syndrome

Table 1: Indications for liver transplantation

The Human Organ Transplant Act (HOTA) governs organ donations in Singapore and is applicable to Singaporeans and permanent residents. HOTA is an 'opt-out' legislation where corneas, kidneys, heart and liver can be removed for transplantation upon death. Organs cannot be removed under HOTA if the individual is below 21 years of age, was of unsound mind or had opted out during life.

Liver transplant was initiated in Singapore in 1990 and despite early adoption of liver transplant in Singapore, deceased donation remained low resulting in low volume of transplants. The waiting list mortality was high and referral rates were low leading to a perpetual cycle of low volume, high waitlist mortality and low referrals.

The critical shortage of available livers and expanding indication for liver transplantation has led to several surgical innovations. Split liver transplantation is a useful strategy to increase the graft supply especially so in Asia where cultural barriers limit donations after brain death. NUH was the second centre in Asia and first in South-East Asia to perform a split liver transplant in July 1997.

Another surgical innovation to alleviate organ shortage is living donor liver transplant (LDLT). Although the concept of LDLT originated started in Western countries, much of the technical innovations and progress was made in Asia. In NUH, the LDLT programme was started in 1996 for paediatrics recipients, and included adult recipients since 2002.

Despite the new legislation, HOTA, in Singapore, the utilisation of cadaveric donor livers showed no increase in the 3 years following the legislation in 2004. NUH then expanded our donor criteria to include marginal donors, thus potentially increase the availability of deceased donor livers to meet our waiting list demands. This strategy paid off with higher utilisation rates and without compromising recipient outcomes. From 2001-2007, the utilisation rate for deceased donors actualised was 31.6%. A one-fold increase was seen from 2008-2011, as the rate increased to 73.8%.

There is an increase in the deceased donor and living donor liver transplant activity since 2006 (Table 2) but it is still falls short in meeting the population's needs.

Year	Total	NUH	%
2007	16	9	56.0
2008	26	15	57.7
2009	32	20	62.5
2010	27	17	63.0
2011	21	14	66.7
2012	22	12	54.6
2013	36	27	75
2014	35	29	83
2015	44	37	84
2016	39	28	72

Table 2: Public sector Liver Transplants in Singapore

LIVER TRANSPLANTATION OUTCOMES AT NATIONAL UNIVERSITY CENTRE FOR ORGAN TRANSPLANTATION (NUCOT)

To date, our Centre has performed more than 340 successful adult living and deceased donor liver transplantations. We continue to provide post-transplant care and medical follow-ups at our Specialist Outpatient Clinic for over 1,500 liver patient visits annually.

Based on our latest survival data over the past 10 years (2007 – 2016, n=133), our short-term post-transplant recipient survival rates are comparable to the international standards for both LDLT and DDLT. In terms of long-term post-transplant recipient survival rates, we are doing better than the international standards with 5-years survival of 81% and 85% for DDLT and LDLT respectively.

We have also developed capabilities of performing complex transplants such as living donor liver transplant for porto-mesenteric thrombosis, Budd Chiari Syndrome, and simultaneous organ transplants (www.nuh.com.sg/nucot).

The key to the success of liver transplantation is the multidisciplinary effort in the truest sense with its contribution of surgeons, anaesthesiologists, hepatologists, organ donation coordinators, intensivists, radiologists, infectious disease physicians, pathologists, immunologists, psychiatrists, blood bank doctors, pharmacists, OT/ICU/Ward nurses and therapists, social workers, nutritionists and all the support staff who come together for the common cause of saving and improving the lives of these critically ill patients. The other key aspect is the ability to manage possible ensuing complications, with support of interventional radiology and endoscopy services – thereby improving graft and patient survival.

Dr IYER Shridhar

MBBS, MS, FRCS, FAMS
Senior Consultant, Liver Transplantation, National University Centre for Organ Transplantation, National University Hospital
Senior Consultant, Division of Hepatobiliary and Pancreatic Surgery, University Surgical Cluster, National University Hospital

Dr Shridhar Iyer graduated from Grant Medical College, Bombay University, India in 1994. He then underwent training in Surgical Oncology at the renowned Tata Memorial Hospital; Mumbai. He was admitted as a Fellow to the Royal College of Surgeons of Edinburgh, UK in 1999. He moved to Singapore in 2001 to pursue his interest in hepatobiliary surgery and liver transplantation. He completed advanced specialty training in General Surgery at the National University Hospital in 2005 and admitted as a Fellow to the College of Surgeons, Academy of Medicine of Singapore.

As a recipient of the Human Manpower Development Programme (HMDP) scholarship in 2006, Dr Iyer went to pursue a Fellowship in Liver surgery and Liver transplantation at the Chang Gung Memorial Hospital, Taiwan, renowned for its living donor liver transplantation programme. Under the mentorship of Professor Chen Chao-Long he trained in different aspects of liver, biliary surgery and living donor liver transplantation.

His research interests are liver regeneration mechanisms, ischemia reperfusion injury of liver and different aspects of living donor liver transplantation. He has several peer-reviewed publications in scientific journals and presentations at international meetings. He has received a best paper award at World Congress of Digestive Surgery in 2005 at Yokohama, Japan.

KIDNEY TRANSPLANTATION AT NUCOT TODAY

Singapore has a high incidence of kidney failure and its treatment to the patient and the nation very expensive and hence unsustainable. It was in this context, that a team of nephrologists and pioneering surgeons led by Prof Chan Kong Thoe of the University of Singapore Surgical Unit proposed kidney transplantation to be a viable sustainable alternative. Prof Chan and the surgeons established an Animal Experimental Surgery Laboratory in 1969 and gained experience on kidney transplant procedures in canine models. By 1970, the team was poised for the clinical programme. Upon approval from the Ministry of Health, on 8th July 1970, the first deceased donor kidney transplant (KTX) was performed by Prof Chan on a patient with end stage kidney disease (ESKD) on dialysis. This first transplant was a resounding success and the patient lived on for over two decades without dialysis, demonstrating that KTX was the best treatment for patients with kidney failure.

Since these early beginnings, two KTX centres have been established in the public sector in Singapore. The KTX programme at the National University Hospital (NUH) was established in 1987 with the first Live-donor KTX performed on 5th October 1987. Subsequently, Deceased donor KTX, live and deceased-donor paediatric KTX and extended criteria (ECD) deceased donor KTX have all contributed to the increased numbers of KTX performed at NUH (Figure 1). Transplant trained nephrologists and urologists, together with a team of trained transplant coordinators, pharmacists, dietitians and social workers, evaluate ESKD patients for suitability for transplantation, evaluate potential kidney donors for suitability for donation, prepare recipients and donors for their surgeries and manage them after the surgeries. Every year, the National University Centre for Organ Transplantation (NUCOT) manages over 100 new referrals for KTX and performs over 40 new KTX. NUCOT is also a referral centre for live donor kidney transplantation from Asia and beyond, and manages complex post-transplant cases from other centres across Singapore. Annually, NUCOT manages nearly 5,000 patient visits by kidney transplant recipients and their live donors or those undergoing evaluation for transplantation or donation.

Live-Donor Kidney Transplantation comprises nearly 48% of the KTX performed at NUH. Any patient with ESKD without cancer or serious heart or cerebrovascular disease can be considered for live-donor KTX as long as they have a suitable and willing live donor. The main causes of ESKD leading to Live-donor KTX at NUCOT are Chronic glomerulonephritis (65%), Diabetic Kidney Disease (14.2%) and Hypertensive Kidney Disease (4.9%). With modern immunosuppression, it has become possible to perform KTX successfully across genetically unrelated donors including spouse, friends and even sisters-in-law or brothers-in-law. More than a third of the Live-donor KTX are hence from emotionally related donors, whereas the remainder are genetically related. Potential Live kidney donors are thoroughly evaluated, and upon Ethics Committee approval, undergo donation surgery through a laparoscopic approach. In NUH all are generally laparoscopically removed. The donor surgery scar is minimal and donors are often discharged on the 3rd post-operative day to be rehabilitated post donation to a full and active life. As NUH is the only transplant centre in Singapore that performs Paediatric KTX, children transitioning into adulthood and young adults with congenital kidney conditions are specially evaluated and managed for their kidney transplant.

Highly complex KTX such as those across blood group incompatibility (eg. Blood group A or B donor donating to Blood group O recipient) or KTX in patients with antibodies against their histo-incompatible donor has become a niche area of expertise at NUCOT. Since 1987, these complex cases constitute more than 25% of the Live-donor KTX performed at NUCOT. With our careful immunological evaluation, the treatment regimen is tailored to the patients' profile. In addition, with the multi-disciplinary care and coordination, attention to prophylaxis and prevention of infections, and management of other long term complications, our success rate surpasses international standards as shown (Figure 2).

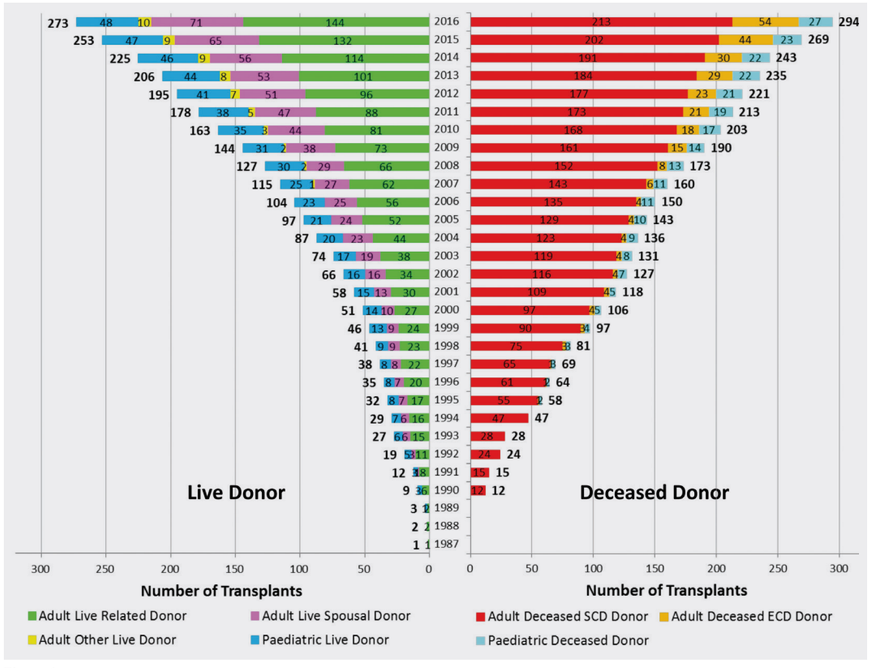
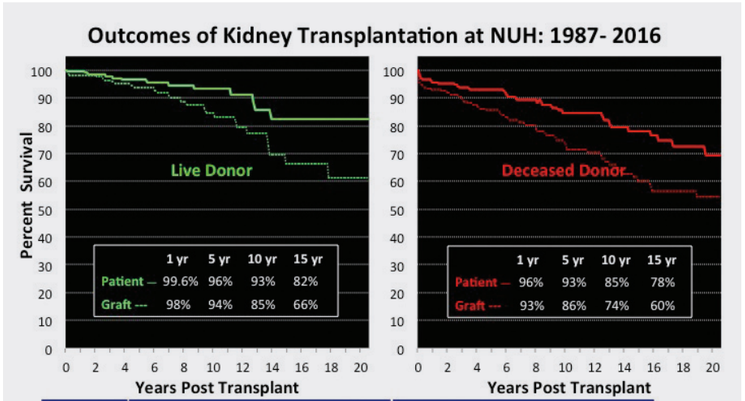


Figure 1.

Deceased-Donor Kidney Transplantation: Kidneys can be procured from individuals who have died in ICUs after brain death or circulatory death according to laws governing organ donation in Singapore. NUCOT is only one of two centres in Singapore that performs kidney transplants from deceased donors; for children, NUH is the only centre in Singapore that performs paediatric KTX from deceased donors. Due to the scarcity of deceased donors, criteria for suitability to receive these transplants are stricter and follow Ministry of Health guidelines. The average waiting time for transplant for those waiting for a deceased donor is 9 years, a period during which ESKD patients on dialysis must remain fit to receive the transplant. There is no age restriction for deceased donors but kidneys procured from older donors need to be evaluated with a kidney biopsy prior to implantation. For many such kidneys, the surgical team performs dual kidney implantation into a single patient, so as to avoid discarding even these older kidneys and to give the best possible outcome for patients. Despite a high proportion of kidneys now coming from such older donors, the success rate of Deceased-donor KTX are excellent as shown.



	Live Donor			Deceased Donor		
	1-year	5-years	10-years	1-year	5-years	10-years
US (SRTR) Patient [1]	99%	92%	78%	96%	84%	63%
US (SRTR) Graft[1]	97%	85%	62%	92%	73%	47%

[1] United States OPTN/SRTR 2012 Annual Report

Figure 2.

In summary, KTX is the treatment of choice for patients with kidney failure. The real limitation is the number of kidney donations from Live and Deceased donors in Singapore. More education on the potential of kidney donation to give life to patients with ESKD to the public is hoped to increase donation rates. With its multidisciplinary team, NUCOT is at the forefront to advance and champion kidney donation and transplantation.

Prof A. VATHSALA

BS (USA), MD (USA), FRCP (Edinburgh), FAMS (Singapore)
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Head and Senior Consultant, Division of Nephrology, University Medicine Cluster, National University Hospital
Professor, Yong Loo Lin School of Medicine, National University of Singapore

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ADVANCES IN LIVING DONOR KIDNEY TRANSPLANTATION AT NATIONAL UNIVERSITY HOSPITAL

OUR PROGRAMME HAS BEEN SINGLE-MINDED IN OPTIMISING AND IMPROVING LIVING DONOR SAFETY. LIVING KIDNEY DONORS ARE MONITORED HOURLY IN HIGH DEPENDENCY WARDS FOR 12 HOURS POST-SURGERY. THE USE OF CLIPS ONLY FOR THE CONTROL OF DONOR RENAL ARTERY HAS BEEN ELIMINATED FROM THE SURGERY, CONVERTING TO LAPAROSCOPIC VASCULAR STAPLER USE. WITH THESE CHANGES, PATIENT SAFETY IS INCREASED.

The first kidney transplant was performed in Singapore on 8 July 1970. Over the next 6 years, only 17 deceased donor (DD) kidney transplants were performed[1]. A living donor (LD) transplant programme was subsequently initiated in Singapore in 1976. For the last 38 years since the first kidney transplant, there have been various legislative initiatives, including the Human Organ Transplant Act (HOTA) to increase the number of transplants. As one of the two public hospitals which performs both DD and LD kidney transplants, National University Hospital (NUH) has kept pace with both surgical and medical advances in the field of kidney transplantation. This enables it to serve as an academic medical center, providing the advanced quality medical care for all patients with kidney failure. This article aims to provide an overview of the surgical advances achieved at the National University Center of Organ Transplantation (NUCOT) in the field of living donor kidney transplantation, with the aim of promoting living organ transplantation to relieve the organ shortage.

ADVANCES IN LIVING KIDNEY DONOR SURGERY

Living kidney donation represents a crucial strategy to address the ever-present problem of organ shortage. Kidney donation traditionally utilizes the open surgical approach with a flank incision. With the advent of minimally invasive surgery, the first laparoscopic donor nephrectomy was performed by Dr Ratner in the United States in 1995. Minimally invasive donor nephrectomy has since been shown to lower the disincentives for kidney donation, thereby promoting numbers of living kidney transplantation[2]. At NUH, Prof Li Man Kay started our hand assisted donor nephrectomy in 2002 and good outcomes were reported[3]. Our programme has been single-minded in optimising and improving living donor safety. Our living kidney donors are monitored hourly in our high dependency wards for 12 hours post-surgery. The use of clips only for the control of donor renal artery has been eliminated from the surgery, converting to laparoscopic vascular stapler use[4]. With these changes, patient safety is increased for the programme at NUH. In addition, we have since worked to further reduce the surgical morbidity of living kidney donation by performing pure laparoscopic donation with the option of vaginal extraction of the donor kidney, resulting only 3 'key holes' on the patient! (Figure 1)[5]. In addition, our work on donor safety has been

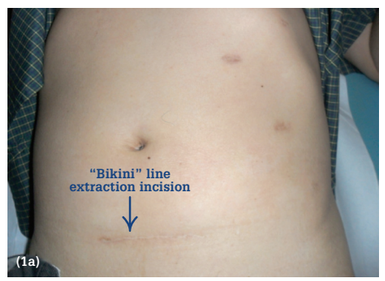

Figure 1a: Patient who has undergone laparoscopic donor nephrectomy with a conventional "bikini" line extraction incision.

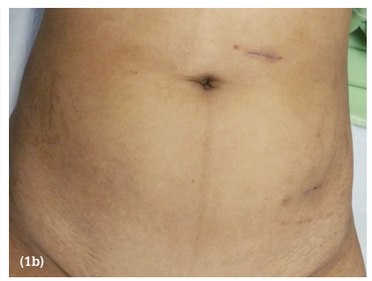

Figure 1b: Patient with option of vaginal extraction does not have "bikini" line extraction incision.

extended to studying and confirming the limited impact of donation on the subsequent kidney function of kidney donors[6-8], as well as finding the best method of assessing kidney donor renal function such as incorporating the use of donor kidney volume on computer tomographic measurements[9]. The quality care given to our living kidney donors are now paying off, with NUHS achieving highest consecutive annual numbers of living kidney donation for the years since 2009.

ADVANCES IN LIVING KIDNEY TRANSPLANT RECIPIENT SURGERY

NUCOT has recently reported excellent short and long-term clinical outcomes of our programme[10]. The 5-year and 10-year graft survivals for 225 LD transplants performed at NUHS were 93.6% and 84.7% respectively. 5-year and 10-year patient survivals for LD transplants performed at NUHS were an excellent 96.5% and 93.2%.The grafts' projected overall half-lives were 21.5 years for LD transplants. These results compare favorably with the 10-year survival rates of 40% and 58% for DD and LD grafts reported by the United States Renal Data System (USRDS) in 2010. Proficient surgical expertise is part of the equation crucial in delivering good outcomes that exceed international standards. In addition to good functional outcomes, surgical morbidity of living kidney transplant patients has been reduced by our wound management programme called STAR – Stentless, Tubeless, Apposed, Renal – Transplantation[11]. By perfecting our surgical technique, the use of ureteric stents, wound drains and skin met clips can be avoided in the majority of our living donor transplant recipients. As such, morbidity and pain from the surgical procedure can be greatly reduced without any safety compromise (Figure 2). Our surgical technical abilities are also recognised in peer-reviewed reporting of our good outcomes for living kidney transplantation of in situations that were previously regarded as contraindication like, multiple arteries[12] in donor kidneys or patients with possible surgical complications[13].

CONCLUSION

The surgeons at NUCOT pursue advances in the surgical techniques for living kidney donor transplantation, with the sole purpose of optimising the operation's safety for each of our living kidney donor and recipient pair. We hope this persistent pursuit for surgical perfection will assure more to step forward to provide the ultimate gift of love for their loved ones suffering from kidney failure.

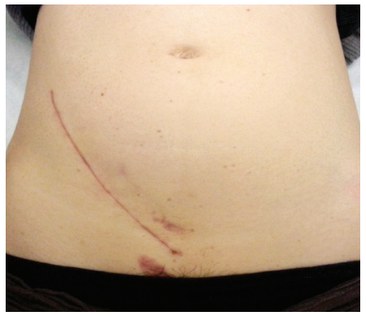

Figure 2: Photo of Living donor kidney transplant patient with STAR transplant wound management at 2 weeks after surgery.

Dr TIONG Ho Yee

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Holding several directorships in NUH, Dr Tiong Ho Yee minimally invasive endoscopic stone, cancer and reconstructive surgeries conjointly with highly technical open operations for kidney cancers and transplantations.

With comprehensive training acquired in world renowned institutions including the Cleveland Clinic, Dr Tiong reported outcomes for advanced surgical approaches such as tubeless percutaneous stone surgery, partial nephrectomy, multi-organ, dual kidney and even auto-transplantations.

Dr Tiong believes in a holistic approach to treating patients and this is reflected in his continued focus on studying the impact of cancer surgery on post-operative kidney function in addition to oncological outcomes.

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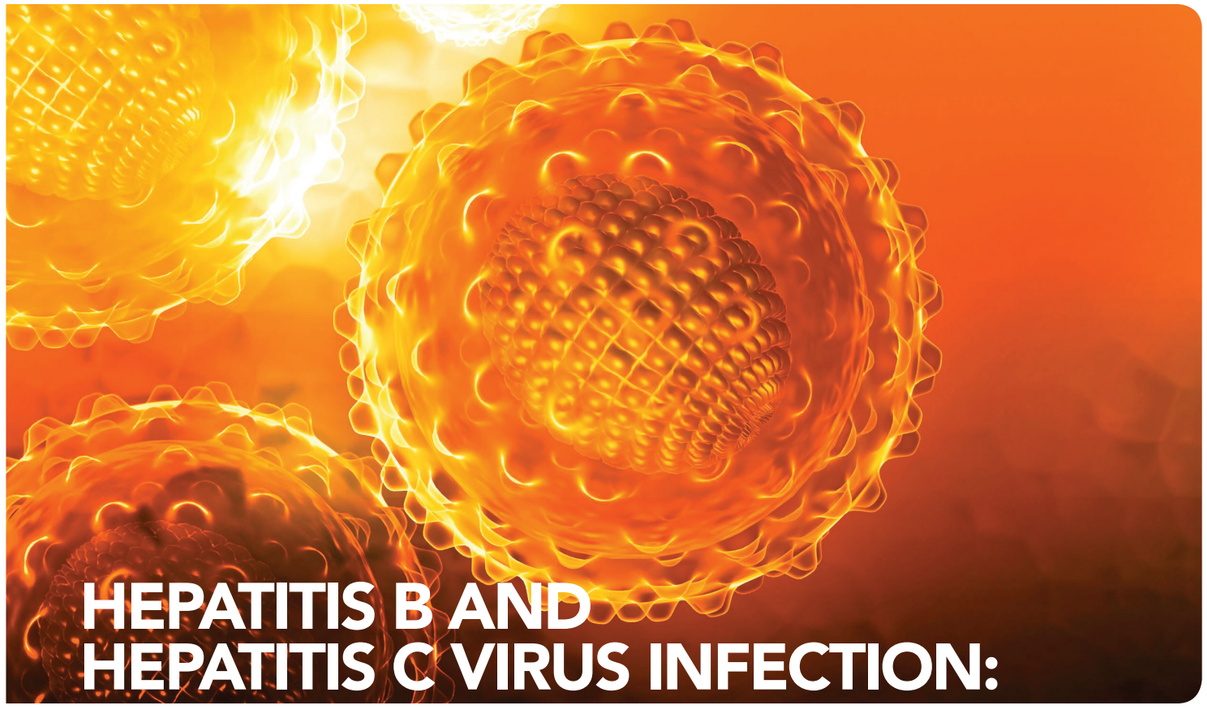


HEPATITIS B AND HEPATITIS C VIRUS INFECTION:

NO LONGER A THREAT IN LIVER TRANSPLANTATION?

Liver transplantation (LT) is now the standard of care for patients with advanced liver cirrhosis and hepatocellular carcinoma (HCC) due to hepatitis B (HBV) and hepatitis C virus (HCV) infection who are within transplant criteria. However, virus reactivation post-LT is a serious complication, which can lead to progressive hepatitis and accelerated graft loss (see Figure 1). Until effective therapies were developed, viral hepatitis was often regarded as a relative contraindication for LT compared to other chronic liver disease.

HEPATITIS B VIRUS

The first successful prophylaxis against HBV reinfection was anti-HBV immunoglobulins (HBIg), as proposed by Samuel et al. in 1993. The researchers were able to reduce the reinfection rate from 75% to 33%, and 5-year survival from 54% to 83% after LT. HBIg binds to circulating virions, blocks the HBV receptor, and

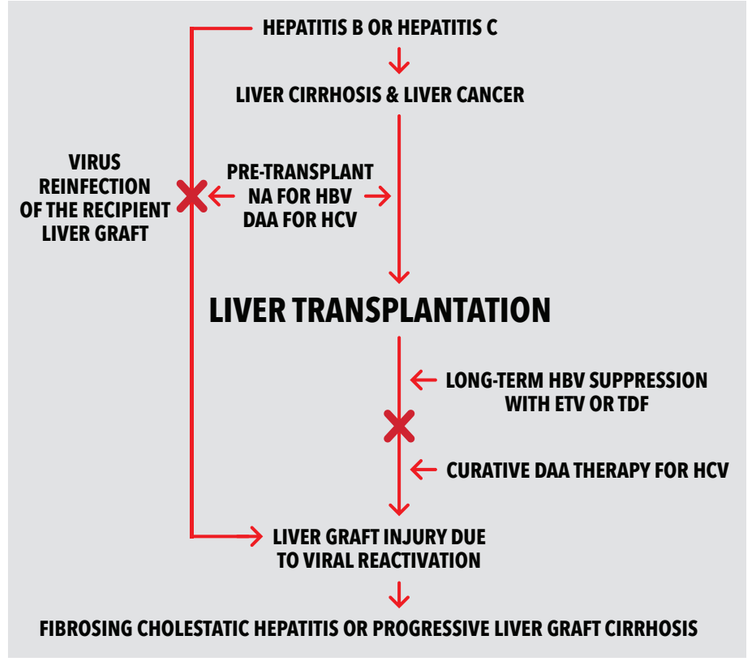


Figure 1: Schematic diagram showing the concept of hepatitis B and C virus reinfection causing liver graft loss, and antiviral therapy before and after liver transplantation.

induces antibody-dependent lysis of the infected cells. However the treatment is very expensive and inconvenient as long-term HBIg injections are needed to maintain HBV control.

The introduction of lamivudine (LAM), a nucleoside analogue (NA), the first direct oral antiviral agent against the HBV polymerase (see Figure 2) transformed the outlook of HBV infection and post-LT prophylaxis immediately. It is very effective in suppressing the viral DNA, prevent viral reactivation and is relatively free of adverse effects or drug interactions with all immunosuppressants. However, it has a significant relapse rate of 34% at 2 years, largely due to the development of LAM-resistant mutations. Thus, LAM monotherapy is not recommended as a sole modality for post-LT prophylaxis. In the western countries, HBIg is usually given in the perioperative and the short-term postoperative period while NAs are administered life-long after LT.

The new-generation of NAs, entecavir (ETV) and tenofovir (TDF), had become the sole antiviral prophylactic agent of choice in several transplant centres in Asia. Although NAs may not be as effective as HBIg in maintaining HBsAg negativity, their high potency plus low drug resistance rate meant that the viral load can be kept undetectable in the circulation, and prevent long-term graft loss.

Fung et al. evaluated 80 consecutive LT recipients and demonstrated that only one patient had positive HBV DNA after a median follow-up of 26 months with ETV alone. 18 patients had positive HBsAg but none had graft dysfunction. Another study comprising 362 patients (142 on ETV and 176 on LAM) supports the conclusion, and further demonstrate that the development of LAM-resistance (salvageable with TDF) and high viral load at LT are significant factors associated with virological rebound. Finally, a meta-analysis of 19 studies suggests that there is no significant difference between non-LAM antiviral drugs and HBIg-NA combination therapy in HBV recurrence (P=0.37; 95%CI (20.02, 0.14)) or 5-year survival [P=0.46; 95%CI (20.21, 0.10)] (see Figure 3).

HEPATITIS C VIRUS

Before the advent of direct antiviral agents (DAAs), recurrence of HCV after LT was almost universal (see Figure 1), leading to accelerated fibrosis of the liver graft. Up to 30% were cirrhotic by year 5 of LT. Interferon-based therapy have been available since the 90's, but the efficacy is poor, even with first-generation protease inhibitors (see Figure 2). The interactions with immunosuppressive agents is another major concern.

DAAs began to be used in liver transplantation in 2013-2014. Several studies had shown that DDAs cure recurrent HCV in almost all liver transplant recipients despite immunosuppression and with an excellent safety profile. In contrast to HBV, which requires life-long therapy, only 3-6 months of DAA therapy is sufficient to achieve long-term sustained virologic response in >90% of the treated patients. Also as more patients were treated and cured before LT, recurrent HCV should virtually disappear as an indication for re-transplantation.

CONCLUSION

As a result of these high efficacy antiviral therapies, there has been no graft loss or death due to HBV recurrence in the past 10 years, or due to HCV recurrence since 2014 at the National University Centre for Organ Transplantation (NUCOT). The medically challenging group to treat are those with 1) poor renal function, especially if they have genotype 3 HCV; and 2) decompensated liver cirrhosis, which may be safer to proceed with LT before treating the virus. The cost of these expensive treatments (HCV) and non-compliance to long-term therapy (HBV) continue to be major hurdles to overcome.

In theory, if all the patients with viral hepatitis are diagnosed and treated early before developing liver fibrosis, there should be almost no need for liver transplantation in this group of patients down the road. However, the sobering fact remains that 90% of the chronically infected HBV and HCV patients are not aware of their diagnosis, and <1% have received antiviral therapy. Overall, DAAs may not affect the total volume of transplantation because of the large gap between the number of candidates and the number of available organs.

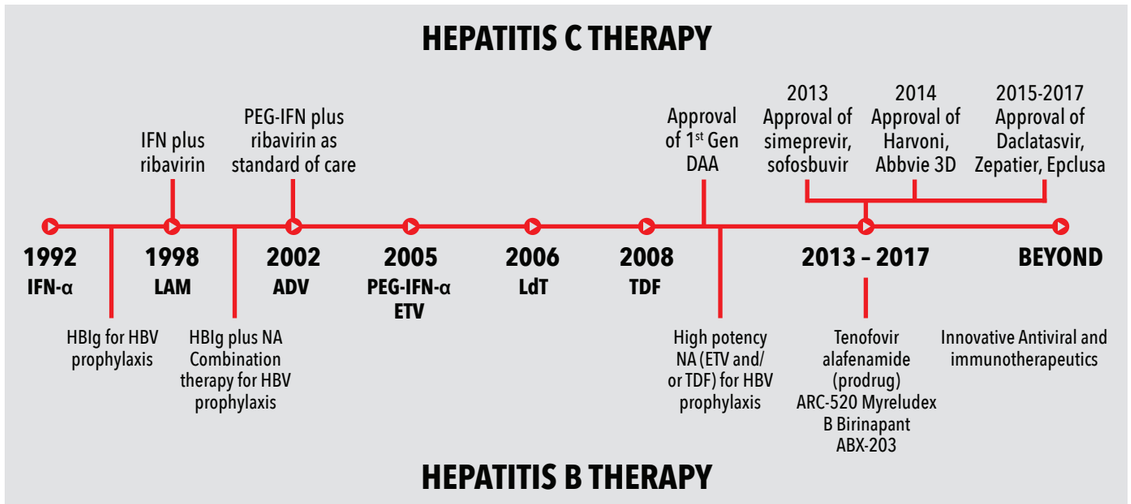
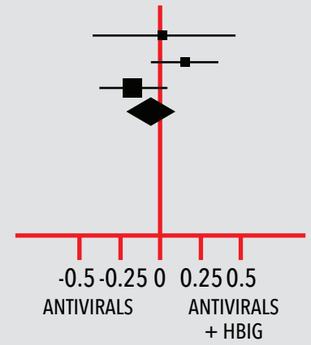


Figure 2: Rapidly evolving hepatitis B and C antiviral therapies and post-transplant prophylaxis. IFN: Interferon; HBIg: Hepatitis B immunoglobulin; NA: Nucleoside/ nucleotide analog; LAM: Lamivudine; ADV: Adefovir; ETV: Entecavir; LdT: Telbivudine; TDF: Tenofovir; DAA: Direct antiviral agents.

5-YEAR PATIENT SURVIVAL

Chun-Hui Yuan 2013	4	6	11	16	17.2%	0.02 (-0.42, 0.46)
Maria Buti 2007	17	20	9	9	24.5%	0.15 (-0.06, 0.36)
Yoshida H 2007	22	26	23	34	58.2%	-0.17 (-0.38, 0.04)
Subtotal (95% CI)		**52**		**59**	**100.0%**	**-0.06 (-0.21, 0.10)**
Total events	43		43			
Heterogeneity: $Chi^2 = 5.03$, df = 2 (P = 0.08); $I^2 = 60\%$						
Test for overall effect: Z = 0.74 (P = 0.46)						



NON-LAM ANTIVIRALS VS. COMBINATION THERAPY

Chung Mau Lo 2005	2	8	0	8	9.9%	0.25 (-0.08, 0.58)
Lewis W. Teperman 2013	0	18	0	19	22.9%	0.00 (-0.10, 0.10)
Peter W. Angus 2008	0	16	0	18	21.0%	0.00 (-0.11, 0.11)
Schiff 2007	2	23	2	34	34.1%	0.03 (-0.11, 0.17)
Xia N X 2006	1	5	3	168	12.1%	0.18 (-0.17, 0.53)
Subtotal (95% CI)		**70**		**247**	**100.0%**	**0.06 (-0.02, 0.14)**
Total events	5		5			
Heterogeneity: $Chi^2 = 4.27$, df = 4 (P = 0.37); $I^2 = 6\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						

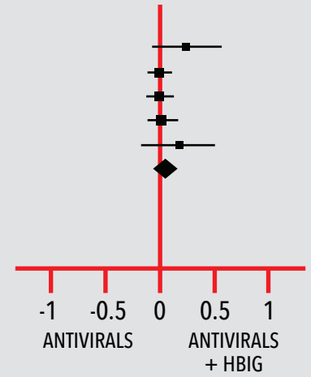


Figure 3: Antiviral drugs or antiviral drugs combined with HBIG in prophylaxis of hepatitis B recurrence after liver transplantation: (A) results of a meta-analysis: 5-year patient survival rate; (B) HBV recurrence rate: Non-LAM antivirals vs. combination therapy.
Adapted from P Wang et al. Hepatitis B Immunoglobulin after Liver Transplantation. PLOS ONE (2014); 9(8):1-9.

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UPDATE ON HEPATOCELLULAR CARCINOMA AND ROLE OF LIVER TRANSPLANTATION

Hepatocellular carcinoma (HCC) is a major cancer burden globally with an annual incidence of 782,000 cases and the second leading cause of cancer death worldwide.[1] Asia alone accounts for more than 75% of this disease burden. The main risk factor for HCC is cirrhosis as a result of underlying chronic liver diseases such as HBV, HCV, non-alcoholic fatty liver disease (NAFLD), alcohol abuse etc. However, HCC can develop in chronic hepatitis B patients without cirrhosis or even among those with past exposure of hepatitis B (HBsAg negative but anti-hepatitis B core total positive).[2] While implementation of HBV vaccination programme and availability of highly effective antivirals have resulted in a reduction in HCC cases due to HBV, an ongoing epidemic of NAFLD, which affects up to 40% of population in developed nations including Singapore, has resulted in NAFLD being the most common liver disease and HCC risk in many countries.[3,4]

A unique aspect of HCC management is both tumor stage as well as underlying liver function are crucial in determining cancer treatment option and prognosis. Unlike many malignancies, there is a wide spectrum of HCC therapies available — from the well-established surgical resection, liver transplantation, thermal ablation, transarterial chemo-embolization and sorafenib to the emerging Y90-selective internal radiation therapy, stereotactic body radiation therapy and immunotherapy. However, as majority of HCC patients have underlying cirrhosis which impacts on treatment tolerability and risk of decompensation, baseline liver function is often a limiting factor in treatment selection process. For example, a 73-year-old patient with a single 7cm HCC and well compensated cirrhosis, ie Child-Pugh A with no portal hypertension, may receive curative surgical resection which offers the best long-term overall survival when compared to other therapies. On the other hand, a 61-year-old patient with 3 small HCC tumors but with decompensated Child-Pugh C liver cirrhosis would only be eligible for liver transplant as other therapies are contra-indicated and could be detrimental in Child-Pugh C patients. These two case examples highlight the importance of personalised HCC management to achieve best patient outcomes, taking into consideration of tumor factors, liver reserve and available expertise.

Apart from the wide armamentarium at our disposal to treat HCC, it is the only solid cancer treatable by organ transplantation provided there is no major vascular invasion and/or extra-hepatic metastases. In fact, HCC has been recognized as an indication for liver transplantation for as long as the history of liver transplantation itself. In the first ever series of liver transplantation performed by Dr Starzl in the early 1960s, the second recipient was a 48-year-old man with HCC. In those early days, overall survival was generally very poor due to limited understanding of selection criteria, surgical techniques and post-operative care. However, we have come a long way since those early days and liver transplantation for HCC nowadays could offer recipients 5-year overall survival of >70% and recurrence-free survival of >80%.[5,6] Traditional HCC selection criteria is based on the so-called Milan Criteria (single tumor ≤ 5 cm or 2-3 tumors each ≤ 3 cm) but many transplant centres around the world also use the slightly expanded criteria known as UCSF Criteria (1 tumor ≤ 6.5 cm, or 2-3 tumors each ≤ 4.5 cm with total tumor diameter ≤ 8 cm). Some centres have also explored the utility of biomarkers such as serum alpha-fetoprotein, molecular signatures and FDG-PET scan in expanding the pool of HCC candidates for liver transplantation. In particular, FDG-PET scan has been shown to be an emerging selection test to discriminate both within- or out-of-Milan/UCSF criteria HCC patients for liver transplantation. One Korean study involving 280 liver recipients found that 5-year post-transplant overall survival of out-of-UCSF criteria HCC patients with negative FDG-PET HCC were comparable to those within-Milan/UCSF but with positive FDG-PET HCC.[7] This could pave the way for incorporation of biomarkers such as FDG-PET scan into liver transplant selection process to benefit patients with out-of-Milan/UCSF criteria.

At the National University Centre for Organ Transplantation (NUCOT), our liver transplant programme adopts the UCSF Criteria and offers both deceased donor as well as living donor liver transplantation. Close to 50% of our liver recipients received living donor liver graft and up to 45% of our liver recipients have had HCC prior to transplant. Our HCC recipients within UCSF criteria have been achieving excellent 5-year overall survival and recurrence-free survival of 75% and 91%, respectively. Bridging treatment such as radio-frequency ablation or transarterial chemo-embolization is often performed on wait-listed HCC candidates, especially if the anticipated wait time to liver transplantation is > 3-6 months. Post liver transplantation, our HCC liver recipients receive individualised immunosuppression regimen to minimise HCC recurrence risk as well as personalised surveillance programme.

In summary, HCC is a significant complication of chronic liver disease and a large health burden in Asia including Singapore. NAFLD is likely to overtake HBV and HCV as the major cause of cirrhosis and HCC in the near future. Despite advances and availability of many HCC therapies, liver transplantation remains the best hope for many cirrhotic patients with HCC due to concomitant liver decompensation. Management of HCC patients who are potential liver transplant candidates requires a multidisciplinary approach from a dedicated transplant team experienced with management of pre- and post-transplant care in order to achieve excellent long-term survival and outcome.

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Dr Tan's clinical expertise includes advanced liver diseases, viral hepatitis, fatty liver, liver cirrhosis, liver cancer and liver transplantation, in addition to common digestive diseases and endoscopic procedures. He has authored or co-authored numerous research publications and is the principal investigator for ongoing clinical studies in the field of liver transplantation, immunosuppression and hepatocellular carcinoma. As an Assistant Professor at the Yong Loo Lin School of Medicine and a core faculty member of the senior residency programme in Gastroenterology & Hepatology, Dr Tan is actively engaged in undergraduate and post-graduate medical education.

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THE MANY FACES OF DIABETES IN KIDNEY TRANSPLANT

Diabetes is the leading cause of kidney failure in Singapore, comprising 67% of incident dialysis patients in Singapore[1], compared to 42% in USA[2] and 26.9% in the UK[3]. However, only 20.5% of the patients who received kidney transplants in Singapore in 2015 were diabetic[1]. This is due to the attendant comorbidities of diabetes, especially cardiovascular disease, which limits the suitability of a person with diabetes for kidney transplantation. With 11.3% of adults in Singapore affected by diabetes, and around 0.2% of these patients at risk of kidney failure, it is no wonder that we are now waging a 'war on diabetes'.

WHAT ARE THE TRANSPLANT OPTIONS FOR THOSE WITH DIABETES AND END STAGE KIDNEY DISEASE (ESKD)?

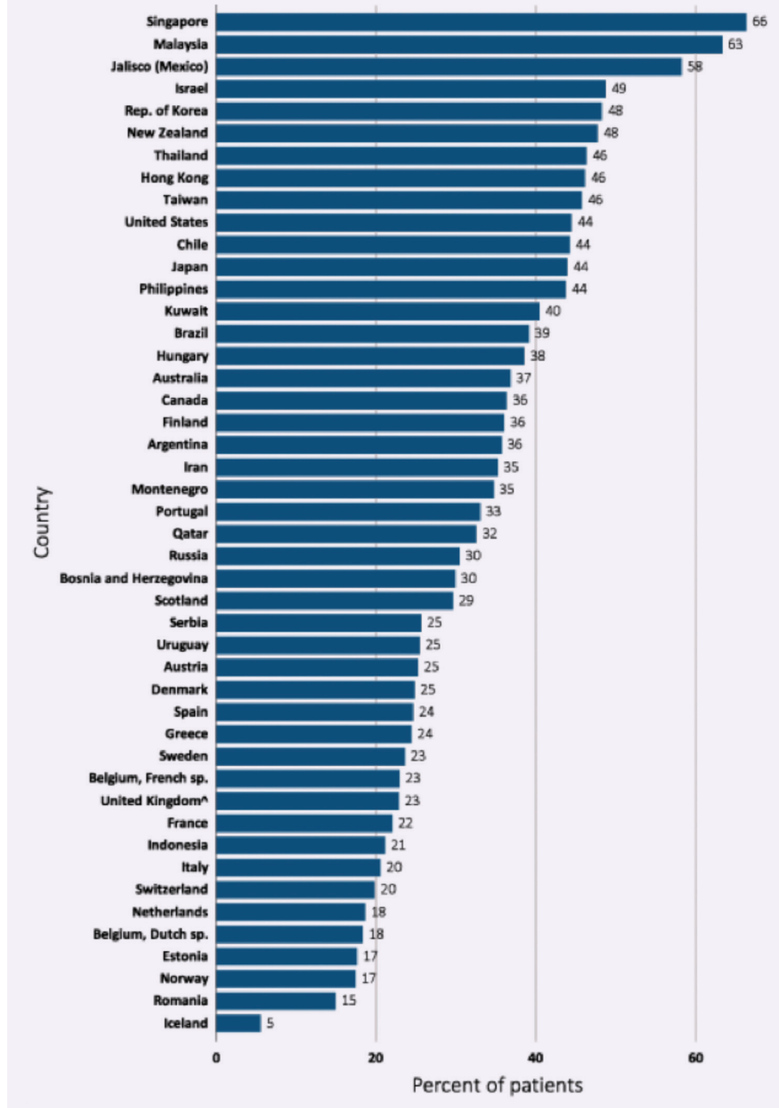
For patients who face diabetes and kidney failure, all is not bleak. It is still clear that the best option for patients who are deemed fit for transplantation is a living donor kidney transplant, and for those without living donors, a deceased donor kidney transplant confers improved mortality and quality of life compared to remaining on dialysis. However, simultaneous pancreas kidney (SPK) transplantation appears to have long-term survival benefits over kidney transplant alone, and this appears to be due to the reduction in cardiovascular risk that comes with a functioning pancreas, and the resultant normoglycaemia.

Another option for these patients is a pancreas after kidney (PAK) transplant. This would involve an initial kidney transplant, usually from a living donor, followed by a pancreas transplant from a deceased donor after an interval. The advantages of this approach includes avoiding the accrual of comorbidity which occurs whilst remaining on dialysis, as well as improving utilisation of the scarce resource that is deceased donor organs.

Since the first SPK transplant in 1966, the evolution of surgical techniques resulting in decreased rates of surgical complications and improvements in immunosuppression over the years. What used to be an option for only those with Type 1 diabetes, has now also been extended to a select group of those with Type 2 diabetes, achieving similar outcomes in terms of graft and patient survival.

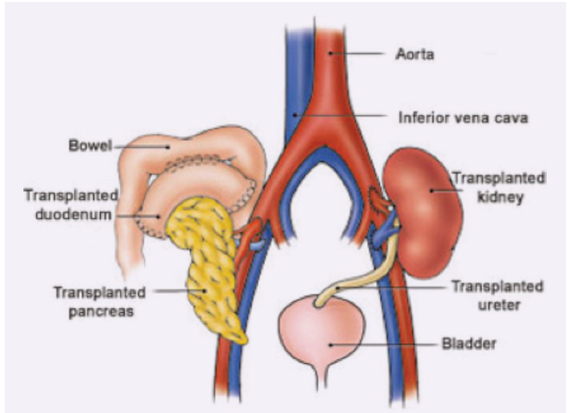
WHO IS ELIGIBLE FOR PANCREAS TRANSPLANTATION?

The main criteria for suitable combined pancreas-kidney or pancreas after kidney transplantation is the absence of significant cardiovascular diseases including coronary artery disease, cerebrovascular disease or advanced peripheral vascular disease. Unlike in kidney transplantation where there is no age limit for eligibility, in pancreas transplantation, older patients are generally excluded due to poorer reported outcomes. Those with diabetes who are obese are also excluded from pancreas transplantation as surgical outcomes are poorer in these patients. Those with Type 2 diabetes should also have a total daily insulin dose of less than 1 unit/kg. Patients requiring high doses of insulin have greater insulin resistance and therefore may not realise the full benefit of a pancreas transplant in terms of achieving a 'cure' for their diabetes and remaining free of medication or exogenous insulin. Inclusion criteria currently also includes a C-peptide cut-off for defining Type 1 diabetes vs Type 2 diabetes. However, it is increasingly clear that there is significant overlap between these two types in terms of C-peptide levels in patients with ESKD. Outcomes of pancreas transplantation are also not related to C-peptide levels. Lastly, a strong indication for pancreas transplantation would be hypoglycaemic



Percentage of Incident ESRD patients with diabetes as the primary cause of ESRD, by country, 2014

THE MAIN CRITERIA FOR SUITABLE COMBINED PANCREAS-KIDNEY OR PANCREAS AFTER KIDNEY TRANSPLANTATION IS THE ABSENCE OF SIGNIFICANT CARDIOVASCULAR DISEASES INCLUDING CORONARY ARTERY DISEASE, CEREBROVASCULAR DISEASE OR ADVANCED PERIPHERAL VASCULAR DISEASE.



Kidney - Pancreas Transplant

and more risky operation, SPK transplantation results in significant prolongation of life compared to dialysis. Patient survival is also equivalent to living donor kidney transplantation, which is better than receiving a deceased donor kidney transplant. This makes SPK transplantation particularly beneficial for young people with diabetes who do not have a living kidney donor. SPK transplantation is also associated with improvements in quality of life, as well as beneficial effects on neuropathy and retinopathy.

So far, NUCOT has performed three SPK transplants since 2012. All three patients have well functioning transplants and significant improvements in their quality of life, compared to being on dialysis. It would be important to ensure that young patients with diabetes remain free of advanced cardiovascular disease, a preclusion, to allow them to benefit from SPK transplants. This would mean holistic care of their chronic disease is needed from the early stages of diagnosis.

unawareness. Patients with 'brittle' diabetes ie. frequent episode of diabetic ketoacidosis may also benefit from the procedure.

The potential candidates have to undergo thorough pre-transplant work-up to ensure fitness for transplantation. This would include assessment for cardiovascular disease, which needs to be repeated at intervals in view of the rapid progression of coronary artery disease in these patients. As with work-up for kidney transplantation, age-appropriate cancer screening is also required. Specialised work-up for pancreas transplant will include assessment of bladder function as a neuropathic bladder may require specific operative or peri-operative management, and assessment for gastroparesis as this will require particular management post-operatively.

WHAT ARE THE OUTCOMES OF PANCREAS TRANSPLANTATION?

Over 50,000 pancreas transplants have been performed worldwide so far, with reported 1-year patient survival of 98% and pancreas graft survival of 86%.[4] Although it is a larger

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Dr Hersharan Kaur Sran graduated from Guy's, King's & St. Thomas' School of Medicine, King's College London, UK in 2003 with distinctions in clinical subjects and basic medical sciences. She completed her basic medical training in the UK and received Membership of the Royal College Physicians of England in 2006. She went on to specialty training in nephrology and general internal medicine in London, UK, completed the Specialty Certificate Examination in Nephrology in 2010, and was dually accredited with Certificates of Completion of Training in Nephrology and General Internal Medicine by the Royal College of Physicians, UK in 2013.

As part of her specialty training in Renal Medicine, she spent 1 year at Guy's Hospital, London specializing in transplantation medicine. She was also awarded the Academic Medicine Development Award in 2016 for a fellowship in pancreas-kidney transplantation at the Oxford Transplant Centre, UK.

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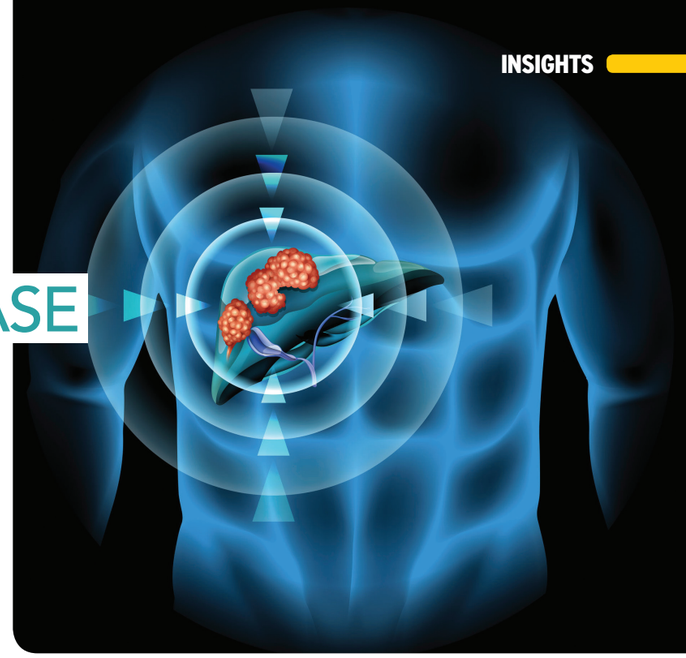

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH)

IT IS IMPORTANT TO NOTE THAT ALTHOUGH THE MEDITERRANEAN DIET HAS BEEN STUDIED IN CLINICAL TRIALS AND OBSERVATIONAL STUDIES, THE APPLICABILITY OF SUCH DIET IN THE ASIAN CONTEXT MAY PROVE TO BE LIMITED IN VIEW OF CULTURAL DIET PRACTICES.

Fatty liver disease is a relatively recent phenomenon that has been increasing rapidly over the past decade.

It has become the most common liver disease in the developed world. New incidences of Hepatitis B and Hepatitis C have been reduced through universal child vaccination and effective treatment respectively.

We should appreciate our ancestral adaptation to be able to store energy in the form of fat. Otherwise, being not able to do so would condemn us to an early extinction and inability to conquer distance lands.

However in the advent of agricultural revolution, modern technologies in transportation and food science, food scarcity is a thing of the past.

NASH is an essentially more severe form of NAFLD and there is an increased risk of progression to liver fibrosis and cirrhosis. Most patients are unaware of the condition because it is an asymptomatic condition until complications of chronic liver disease such as ascites, gastrointestinal (GI) bleeding, hepatic encephalopathy and liver cancer, begin to appear.

Frequently asked questions include:

1. Those who already have NAFLD or NASH, how do they effectively reverse this change?
2. Is there a special diet to reverse fatty liver disease and obesity?
3. How much weight should I lose to reverse NAFLD/NASH?
4. How to prevent NAFLD in the first place?

The good news is that we currently have a wealth of clinical research that have been painstakingly performed in areas of diet and exercise to compare what may be efficacious in prevention and reversal of NAFLD and NASH.

It has been well established that metabolic syndrome is closely related to NAFLD. Therefore, dietary and exercise strategies dealing with pre-diabetes state co-exist with the management of NAFLD and NASH.

It is important to note that although the Mediterranean diet has been studied in clinical trials and observational studies, the applicability of such diet in the Asian context may prove to be limited in view of cultural diet practices.

It must be stressed that over-emphasising one dietary component over another may be counterproductive. For example, low-carb high-fat hypocaloric diet does not equate to permission to indulge in fried and oily foods.

REVERSAL OF NAFLD AND NASH:

Achieving weight loss targets of 7% to 10% of body weight has been shown to reverse of NAFLD/NASH. This can be achieved by an energy deficit of 500 to 750 kcal per day (depending on the baseline body weight of the patients) utilising either a low-fat or a low carbohydrate hypocaloric diet.

The hypocaloric diet utilising the principles of the Mediterranean diet (diet high in vegetables, nuts, and healthier oils such as olive oil and fish oil) also has been shown to reverse NAFLD.

Reduced sugar and fructose consumption by cutting down soft/high energy drinks and processed food has been shown to be helpful.

Low carbohydrate diet may be misinterpreted as restricting carbohydrates consumption ie. consuming only 10% of total energy requirements. This should be avoided. Therefore, it is important to be guided by a dietician. The general principle is to follow a hypocaloric diet either by reducing carbohydrate or fat intake.

The prevention of liver cancer in the NAFLD/NASH with dietary intervention is still being studied. Coffee intake of more than 2 to 3 cups a day has been shown in meta-analysis to reduce the risk of NASH and liver cancer in observational studies. However, patients need to be discerning. They should know that drinking the regular 'kopitiam' coffee or 3-in-1 coffee mix may result in weight gain and worsening blood glucose levels.

Patients who have liver cirrhosis due to NASH should be advised to avoid alcohol consumption (this is based on observational studies).

Exercise offers tangible benefits in NAFLD as it results in significant changes in the liver by increasing insulin sensitivity therefore reducing lipogenesis in the liver. It also reduces visceral fat and increases the VLDL clearance.

Patients who are of normal body weight and utilising the principles of Mediterranean diet can prevent fatty liver by maintaining an isocaloric diet.

Both aerobic and resistance exercise has been shown by clinical trials to be prevent and reverse fatty liver disease.

Making lifestyle changes that involve diet and exercise will be a profound challenge to many. Effective behavioral changes can be initiated via a multidisciplinary approach which should involve the physician, dietician and other healthcare workers.

It is very important to evaluate the patients' understanding of fatty liver disease/liver fibrosis and the positive impact of exercise and dietary interventions in reversing NAFLD/NASH. Regular follow-ups on the patient's adherence to a dietary and exercise regime, and monitoring of weight targets is useful. There should be regular discussions between the patient and the physician to improve compliance, and dietary and exercise intervention.

Dietary approach in patients with diabetes, hypertension, ischaemic heart disease and renal disease should be individualised. Physical disabilities and fitness levels should be taken into account when exercise interventions are undertaken.

HOW ABOUT PATIENTS WHO DO NOT HAVE FATTY LIVER DISEASE AND WOULD LIKE TO PREVENT THIS FROM HAPPENING?

The maintenance of a healthy body weight through healthy eating and regular exercise is crucial.

Comprehensive easy-to-understand information can be obtained from the Health Promotion Board (Singapore) website where healthy diet options and more information on My Healthy Plate can be found.

Patients who are overweight and wish to prevent the development of fatty liver disease should embark on a gradual weight reduction programme with hypocaloric intake (either low carbohydrate intake or low-fat diet).

Exercise is also an important tool to maintain muscle mass and reduce body fat.

At NUH, we have a multi-disciplinary approach to treating NAFLD and NASH. The hepatologists at the University Digestive Clinic assess patients with fatty liver to determine if there is risk for progression to liver fibrosis / cirrhosis and will advise appropriate management.

The Weight Management Clinic specialises in the management of severe obesity, of which strategies may include bariatric surgery. Our dieticians play an important role in planning and advising patients on effective weight reduction plans.

All diet plans have to be discussed with their doctors first.

Further reading:
Treatment of NAFLD with diet, physical activity and exercise
Manuel Romero-Gómez
Journal of Hepatology 2017

Appropriate Care Guide (Ministry of Health, Singapore) Managing pre-diabetes - a growing health concern 3 July 2017

Dr LOW How Cheng

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Dr Low How Cheng graduated from the Universiti Kebangsaan Malaysia (UKM) in 1997. He went on to complete his basic specialty training and obtained the Master of Internal Medicine from Singapore and Malaysia in 2003 and 2004 respectively. He also gained membership of the Royal Colleges of Physicians of the UK in 2003. He completed his gastroenterology training in the National University Hospital from 2005 to 2008. Thereafter he attained his fellowship from the Academy of Medicine, Singapore in 2008. He was also inducted as a member of the Academy of Medicine, Malaysia in 2009.

In 2010, he was awarded the HMDP scholarship to pursue a year's fellowship in endoscopic ultrasound in the St Thomas' Hospital and transplant hepatology in Royal Free Hospital, London. He currently serves as a Consultant in the Division of Gastroenterology and Hepatology, NUH and an Assistant Professor at the Yong Loo Lin School of Medicine. NUS. His clinical interests are in transplant hepatology and endoscopic ultrasound (EUS). Dr Low is involved in undergraduate and postgraduate teaching. He is currently the Gastroenterology Senior Residency Director and a core faculty member of the Internal Medicine Residency programme at NUH.

PHARMACY TIPS

UP TO 50%
develop renal dysfunction post-liver transplant. Therefore it is important to avoid nephrotoxins and to monitor patients' renal function closely.

POST-TRANSPLANT DIABETES
New-onset diabetes after transplantation (NODAT) can occur in up to 25% of post-transplant patients and is detrimental to patient and graft survival. Early diagnosis through the identification of modifiable and non-modifiable risk factors for NODAT and appropriate screening, accompanied by good glycemic control is imperative.

COMMON MEDICATIONS POST-TRANSPLANT PATIENTS RECIEVE

	Anti-infectives		
	Medication Name	**Common Side Effect**	**Monitoring**
PCP Prophylaxis	Sulphamethoxazole-Trimethorprim (Bactrim®, Co-trimoxazole®)	Marrow Suppression Hepatitis Renal Impairment Hypokalemia	RP, FBC, LFT
	Dapsone	Anemia Hepatitis	RP, FBC, LFT
CMV Prophylaxis	VALGANCICLOVIR (Valctye®)	Marrow Suppression	RP, FBC
BK Virus Treatment	CIPROFLOXACIN	Tendonitis	RP
	Immunosupressants		
	Medication Name	**Common Side Effect**	**Monitoring**
Calcineurin Inhibitors	TACROLIMUS (Prograf®, Advagraf®)	Renal Impairment Hypertension Hyperglycemia	RP,LFT, Glucose, HbA1C
	CYCLOSPORIN (Neoral®)	Renal Impairment Hypertension Hyperlipidemia	
Anti-Proliferatives	MYCOPHENOLATE (Cellcept®, Myfortic®)	Marrow Suppression Diarrhea	FBC
	AZATHIOPRINE (Imuran®)	Neutropenia Increased LFT	FBC, LFT
mTOR Inhibitors	EVEROLIMUS (Certican®)	Hyperlipidemia Hypertriglyceridemia Proteinuria Mouth Sores Poor Wound Healing	Lipid Panel Urine Protein LFT
	SIROLIMUS (Rapammune®)		
Corticosteroid	PREDNISOLONE (Orapred®)	Hypertension Hyperglycemia Osteoperosis Peripheral Edema Increased Appetite	BP, Glucose

mTOR=mammalian target of rapamycin; BP=blood pressure; LFT=liver function rest; FBC=full blood count

MEDICATIONS, HERBS AND FOOD TO AVOID

INCREASE
IMMUNOSUPPRESSANT DRUG LEVELS
clarithromycin, erythromycin, diltiazem, fluconazole, ketoconazole, cimetidine, nifedipine, grapefruit, pomegranate, pomelo, starfruit, ginseng.

DECREASE
IMMUNOSUPPRESSANT DRUG LEVELS
Rifampicin, dexamethasone, carbamezapine, phenytoin, St John's Wort, garlic supplement.

NEPHROTOXINS
ADDITIVE RISK FOR RENAL DYSFUNCTION
Ibuprofen, ketoprofen, naproxen, diclofenac, celecoxib, etoricoxib, mefenamic acid, meloxicam.

HERBS
TO AVOID
ALL herbs, supplements and TCM should be avoided in transplant patients, especially
- **Immunostimulants: Echincacea, cordyceps**
- **Increased blood pressure: Dang gui, ginseng, licorice.**

Dr KOH Tsingyi

Principal Clinical Pharmacist
National University Hospital

Dr Koh Tsingyi is a Principal Clinical Pharmacist in Solid Organ Transplantation at the National University Hospital (NUH). She has practiced in the area of solid organ transplantation for over 10 years. She is also a lecturer for the Doctor of Pharmacy Programme at National University of Singapore in the topics of transplant pharmacotherapy and hepatology. Her areas of interest include medication adherence and transplant infectious diseases.

COMMON CONDITIONS ENCOUNTERED WHEN MANAGING TRANSPLANT PATIENTS

RESPIRATORY TRACT INFECTIONS

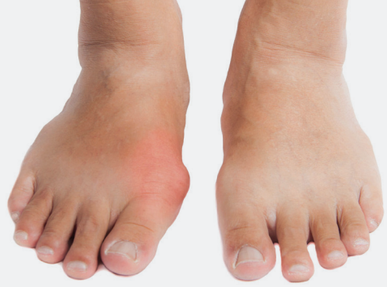
Diagnosis: These are commonly due to viral infections that start with upper respiratory tract symptoms. However given the immune suppressed state of transplant patients, be mindful of superimposed bacterial infection and progression to pneumonia if patients have persistent or worsening symptoms for more than 5 days.

Treatment: Carry out symptomatic treatment to relief symptoms. If bacterial infection is suspected, antibiotics treatment for at least 7 - 10 days should be initiated. Refer to Transplant Centre for admission if oxygen supplementation, intravenous therapy or monitoring is deemed necessary. Antibiotics (eg. clarithromycin, erythromycin) with significant drug interactions with immunosuppressants should be avoided.

URINARY TRACT INFECTIONS

Diagnosis: Patients may have one or more of the typical symptoms of dysuria, frequency or suprapubic discomfort. Urine microscopy and culture should be done. If the patient is systemically unwell (eg. chills/rigors, fever, nausea/vomiting, kidney graft pain), he/she will need to be referred to the Transplant centre for admission and treatment.

Treatment: Commence empirical therapy until urine cultures are available to administer specific antibiotic therapy. Treatment duration needs to be at least 14 days. Antibiotic dosages (eg. Augmentin, Ciprofloxacin) may require adjustment based on kidney function. Following treatment, urine tests should be repeated to ensure recovery.



GOUT

Diagnosis: Patients can present with monoarticular or polyarticular pain, swelling and erythema. Recent diet indiscretion may be the precipitant. A history of gout would support the diagnosis as well.

Treatment: Colchicine may be used to treat the acute flare, the dosage should be adjusted according to kidney function. A short course of increased prednisolone dose is an alternative (eg. 20mg for 3 days with 5mg weaned every 3 days down to previous maintenance dose) for those who are unable to tolerate colchicine. Longer term prevention (eg allopurinol, probenecid) should be started after the acute attack has well resolved. Care with allopurinol use is required in patients with impaired kidney function – dose adjustment is required and patients should be warned regarding severe cutaneous reactions.

HERPES ZOSTER

Diagnosis: Vesicular rash over a dermatome is the classical presentation, however transplant patients may have multi-dermatomal involvement due to disseminated zoster. This is usually a clinical diagnosis, but testing vesicular fluid for VZV DNA can be done for confirmation.

Treatment: Early start of anti-viral therapy (eg. acyclovir or valacyclovir) will reduce duration of disease and prevent or reduce the severity of post-herpetic neuralgia. Dose adjustment is required according to kidney function. Agents to manage post-herpetic neuralgia (eg. gabapentin, opioid analgesia) can be used with dose adjustment for kidney function. If symptoms are severe, disseminated zoster is present, or there is ophthalmic or meningoencephalopathic involvement, the patient should be referred to the Transplant centre for admission. It is important to watch out for bacterial superinfection. Patients should be advised to keep lesions clean and avoid scratching. Patients would need to undertake contact precautions at home. They should also be advised to avoid contact with the elderly, pregnant women, those with no prior chicken pox infection and other immunocompromised people until all lesions are crusted.

GASTROINTESTINAL INFECTIONS

Diagnosis: Patients typically present with diarrhoea. However, due to immunosuppression, as well as the frequent use of antibiotics in these patients, more sinister pathogens such as Clostridium difficile and Cytomegalovirus (CMV) may be the cause of the symptoms. Care should be taken to identify higher risk patients.

Treatment: Supportive treatment with rest and hydration is important. Empiric antibiotics are not recommended without proper investigations such as stool cultures. If symptoms do not improve within 48 - 72 hours, or the patient has evidence of severe disease (fever, more than 6 stools per day, significant dehydration, bloody or mucoid stools), the patient should be referred to the Transplant Centre. Anti-motility agents (eg. loperamide) should be avoided, especially until the stool cultures results are negative. Charcoal tablets should also be avoided as they may affect the absorption of other medications the patient is taking.

TRAVELLER'S DIARRHOEA

Diagnosis: Patients present with diarrhoea while travelling to areas with poorer sanitation, or within 10 days of returning from such an area.

Treatment: Fluid replacement is the most important aspect of therapy. Given the risk of pathogens, antibiotics should be prescribed early. If patients are going to an area where the medical system is not good, they can consider taking Azithromycin for 3 days and immediately returning to an area where they can get good medical treatment. Azithromycin can cause some interaction with immunosuppressants. If possible, they should seek medical attention at a transplant centre as soon as possible. Prior to travel, all patients are encouraged to visit a travel clinic to receive proper counselling and vaccination. Live vaccines should be avoided in post-transplant patients.

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Associate Consultant, Department of Nephrology, National University Hospital

Graduated with BMedSci in 2002 and MBBS (Hons) in 2006 from University of Sydney, Australia. She completed her advanced training in Nephrology to become a specialist in Nephrology and General Medicine, and received her FRACP in 2014. Her subspecialty interest is in Transplant Medicine with hopes to advance research in kidney transplantation in Singapore.

Dr Mark MUTHIAH

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Associate Consultant, Liver Transplantation, National University Centre for Organ Transplantation (NUCOT), National University Hospital
Associate Consultant, Department of Gastroenterology and Hepatology, National University Hospital

Dr Mark Muthiah did his general medical training in the National University Hospital, Singapore, and subsequently continued with his training in gastroenterology in the same institution. He has a keen interest in liver transplant, and is a member of the liver transplant team in the National University Hospital, Singapore.

Dr Muthiah's research interest is in cellular therapies to reverse liver fibrosis, and is involved in both basic and clinical research on the above subject. He is also actively involved in teaching medical undergraduates and post-graduates, with multiple teaching awards from the medical school.

THE PEOPLE YOU MEET DURING YOUR TRANSPLANT JOURNEY

PATIENT WITH ORGAN FAILURE

RECIPIENT ASSESSMENT

NTRS team: Choong Jia Foong & Joyce Valereine

Upon receiving referrals of patients who could potentially be considered for the national waiting list, we would proceed to arrange a formal consultation appointment with the transplant team. We would also counsel patients and family members to explain about the process of transplant, available financial schemes, and explore the living donor options amongst their loved ones. After review, patients would then be scheduled for various assessments to assess their suitability for transplant. Once patient is medically cleared, we would then proceed to register patients in the National Transplant Registry System (NTRS). We would continue to maintain the patient's suitability in the waiting list with routine screenings and consultations. Living donor option would be re-explored with patients at regular intervals. We also motivate patients as a team, to keep them going for their transplant!

TRANSPLANT SURGERY

LIVING DONOR ASSESSMENT

Living Donor team: Priscilla Wee, Samantha Goh, Tan Chin Ling

Aside from deceased donor transplants, NUCOT also offers live donor transplants.

We counsel potential donors and recipients and provide them with information regarding the process of undergoing a live donor transplant. Thereafter if the donor is keen to proceed, we will coordinate the donor assessment which includes scheduling and tracing of investigations to determine the medical suitability of the donor. After the investigations have been completed, the donor will see a team of doctors who will assess his or her fitness to donate. Once deemed medically suitable to donate, we will arrange for a Transplant Ethics Committee (TEC) meeting, whose aim is to ensure the transplant will be done in accordance to the Human Organ Transplant Act (HOTA).

After TEC approval has been obtained, we will coordinate the live donor transplant by booking the operating theatre, ordering of blood products, informing the multidisciplinary transplant team of the surgery and arranging for the admission of the donor and recipient. After the surgery, we participate in the care management with the medical team.

Throughout this process, we are our donors' advocate and provide them with any needed support pre and post-surgery.

DECEASED DONOR ASSESSMENT

Procurement team: Tong Boon Jie & Winnie Chong

Procurement Transplant Coordinators (TC) are required to be on standby for potential deceased donor nationwide around the clock.

Upon activation, procurement TCs will attend to the case within a short timeframe together with a multidisciplinary team comprising of doctors, nurses, medical social workers and laboratory technicians. Due to the complexity of assessment process, procurement TCs would provide support, timely updates to family members and attend to their queries.

Procurement TCs would then coordinate the investigation and consultation from various specialists such as cardiologist, hepatologist, nephrologist and ophthalmologist. Upon confirmation of suitability, procurement TCs would then work closely with different teams of surgeons to facilitate donation surgery.

POST-TRANSPLANT MANAGEMENT

Clinical team: Chan Foong Kheng, Goh Chee Ling, Joreen Poh, Samantha Lim, Tan Tse Ling

NUCOT takes care of pre and post kidney, liver & pancreas transplant patients.

Clinical Transplant Coordinators work closely with a team of multidisciplinary professionals (transplant physicians, pharmacists, dieticians, medical social worker, nurses, diagnostic imaging colleagues & etc.) to take care of the post-transplant patients and ensure smooth running of the transplant clinic and program.

Post-operatively, before patient's discharge, transplant coordinators will educate & counsel the patient and family on home care post-transplant, on information on transplant medications, chronic disease medications, hepatitis medications & food safety. Each patient will also be equipped with a Post-Transplant Care leaflet; this serves as a very useful reference guide – patients will have a clear picture of their medications and dietary intake, and thus help in building up patients' confidence in self-care management.

During a patient's entire post-transplant journey, we will continue to provide a continuation of care - follow up closely with their well-being, medications titrations ordered by their physicians and laboratory investigations. These not only help to minimize discrepancies and malpractice in patient's post-transplant care, but also helps to enhance a successful transplant journey.

Yorleny R Long
Senior Medical Social Worker

Thomas Lee
Senior Medical Social Worker

MEDICAL SOCIAL WORKERS

Medical social workers are part of the NUCOT multidisciplinary team. We are qualified professionals with Social Work degrees and generally with several years of experience.

Our role within the multidisciplinary team is to undertake a comprehensive psychosocial assessment for all patients referred for transplant and any potential live organ donor. Part of this assessment includes pre-evaluation, informed consent, compliance to their current treatment and likelihood of compliance post-transplant and family support. For live organ donors, we also assess any potential ethical issues in donating.

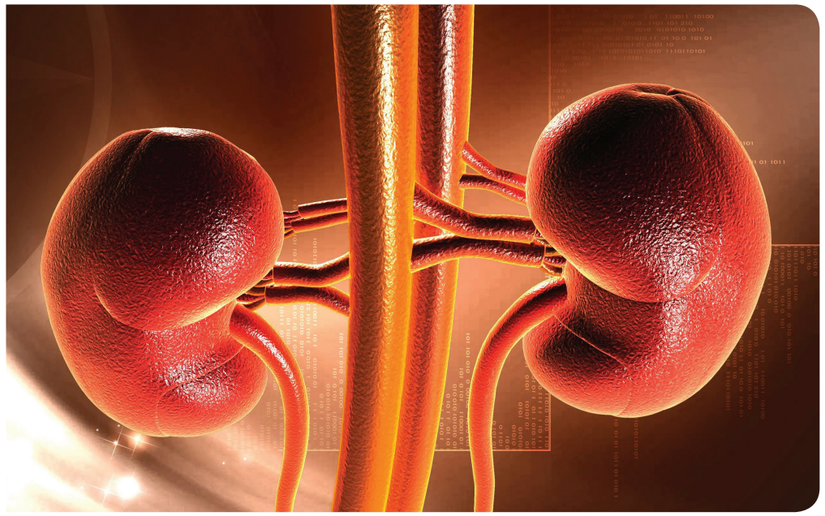
In addition to the above, we understand the different complexities and practicalities that may arise from receiving a transplant or donating an organ and therefore, we also provide counseling support, patient and family education, care arrangement support, referrals to community resources and financial assistance.

DIETETICS ROLE IN THE TRANSPLANT JOURNEY

Transplant dietitians follow a patient from pre-transplant through transplant and post-transplant. They provide nutritional assessments, nutrition support recommendations and interventions as well as dietary counseling, to ensure an appropriate nutrient intake for the recovery and maintenance of health in the long-term post-transplantation patients. Nutritional recommendations and medical nutrition therapy are tailored individually based on a thorough evaluation using the nutrition care process. After transplantation, transplant dietitians provide dietary counseling on recommended food safety guidelines; wound healing and immunosuppressant drug-nutrient interactions. For the long-term post-transplantation patients, transplant dietitians monitor them for general health issues and comorbidities such as diabetes mellitus, hyperlipidemia and excessive weight gain.

Liver Transplant Senior Dietitian Ang Yi Pei & Renal Transplant Dietitian Lim Jia Qi

KIDNEY PAIRED DONATION @ NUH



Living related renal transplant is the optimal treatment to end stage renal disease (ESRD) with higher long term graft and patient survival. Donor shortage is a significant limiting factor in most kidney transplant program. Patients can remain on the dialysis wait list for 7 to 10 years before getting a suitable organ for transplant, with attendant increase in morbidity and mortality.

The National University Centre for Organ Transplant (NUCOT) has increased our donor pool and successful kidneys transplants with a developed ABO (blood types) incompatible transplant programme.

Over the last decade, kidney paired donation (KPD) is the most rapidly increased source of living kidney donors worldwide. KPD affords the opportunity for patients with renal failure and an incompatible donor to enjoy the benefits of living related renal transplant without the costly desensitization regimens and minimizes side effects of required immunosuppression.

KPD has been approved in Singapore since 2009 and in April 2015, NUCOT performed our nation's first paired kidney exchange transplant in NUH. Ms Siti Rasyidah Lokman Hadan was born with dysplastic kidneys, diagnosed with systemic lupus erythematosus (SLE) and developed ESRD by age 15. While her mother, Mdm Noor Rafidah Nasir was a willing donor, immune incompatibilities precluded a straightforward living donor transplant. The KPD programme at NUH allowed Ms Siti to have a more compatible donor kidney implanted while Mdm Noor Rafidah donated a kidney to another recipient. It was an emotional moment for Ms Siti, who was wheelchair bound for 4 years, to be able to walk after the transplant and pursue her dreams of becoming a teacher.

The KPD programme is in its infancy and shows great promise to increase the donor pool in Singapore with more KPD performed. There are many permutation of this programme – from a simple simultaneous paired kidney exchange to complex strategies with non-simultaneous donor surgery involving multiple donor-recipient pairs in chains or loops. The end result is better donor human leukocyte antigen (HLA) and age matching without costly and detrimental desensitization regimen towards lower lifetime mortality for our recipients.

NUCOT has a team of professionals with enthusiasm, patience, mathematical modeling and teamwork to support a successful and beneficial KPD programme for our potential kidney transplant recipients.

Dr GOH Yen Seow Benjamin
Associate Consultant, Department of Urology, NUH
Clinical Faculty Staff, Yong Loo Lin School of Medicine, NUS

Dr Goh became a fellow of the Royal College of Surgeon (Urology)(Glasgow) in 2015 and a fellow of the Academy of Medicine (Singapore) in 2016 as a Gold Medalist. He currently manages general Urology conditions with a special interest in kidney transplantation and kidney surgery including open and minimally invasive kidney cancer surgery.

Dr Goh participates actively in undergraduate and postgraduate education, applying different educational pedagogy and rationalizes curriculum. He is passionate about educating the next generation of doctors and has won multiple awards for undergraduate medical education.

Dr Goh has an interest in translational research, collaborating with Molecular Diagnostic Centre in testing DNA polymorphism in donor-recipient pairs undergoing kidney transplantation. There is also ongoing collaboration with Biomedical Engineering Department for microfluidic enrichment of urine towards improved bladder cancer detection.

HOW SAFE IS LIVING DONOR LIVER TRANSPLANTATION (LDLT)?

MORE HOPE FOR THOSE WHO NEED TRANSPLANT

FIRST LOOK

LDLT is a well-accepted treatment option for patients needing liver transplantation. As the cadaveric organ donation rate in Singapore is very low, many patients on the organ waiting list have to wait for a long time before a suitable liver organ will be available to provide them with a chance to lead a new life without chronic liver disease. It is common for patients with hepatocellular carcinoma (HCC) to be on the waiting list for so long that their HCC progresses beyond the transplant criteria and they are eventually removed from the list. To overcome the problem of organ shortage, LDLT is an excellent alternative.

INSIGHTS

LDLT requires a healthy donor to undergo partial liver resection through an operation to remove part of the liver (but preserving the essential structures including a branch of the hepatic artery, portal vein, bile duct and branches of the hepatic vein) to be implanted into the recipient. As the liver can regenerate, as long as the functional liver remnant (FLR) volume is adequate, the operation is generally considered safe for the donor. The surgical team looking after the donor will always ensure that donor safety is upheld at all aspects. We are glad to share that in the past 30 years or so, all our living donors in our programme have been well with 0% mortality rate.

In fact, NUCOT is one of the leading centers for LDLT in Southeast Asia in the past 5 years, doing one of the largest number of LDLT. Till date, we have performed more than 180 cases since the beginning of the liver transplant program in Singapore.

There are many different types of liver grafts used in LDLT, and the consideration of which portion of the liver to harvest depends on the vascular and biliary anatomy of the donor, the volume of the liver graft compared to the functional liver remnant and the body weight of the recipient. Paediatric LDLT often requires a much smaller liver graft and thus the left lateral section of the liver would suffice, reducing the risk of the operation. As adult recipients usually require a larger liver graft, the right half of the liver is usually considered. As long as the FLR is ≥ 30% of the total liver volume, the risk to the donor is minimised considerably.

TREATMENT ROOM

Patients that require liver transplantation can be divided into 3 categories:

- Acute liver failure or acute-on-chronic liver failure – drug-induced, viral hepatitis flare etc
- Chronic liver failure – all the causes of cirrhosis with its associated complications from portal hypertension
- Liver malignancies – predominantly HCC (within UCSF criteria*) and other rarer malignancies (selected neuroendocrine tumor with liver metastasis and well-responded hilar cholangiocarcinoma within trial criteria).

In NUCOT, we offer LDLT to patients with acute or acute-on-chronic liver failure who need liver transplant urgently; or patients with HCC who are in the upper limit of the transplant eligibility criteria. In addition, LDLT is always counselled as an option to consider at the first consult for non-urgent cases. Potential recipients are encouraged to speak to their family members and friends about the option of LDLT. Potential donors who are keen to find out more about LDLT can then see one of the donor's liver surgeons to gather more understanding before deciding if he/she will proceed with the donor work-up. At NUCOT, we uphold the principle of non-coersion and make sure that donors are fully informed of the risks and that they are fully willing to undertake this process.

IN SINGAPORE, AND IN THE REGION OF SOUTHEAST ASIA, THERE IS A HIGH DEMAND FOR LIVER TRANSPLANTATION. THIS IS MAINLY DRIVEN BY THE HIGH INCIDENCE OF HEPATITIS B INFECTION IN THE POPULATION. ONE IN 35 ADULTS IN SINGAPORE IS A CHRONIC HEPATITIS B CARRIER. AS A RESULT, THE RATE OF CHRONIC LIVER DISEASE AND HCC IS VERY HIGH. MANY OF THESE CONDITIONS, WHEN DETECTED EARLY, WILL BE AMENABLE TO LIVER TRANSPLANTATION. LIVER TRANSPLANTATION IS THE BEST TREATMENT OPTION THAT YIELD THE BEST LONG-TERM RESULTS.

We walk with them in every step to complete the journey of a successful liver transplantation. Potential donors are also given the avenue to meet and speak with previous donors to understand their journey. We hope this allows them to gain a complete perspective of this act of altruism that they are thinking of undertaking.

LANDSCAPES

In Singapore, and in the region of Southeast Asia, there is a high demand for liver transplantation. This is mainly driven by the high incidence of hepatitis B infection in the population. One in 35 adults in Singapore is a chronic hepatitis B carrier. As a result, the rate of chronic liver disease and HCC is very high. Many of these conditions, when detected early, will be amenable to liver transplantation. Liver transplantation is the best treatment option that yield the best long-term results. In fact, patients with liver cirrhosis and HCC will be able to 'kill two birds with one stone' by receiving liver transplantation as the problem of portal hypertension will be resolved together with the complete removal of the HCC-laden liver.

Patients with chronic liver disease should receive regular surveillance in the primary care setting. In addition, patients with past hepatitis B infection (HBs Ag negative but anti-HBc total positive) should also be encouraged to receive surveillance as they remain at risk of developing HCC.

Dr KOW Wei Chieh Alfred

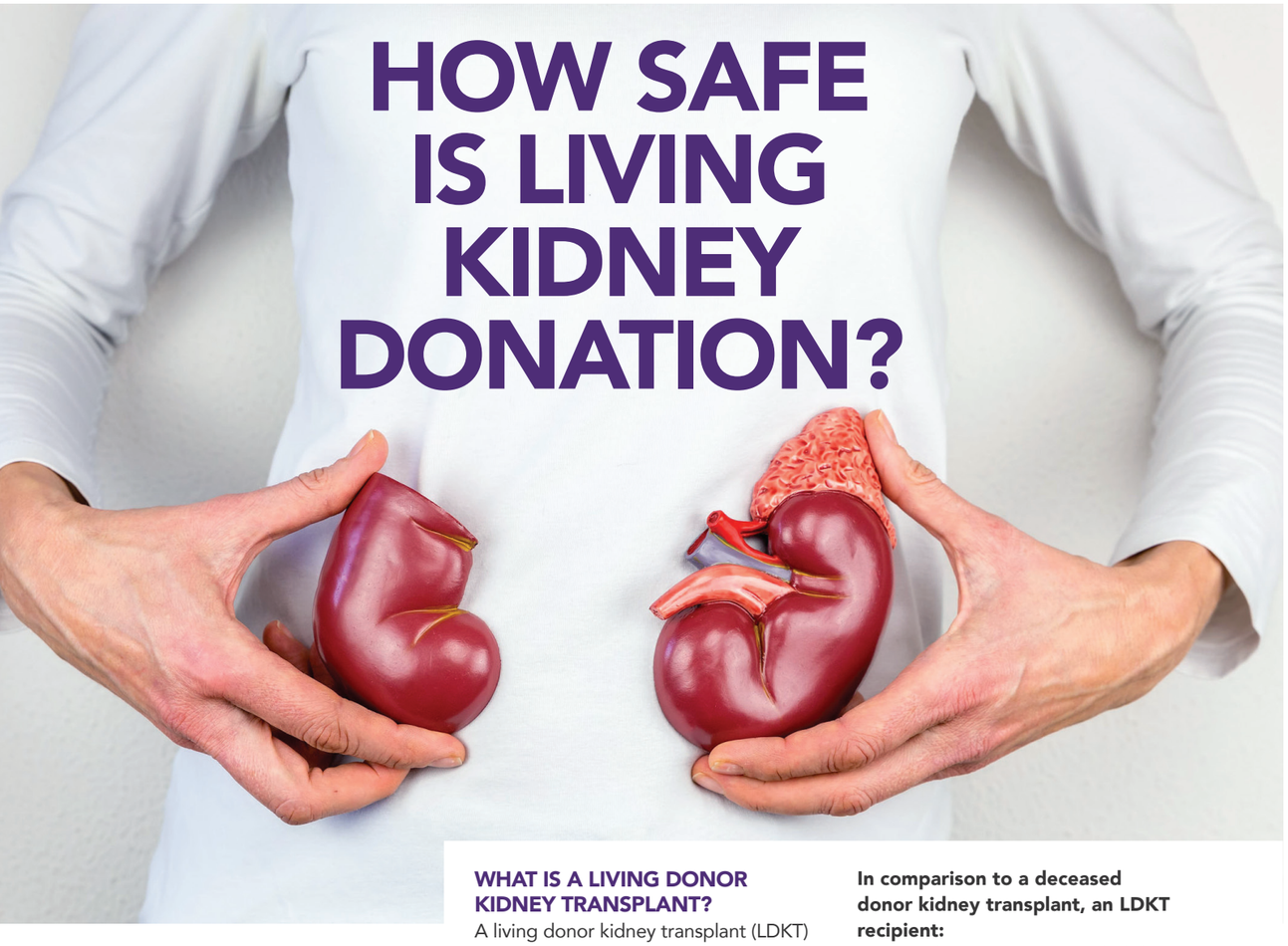
MBBS, M Med (Surgery), MRCS (Ed), MRCS (Ire), FRCSEd (Gen Surgery)
Senior Consultant, Division of Hepatopancreatobiliary Surgery & Division of Liver Transplantation, Department of Surgery, University Surgical Cluster, National University of Singapore
Undergraduate Medical Education Director, Department of Surgery, National University of Singapore

Dr Alfred Kow underwent fellowship training in living donor liver transplantation (LDLT) and hepatobiliary & pancreatic surgical oncology in Samsung Medical Center & Samsung Cancer Center, Sungkyunkwan University School of Medicine in Seoul, South Korea. Dr Kow is strongly interested in liver transplantation (both deceased donor and living donor) as well as minimally invasive (laparoscopic) surgery for hepatobiliary and pancreatic conditions. He is also one of the core members to drive minimally invasive surgery in HPB in Singapore.

In addition, Dr Kow has keen interest in research activities involving development of surgical techniques in HPB surgery and outcome of surgical treatment for HPB malignancies. The other areas that he is keen to research on are liver transplantation, peri-transplant management and outcome studies. Furthermore, he is also actively developing research to help improve surgical education and training for both undergraduate and postgraduate setting. Many of his research work on education aim to understand the art and science behind training the junior doctors to be excellent surgeons for the future. He has won grants to study the use of mobile apps in teaching patient safety in surgery.

TREATMENT ROOM

HOW SAFE IS LIVING KIDNEY DONATION?



STUDIES SHOW THAT 3 IN 1,000 LIVING KIDNEY DONORS GO ON TO DEVELOP END-STAGE KIDNEY DISEASE IN THEIR LIFETIME. SOME KIDNEY DONORS MAY ALSO BE AT SLIGHTLY HIGHER RISK FOR PROTEINURIA AND REDUCED KIDNEY FUNCTION. HENCE, ALL LIVING KIDNEY DONORS REQUIRE REGULAR LIFELONG MEDICAL SURVEILLANCE. IF FOUND TO HAVE EARLY KIDNEY DISEASE OR ANY OTHER MEDICAL CONDITION, THEY WILL BE REFERRED TO THE APPROPRIATE SPECIALISTS FOR FURTHER CARE.

WHAT IS A LIVING DONOR KIDNEY TRANSPLANT?

A living donor kidney transplant (LDKT) is an operation in which a patient with kidney failure (the recipient) receives a kidney from another living person (the living donor). Immunosuppressive medicines prevent rejection of the kidney transplant and allow it to function just like a normal kidney, cleansing the recipient's body of toxins, removing excess salt and water and producing hormones needed to maintain health.

WHY HAVE A LIVING DONOR KIDNEY TRANSPLANT?

Patients generally enjoy a better quality of life when they receive a kidney transplant instead of remaining on dialysis. They live longer as their kidney functions are restored, enjoy better health, face fewer diet and water restrictions and have more time and energy.

In comparison to a deceased donor kidney transplant, an LDKT recipient:

- Has a lower rejection probability and better kidney function as a kidney from a live donor is healthier,
- Has a higher success rate from the transplant surgery,
- Faces less anxiety as they are not on a waiting list and dialysis.

WHO CAN BE A LIVE KIDNEY DONOR?

A live donor can be:

- Biologically related to the recipient, such as a parent, sibling, offspring or a relative like an aunt, uncle, cousin, nephew or niece.
- Emotionally-related to the recipient, such as a spouse, friend, or in-laws.
- Occasionally, even a stranger who wishes to donate a kidney to someone in need of a transplant (altruistic donor).

A live donor must be:

- At least 21 years of age; though donors older than 65 years can be considered on a case by case basis.
- Free from the following conditions: cancer, heart disease, HIV infection or AIDS, diabetes or pre-diabetic conditions, hepatitis B and C, kidney disease.

WHAT IF THE BLOOD GROUPS BETWEEN THE LIVE DONOR & RECIPIENT ARE DIFFERENT?

A kidney transplant be performed across different blood groups. It is ideal if the blood groups are compatible, as shown in the table below.

If the blood groups are incompatible, an LDKT can still be done, although this type of transplant carries a slightly higher risk of rejection.

ARE THERE ANY RISKS TO THE LIVE KIDNEY DONOR?

A healthy individual requires only one kidney to live normally. Kidney donation will not affect the health, life span or energy level of the donor, as long as the donor was carefully and thoroughly evaluated prior to the operation.

All potential living kidney donors are evaluated by a medical team, comprising at least a nephrologist (the primary donor physician), psychiatrist, transplant coordinator and medical social worker. Doctors from other specialties may be called upon as required for further evaluation if the primary donor physician deems necessary. All potential living donors are extensively screened through blood, urine and specialised laboratory investigations to identify medical conditions that could predispose them to kidney disease, such as diabetes; and also to identify psychosocial conditions that could influence their decision to be a living kidney donor. Potential donors above the age of 50 are also required to undergo specialised cardiac investigations to determine their cardiovascular risk for surgery under general anaesthesia.

Studies show that 3 in 1,000 living kidney donors go on to develop end-stage kidney disease in their lifetime. Some kidney donors may also be at slightly higher risk for proteinuria and reduced kidney function. Hence, all living kidney donors require regular lifelong medical surveillance. If found to have early kidney disease or any other medical condition, they will be referred to the appropriate specialists for further care.

RECIPIENT BLOOD GROUP	COMPATIBLE DONOR BLOOD GROUP	INCOMPATIBLE DONOR BLOOD GROUP
O	O	A, B, AB
A	A, O	B, AB
B	B, O	A, AB
AB	A, B, AB, O	NIL

THE LIVING DONOR KIDNEY TRANSPLANT SURGERY

Surgery for the donor is discussed elsewhere in this issue of Medico.

For the recipient, an incision is made in the front lower abdomen. The new kidney is stitched into place within the pelvis & the incision is closed. The recipient's own kidneys are usually not removed.

Each surgery takes about 3 - 4 hours and both donor and recipient must be monitored in a High Dependency Unit postoperatively. The donor is usually discharged 3 days after the surgery, while the recipient can be discharged within 7 - 10 days of the transplant.

WHEN CAN A LIVING DONOR KIDNEY TRANSPLANT BE DONE?

Living and deceased donor transplants can be done after starting dialysis. However, clinical guidelines in Singapore mandate that a patient must be on dialysis before he/she can be placed on the National Transplant Registry System to await a deceased donor kidney transplant. In some other countries, pre-emptive deceased donor transplants are done.

WHAT IS THE SUCCESS RATE FOR LDKT?

The success rate is greater than 99%, however, over 20 years or so, some kidney transplants are lost to rejection or other causes.

While living donation is indeed a sacrifice, it is the noblest gift an individual can make to someone he or she cares for; all that is required is a willing and suitable donor.

Dr Angeline GOH

MBBS (NUS), MRCP (UK), Specialist Accreditation in Renal Medicine
Senior Consultant, Kidney Transplantation, National University Centre for Organ Transplantation, National University Hospital
Senior Consultant, Division of Nephrology, University Medicine Cluster, National University Hospital

Dr Angeline Goh completed her housemanship in Changi General Hospital and Singapore General Hospital, followed by her Basic Medical Training in the same hospitals. She completed her training as an Advanced Specialist Trainee in Renal Medicine, at the Department of Renal Medicine, SGH, and subsequently went on to sub-specialise in Renal Transplantation.

With a special interest in histocompatibility and tissue typing, Dr Goh went on to spend one year training under Dr Paul Terasaki in Los Angeles for her HMDP fellowship.

PAEDIATRIC LIVER TRANSPLANTATION

Human liver transplant was first performed by Starzl in 1963 for a child with hepatoblastoma. Since then, much progress have taken place in several areas, such as better understanding of the segmental anatomy of the liver, immune-suppression drugs and its use, intensive care, infection control, anaesthesia and micro-vascular surgery have vastly improved survival rates. These developments have extended liver transplants to the neonatal age group. Paediatric liver transplant now accounts for about 20% of all liver transplants.

Liver transplant is the only chance of cure for end-stage liver disease and for some metabolic disease. The indications for transplant can be divided into bile duct anomalies, metabolic disease, malignancies and fulminant liver failure.

Among the indications bile duct anomalies are the commonest, biliary atresia accounts for 75% of the total transplants.

A) BILE DUCT ANOMALIES

1. **Biliary Atresia**
   The earliest sign is jaundice persisting beyond two weeks of life and pale stools. Any baby with 20% or more of serum bilirubin is conjugated must be suspected. Any of these findings should alert the physician for early investigation.
2. **Hypoplastic ducts**
3. **Choledochal cyst (rarely)**
4. **Progressive intrahepatic cholestasis**

B) METABOLIC CAUSES

1. **Glycogen disease**
2. **Wilson's disease**
3. **Crigler-Najjar syndrome**
4. **Hyperoxaluria**
5. **Familial hypercholesterolemia**

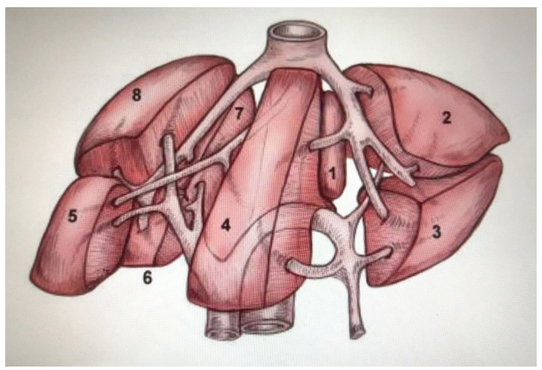
C) FULMINANT LIVER FAILURE

Contraindications

Systemic sepsis, malignancy out of the liver, poor cardio, vascular respiratory disease, neurologic disorders and when poor outcome is expected.

Operative procedures

Paediatric patients extend from birth to 16 years of age. Smaller size paediatric patients require partial liver transplants. The anatomy of the liver allows for segmental/lobar procedure.



Paeds liver.

Transplant types in children:

a) Whole organ from deceased donor
b) Split liver from deceased donor
   Segment 2 & 3 to paediatrics
   (Segment 5, 6, 7 & 8 to the adults)

LIVER TRANSPLANT IS THE ONLY CHANCE OF CURE FOR END-STAGE LIVER DISEASE AND FOR SOME METABOLIC DISEASE. THE INDICATIONS FOR TRANSPLANT CAN BE DIVIDED INTO BILE DUCT ANOMALIES, METABOLIC DISEASE, MALIGNANCIES AND FULMINANT LIVER FAILURE.

c) Living related donor
   1. Left lateral lobe
      Segments 2 & 3
   2. Left Lobe
      Segments 2, 3 & 4
   3. Right Lobe
      Segments 5, 6, 7 and 8

Most paediatrics transplants are performed with a living donor's left lateral lobe. This is also true for NUCOT where it accounts for about 90% of the paediatrics transplants.

Complications

Acute rejection is fairly common and easily treated with prednisolone pulsing. Infections and vascular complications are major concerns.

Results

Smaller infants generally fairer poorer largely due to size discrepancy of the graft, and to smaller vessel sizes.

Acute liver failure patients and re-transplants also have a poorer outcome.

In our review of 132 cases, the one-year survival is 90% and the five-year survival is 85%. . All our patients are on tacrolimus and prednisolone which are slowly tapered during the 1st year of transplant.

The aim of liver transplant is not just to achieve a survival but also to return the patient to a normal active and useful life.

Pregnancies after transplant is common. During pregnancy, the tacrolimus level is reduced and babies should not be breastfed.

A long-term survivor in our centre was transplanted 23 years ago at the age of 11. She is married with two kids and now runs a restaurant business of her own.

Liver transplant has also been carried out in the neonates and in ABO incompatible young infant below the age of 15 months.

Professor K Prabhakaran

Senior Consultant
Paediatric Surgery

Professor K Prabhakaran, received further sub-speciality training in Paediatric Surgery in the Royal Children's hospital in Melbourne, Australia. He also underwent training in Liver Transplantation in Cambridge, UK (1990) and in Pitsburgh, USA (1995).

Prof Prabhakaran has presided over many committees and review boards such as Chairman of Specialist Training Committee (now known as RAC) and he is also the director of the Paediatric Solid Organ Transplant, NUH and Chairman for the Liver Sub-Committee, MOH.

In 1995, Prof Prabhakaran performed the first successful paediatric liver transplant in Singapore in NUH and has also performed the first paediatric liver transplant in Indonesia (2006, Semarang) and the second paediatric liver transplant (public sector) in Malaysia (2002). In an outreach programme, he has performed 4 renal transplants in Myanmar, Mandalay. He was involved in charity works and have also set up a urology facility in Sri Lanka.

He was awarded the National Outstanding Clinician Award by the National University Singapore and in 2014 he received the award Lee Foundation – NHG-NUHS Lifetime Achievement Award.

POST EVENT HIGHLIGHTS

NUCOT PUBLIC ENGAGEMENT AND ORGAN DONATION AWARENESS ACTIVITIES

The National University Centre for Organ Transplantation (NUCOT) aims to engage individuals and institutions to raise public awareness for organ donation and transplantation. Through the media, organized roadshows and events, we seek to educate with accurate information and share the success stories of organ donors and recipients whose lives are greatly improved by organ transplantation.

This year, we organized the **Game of Survivors 2017** on 16 February at the National University of Singapore (NUS) in partnership with TeamNUS and the NUS Medical Society (MedSoc) of the Yong Loo Lin School of Medicine. This event was held at the University Town Forum and aimed to raise awareness for the Human Organ Transplant Act and the organ donation programme in Singapore, as well as raise funds for the NUHS Fund Ltd, in support of organ transplant patients.

The event featured a six-hour fund-raising treadmill charity run, with 15 treadmills kept running continuously over 6 hours. Every 1km that was run raised $10 for the Fund with over $6,000 raised by the end of the event. The New Chords Band, an 11-member group consisting of NUCOT post-transplant patients, NUH healthcare workers and NUS MedSoc undergraduate, also treated participants to performances of contemporary and classic tunes. Game booths and a public discussion forum also helped participants to discover different facts and information on organ donation and transplantation, thereby putting to rest any misconception or myths they may have, NUCOT celebrates 30 years of medical expertise and successes in organ transplantation, since 1987. In the month of October, the **30th Anniversary "Colours of Life" photo-exhibition** is on display at NUH Main Building Lobby B in conjunction with our commemoration activities. This photo exhibition showcases the organ transplant milestones over the past three decades in NUH. In addition, ten organ donors and recipients share their positive life transformations enabled by organ transplants. They recount their transplant journeys and gratitude for new and colourful leases of life.

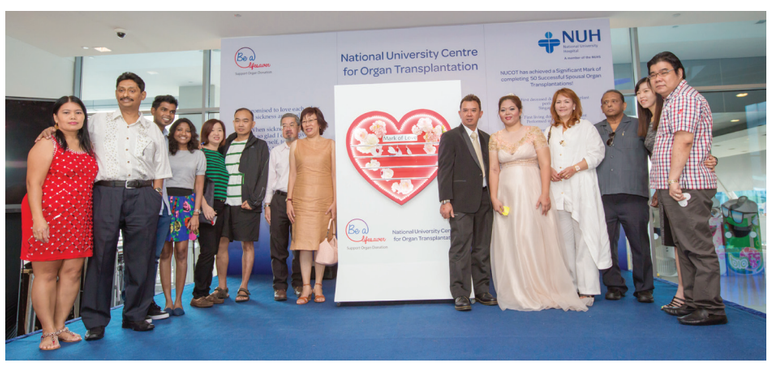
NUCOT PATIENT SUPPORT ACTIVITIES

NUCOT also endeavours to provide platforms for organ transplant patients and their families to network and provide support and encouragement to one another. These are usually educational activities or recreational events that allow participants to learn and share knowledge at the same time.

In the past years, some of the activities and events include:

MARK OF LOVE

NUCOT organised the "Mark of Love" event on 8 February 2015 to mark 50 successful local organ transplants through organ donation from spouses. Held in conjunction with Valentine's Day, the event celebrates the invaluable gift of love between organ donors and recipients. It was well attended by 24 couples, comprising spouses, siblings, parent and child, who are organ donors or recipients. They were joined by their family members and other NUCOT transplant patients.



GAME OF SURVIVORS

More than 100 post-transplant patients and their family members got together on a sunny weekend morning at the Labrador Park on 5 December 2015 to put their fitness levels to the test at NAPFA exercise stations. "Don't Wait, Just Do It" was the motto of the day. Participants were awarded gold, silver and bronze medals for their efforts and were also taught proper warm up and cool down exercises by National University Hospital (NUH) physiotherapists. Dr Wang Ming Chang of the NUH Sports Centre also gave a talk to participants on 'Tips to Exercising Post-Transplantation'.

PATIENT SUPPORT GROUP MEETINGS

Organised by NUCOT, post-liver transplant patients and their family members get together periodically to learn about health and wellness, and support one another on their transplant journeys. In the most recently meeting, patients and their family members gathered in the morning of Saturday 26 August 2017 at the NUHS Tower Block to discuss about healthy diet and exercise. Dr Low How Cheng of NUCOT gave a talk on 'Health In General for the Transplant Patient' and patients also took the opportunity to clarify questions they had regarding their post-transplant lifestyle and diet.

THE LIVER TRANSPLANT SYMPOSIUM 2017

NUCOT will be organising its 4th edition of The Liver Transplant Symposium on 27 - 29 October 2017 in Singapore at the NUHS Tower Block. Organised in partnership with the International Liver Transplantation Society (ILTS), this annual symposium is a nod to the growing acceptance of liver transplantation as a treatment option with excellent outcomes, in the South-East Asia region.

Half-day workshops take place on Friday 27 October at various locations within NUHS to offer in-depth sharing of relevant clinical experience and best practices. They include the Infectious Diseases Regional Grand Round, Liver Transplant Surgical Workshop, Simulation in Anaesthesia for Liver Transplantation (SALT) Workshop and Transplant Hepatology Workshop. Plenary sessions follow on 28 – 29 October at the Main Symposium.

The Liver Transplant Symposium aims to bring together healthcare professionals from South-East Asia and a global faculty to exchange the latest liver diseases research and discuss treatment outcomes. The Main Symposium scientific programme will features current topics and discuss the latest evidence in transplant surgery, transplant hepatology, anesthesia and critical care, immunosuppression, transplant infectious diseases; reflecting the multi-disciplinary nature of liver transplantation.

Through continual education, integration of new techniques and scientific breakthroughs in liver transplantation, we aim for the community of liver transplantation in south-east asia to continue pushing boundaries and transforming patients' lives.

Visit **www.livertransplantsymposium.sg** for more information.

FRONTIERS IN TRANSPLANT RESEARCH 2017

Frontiers in Transplant Research 2017 is organised by NUCOT to share the outcomes of the ongoing research in this exciting field of organ transplantation. This research seminar will be held on 27 October 2017 in Singapore at the NUHS Tower Block.

Solid organ transplant recipients enjoy outstanding long term survival at NUCOT. 10-year live donor kidney transplant patient survivals are 93.2% in comparison to the survival rates of 78% from the United States OPTN database.

These results were achieved with 30 years of development and consolidation of clinical transplantation data at NUCOT. With these outstanding results, research in transplantation at NUCOT is centered on the signature of chronic allograft survival, with interest focused on

- Antibodies that mediate chronic alloantibody mediated rejection in kidney transplants,
- Cytokines and Immune Cellular profiles that mediate immunological quiescence in the presence of alloantibodies

This year, we are proud to have world-renowned immunologist, Prof Kathryn Wood, The Khoo Oon Teik Professor of Surgery at NUS to deliver a plenary presentation on B Cell biology in transplantation. Distinguished faculty from the NUHS campus will deliver lectures on unmet needs in transplantation and the potential for new approaches to advance the care of transplant recipients worldwide.

GPLC

NUH GP Liaison Centre

At the NUH, we recognise the pivotal role general practitioners (GPs) and family physicians play in providing and ensuring that the general public healthcare is of the highest quality and standard. As such, we believe that through closer partnerships, we can deliver more personalised, comprehensive, and efficient medical care for our mutual patients.

The GPLC aims to build rapport and facilitate collaboration among GPs, family physicians and our specialists. As a central coordinating point, we provide assistance in areas such as patient referrals, continuing medical education (CME) training, and general enquiries about our hospital's services. Through building these important platforms of shared care and communication, we hope that our patients will be the greatest beneficiaries.

If we could be of any assistance to you, please feel free to contact our office from

Mon - Fri: 0900-1200hrs, 1400-1800hrs

GP Appointment Hotline
Tel: +65 6772 2000
Fax: +65 6777 8065

GP Liaison Centre
Tel: +65 6772 2535 / 5079

NUH CME EVENTS

At the NUH, we strive to advance health by integrating excellent clinical care, research and education. As part of our mission, we are committed to provide regular CME events for GPs and family physicians. These events aim to provide the latest and relevant clinical updates practical for your patient care.

Organised jointly by the GPLC and the various clinical departments within NUH, our specialists will present different topics in their own areas of specialties in these monthly symposiums.

For more information on our CME events, you can go to **www.nuh.com.sg**.