ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2020 October 18; 10(10): 277-290

Published by Baishideng Publishing Group Inc

World Journal of Transplantation

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ABOUT COVER

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INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Maurizio Salvadori, Sami Akbulut, Vassilios Papalois

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3230/editorialboard.htm

PUBLICATION DATE
October 18, 2020

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https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
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https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

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World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2020 October 18; 10(10): 277-282

DOI: 10.5500/wjt.v10.i10.277

ISSN 2220-3230 (online)

OPINION REVIEW

COVID-19 pandemic: Building organisational flexibility to scale transplant programs

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Author contributions: Gopal JP performed the literature search and wrote the manuscript; Papalois VE identified key areas to be addressed, made critical corrections to the manuscript and approved the final version.

Conflict-of-interest statement: The authors declare that they have no competing or conflicts of interests.

Manuscript source: Unsolicited manuscript

Received: July 11, 2020
Peer-review started: July 11, 2020

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Abstract

The prevailing coronavirus disease 2019 pandemic has challenged our lives in an unprecedented manner. The pandemic has had a significant impact on transplantation worldwide. The logistics of travel restrictions, stretching of available resources, unclear risk of infection in immunosuppressed transplant recipients, and evolving guidelines on testing and transplantation are some of the factors that have unfavourably influenced transplant activity. We must begin to build organisational flexibility in order to restart transplantation so that we can be mindful stewards of organ donation and sincere advocates for our patients. Building a culture of honesty and transparency (with patients, families, colleagues, societies, and authorities), keeping the channels of communication open, working in collaboration with others (at local, regional, national, and international levels), and not restarting without rethinking and appraising all elements of our practice, are the main underlying principles to increase the flexibility.

Key Words: Organisational flexibility; Clinical decision making; COVID-19; Organ donation; Care delivery; Transplantation

Core Tip: We have described our views and the underlying principles regarding building a flexible organisation to optimize the ability to efficiently handle a pandemic. As we are significantly advanced through the pandemic, the desire to go back to routine is gaining momentum, and as most of the programs around the globe are planning to safely restart or

First decision: July 25, 2020
Revised: August 4, 2020
Accepted: August 31, 2020
Article in press: August 31, 2020
Published online: October 18, 2020

P-Reviewer: Cantarovich F, MD GC, Tan YQ
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Wang LL

expand their activity, it is crucial for any organisation to be flexible in order to maintain sustainability.

Citation: Gopal JP, Papalois VE. COVID-19 pandemic: Building organisational flexibility to scale transplant programs. *World J Transplant* 2020; 10(10): 277-282
URL: https://www.wjgnet.com/2220-3230/full/v10/i10/277.htm
DOI: https://dx.doi.org/10.5500/wjt.v10.i10.277

INTRODUCTION

An estimate of more than six million people worldwide has been affected by end-stage organ failure[1]. Scarcity of suitable donor organs for transplantation is already one of the foremost challenges faced by transplant community, and the current pandemic has worsened this even more for various reasons. It has been reported that transplant patients acquiring coronavirus disease 2019 (COVID-19) have increased mortality, with more atypical presentations and longer duration of virus shedding[2,3]. Loupy *et al*[4] has reported a strong association between rising coronavirus infections and a marked reduction in the overall number of solid-organ transplantation, even in geographic regions with low infection prevalence. All of these could be devastating for patients awaiting organ transplantation. We should not be withholding life-saving transplant procedures out of fear that our patients might get an infection, instead, we just need to figure out how best to do it safely. Rapid adaptation by the transplant professionals to the evolving circumstances is the need of the hour for getting back on track. This article focusses on the challenges and the potential answers to reinvigorate a flexible transplant organisation during the crisis.

WHO WILL BE TRANSPLANTED?

Re-visiting the transplant waiting lists would be the foremost step while making this challenging decision. Due importance should be given to the following considerations: (1) Immunosuppressing a patient in the middle of a pandemic-does it serve in the best interests of the patient? (2) The risk benefit assessment of proceeding to transplant *vs* waiting in the list; (3) Conservation of healthcare resources; (4) The current status of the patient and their eligibility for transplantation; (5) Patient's wish for and against transplantation considering the pandemic; and (6) Ominous possibility for donor derived transmission. In addition to the above, the need for caregivers should also be considered. There is a complicated dynamic regarding the importance of caregivers accompanying patients to pre and post-transplant visits and during the post-transplant hospitalization and avoiding unnecessary persons into medical facilities. Transplantation of organs that are not immediately life-saving such as the kidney, the pancreas, and the small bowel must be decided on an individual case basis considering the loco-regional prevalence of COVID-19 and whether to introduce immunosuppression in patients and sending them into the community amidst the pandemic. The risk of infection can possibly be mitigated to some extent with the use of low intensity immunosuppression protocol (especially for recipients with a low immunological risk) such as an interleukin-2 receptor antagonist for induction rather than depleting antibodies. Written information pertaining to issues related to COVID-19 pre- and post-transplant should be available to all potential transplant candidates to help them in the decision-making process and to provide an informed consent. It is also vital to acknowledge to the patients about the continuously evolving nature of evidence. Patients must be informed if they are suspended or re-activated on the list. Psychologist consultation prior to the operation could relieve the panic and anxiety regarding COVID-19 for the recipients, as proposed by Wang *et al*[5].

PREFERRED MODALITY-DECEASED DONATION VERSUS LIVING DONATION

Deceased donor transplantation takes place in an acute setting and is more resource dependent. In order to follow safe transplant practices, screening of the donor and their contacts, the recipient, family members and contacts of the recipient, and healthcare professionals could be more laborious and difficult to do in a timely manner. Organ retrieval or transplantation from COVID-19 positive donors must be avoided at all cost. Team travel for retrieval must be avoided, and local organ recovery teams must retrieve in every possible scenario.

On the other hand, living donor transplantation is often carried out in a planned and elective setting, thus allowing sufficient time to prepare and also has the advantage of shorter hospital stay. Moreover, screening could be much more contained and can be done in a timely way. Donor safety is the utmost priority in living donation. As COVID-19 can be transmitted from healthcare professionals to donors and due to the unknown variables during the evolving circumstances, unfavourable donor outcomes could potentially have a detrimental effect.

In the context of consenting, in addition to the routine risks/complications, the following COVID-19 related issues should be discussed: (1) Risk of donor derived transmission; (2) Risk of nosocomial transmission; (3) Chances of not proceeding to transplantation including logistical issues; and (4) The rationale for social distancing and self-isolation pre- and post-transplant[6].

The important issue to consider is COVID-19 screening of donors (deceased/ living) and recipients before transplantation. Various transplant societies have published their guidance for screening[7-10]. While screening and testing strategy varies between jurisdictions, some of the common themes are: (1) Deceased donors should be screened by clinical history and epidemiology in addition to nucleic acid testing (NAT) of the respiratory samples; (2) If testing or test results are not available prior to retrieval, clinical and epidemiological information should be used to screen the donor; (3) Living donors should be tested by NAT of nasal/oropharyngeal specimen and chest X-ray close to the donation (ideally not less than 3 d before donation); (4) Recipients should be tested by NAT before transplantation (while a negative result should not be an absolute pre-requisite for proceeding with transplantation, the decision to wait for the results or not depends upon the turnaround time for results, urgency of transplantation, cold ischemia time, and local policy); and (5) A computed tomography scan of the chest alone or in conjunction with polymerase chain reaction is not appropriate for screening. It is equally important to acknowledge that none of the tests are 100% sensitive or specific, and false positive or false negative results are common.

Boyarsky *et al*[11] has reported the results of a national survey conducted in the United States linked to COVID-19 and transplantation. In this survey, complete suspension of living donor kidney and liver transplantation were reported by 71.8% and 67.7%, respectively, whereas a majority of the deceased donor programs continued to function with some restrictions, especially in regions with higher incidence of COVID-19. This is in contradiction to most of the centres in the United Kingdom, including our own, whereby a majority of the transplant programs (particularly kidney only or kidney-pancreas units) had to suspend temporarily both the deceased and living donor transplantation, whilst other units had to restrict their donor and/or recipient acceptance criteria. The underlying reasons were the following: To release/create more intensive care beds, to liberate the work force to support intensive care unit, and more importantly, because of increased mortality due to COVID-19 in immunosuppressed individuals.

WHERE TO TRANSPLANT?

The prevailing COVID-19 pandemic has largely depleted the healthcare systems of their capacity to continue transplantation with the transplant team members being redeployed into the care of virus infected patients. Individual programs must assess the local prevalence of infection and the availability of resources for the foreseeable future before expanding/restarting transplantation. Resource consideration should include the availability of the following: Critical care beds, ventilators, blood and blood products, operating theatres, anaesthetic cover with appropriate staffing, organ support services like dialysis machines and their consumables, testing facility, personal protective equipment, and availability of appropriate multidisciplinary team.

Social distancing measures and COVID-free areas in the hospital should be commonplace. Transplant recipients and living donors should be separated from suspected or confirmed COVID-19 infected patients during the in-hospital stay and outpatient visits. Wherever possible, they should be cared for in single rooms or in COVID-19 free wards.

Due to varying extent of resource constraints in different centres, consolidation and sharing of resources would be vital to resume transplant programs. By doing so, transplant centres can consider using "clean sites" or alternative hospital establishments to their original base site in order to carry on their services. As part of the planning measures, the alternative premise should obtain the necessary license to provide transplant services. They should also consider adopting a standard policy or obtaining accreditation for sterilisation and standardisation of equipment. In addition to that, organ perfusion fluids must be stored appropriately, staff who are less familiar with transplantation should have the relevant training and briefing, tissue typing should be done only in accredited laboratories, and the relevant transplant authorities should be kept in the loop in order to co-ordinate the efforts[12].

As a result of the co-ordinated efforts of various networks, we have restarted the living donor kidney transplant program in an independent sector premise and the deceased donor kidney transplant program at our base hospital in a phased manner with several restrictions to donor/recipient selection (immunologically and surgically low risk patients without needing intensive care unit admission post-transplant) along with changes to the immunosuppression protocol (basiliximab for induction rather than alemtuzumab, tacrolimus and mycofenolate mofetil maintenance rather than tacrolimus monotherapy). Pertaining to the live donor program, the donor, the recipient, and their households were isolating for 14 d prior to transplantation, and were tested at 2 wk, 3 d, and 24 h before transplantation. The medical staff were either working in COVID-19 free sites or working remotely for 14 d prior to transplantation with weekly testing.

WORKFORCE PLANNING

Workforce planning is equally important. Non-transplant professionals could be called in to help. Transplant teams should work with the understanding that they can be asked to come in for work at any time to provide every possible assistance. At the same instance, team members must think about measures for taking care of themselves and ensure they stay healthy to take care of the patients. The risk associated with exposure due to travelling for organ retrieval to high risk areas can be avoided by appropriate use of personal protection measures, and if necessary completely avoiding the high-risk situation. There should be a backup team readily available if in case a staff member falls ill or is isolating. A frequently ignored issue is the mental well-being of the team members. Anxiety and distress owing to virus exposure concerns and grim outcomes in recipients may all can contribute. This can be addressed by working closely with the relevant occupational health support services.

FOLLOW UP

Switching over to virtual clinics and remote blood testing facilities is certainly helpful in minimising patient contact and turn over. This is the real arena for technology to produce miracles. Outpatient clinics can be modified such that only urgent visits or patients requiring re-admission need to be seen. Prior to the clinic visit, staff may virtually screen the patients over telephone for symptoms suspicious or compatible with COVID-19. Segregating transplant recipients from suspected or confirmed COVID-19 patients in outpatient clinic is of paramount importance. Clinicians can advise patients to refer to government health websites or transplant-specific websites for guidance and general queries regarding coronavirus.

DEVELOPMENT OF CLINICAL PATHWAYS

All clinical pathways need to be re-written from scratch with emphasis on the following: (1) Doing what is absolutely necessary rather than doing what we are used to or like to do; (2) Logistics should be less complicated and services should adopt a

minimalistic approach; (3) Keeping patients away from the hospital as much as we can; (4) Regular appraisal of performance and outcomes of transplantation; and (5) Defining triggers to pause the program or halt the expansion, if need be. Guidance from professional societies would aid transplant programs in developing their customised clinical pathway. National organ allocation network could identify centres with low loco-regional prevalence of COVID-19 that can resume transplant activities much faster in order to maximise organ utilisation[13]. Organisations, commissioners, and networks working on developing the clinical pathways should keep in mind that there will be ongoing long-term effects from this pandemic like lengthy waiting lists, resultant increased mortality in the waiting list, and adverse pre-transplant conditions. Therefore, it is of utmost importance to pick the correct momentum to restore completely transplant programs[14]. In these exceptional times it is very important that we team up together to share knowledge and experience to benefit our patients[15].

RESEARCH

Even in times of major crisis, research is absolutely necessary, and researchers should continue their work especially in areas such as outcomes in transplant recipients and approach to optimal immunosuppression. A trial of vaccine in transplant patients is definitely warranted and whether a pre-transplant patient should be in early vaccine trials is more controversial, if a vaccine becomes available. As lower intensity immunosuppression protocols are becoming more common, it would be interesting to know if the benefits outweigh the risk of rejection. Research teams should work on virtual meetings with testing or drug dispensing in dedicated areas for research patients in order to avoid contact with unwell patients. Most importantly, research should be patient or disease focused and not carrier-oriented.

CONCLUSION

Bolstering flexibility of transplant programs and rapid adaptation are crucial for successfully navigating through any pandemic. These unprecedented situations are the time for togetherness and not appropriate for politics or blame games. Phased restarting or expansion of transplant programs should be done where emergency and life-saving transplants could proceed earlier, with more elective and quality of life improving transplants phased in later. Consolidation and sharing of resources and safe donation and transplant practices are the efficient ways to get the ball rolling again. These are crucial steps to get us through the current pandemic and similar future challenges.

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World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2020 October 18; 10(10): 283-290

DOI: 10.5500/wjt.v10.i10.283

ISSN 2220-3230 (online)

MINIREVIEWS

Combined liver and kidney transplantation in children and long-term outcome

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Author contributions: Ranawaka R, Dayasiri K, Gamage M performed literature survey; Ranawaka R, Dayasiri K, Gamage M wrote the manuscript; Ranawaka R edited the final version of the manuscript. All authors read and approved the final version of the manuscript.

Conflict-of-interest statement: No conflict of interest to be declared.

Manuscript source: Invited manuscript

Received: July 8, 2020

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Abstract

Combined liver-kidney transplantation (CLKT) is a rarely performed complex surgical procedure in children and involves transplantation of kidney and either whole or part of liver donated by the same individual (usually a cadaver) to the same recipient during a single surgical procedure. Most common indications for CLKT in children are autosomal recessive polycystic kidney disease and primary hyperoxaluria type 1. Atypical haemolytic uremic syndrome, methylmalonic academia, and conditions where liver and renal failure co-exists may be indications for CLKT. CLKT is often preferred over sequential liver-kidney transplantation due to immunoprotective effects of transplanted liver on renal allograft; however, liver survival has no significant impact. Since CLKT is a major surgical procedure which involves multiple and complex anastomosis surgeries, acute complications are not uncommon. Bleeding, thrombosis, haemodynamic instability, infections, acute cellular rejections, renal and liver dysfunction are acute complications. The long-term outlook is promising with over 80% 5-year survival rates among those children who survive the initial six-month postoperative period.

Key Words: Combined liver-kidney transplantation; Immunoprotection; Long-term outcomes; Renal allograft survival; Acute cellular rejection; Autosomal recessive polycystic kidney disease

Peer-review started: July 8, 2020
First decision: August 22, 2020
Revised: September 17, 2020
Accepted: September 25, 2020
Article in press: September 25, 2020
Published online: October 18, 2020

P-Reviewer: Cimen SG
S-Editor: Zhang L
L-Editor: A
P-Editor: Wang LL

Core Tip: Combined liver-kidney transplantation (CLKT) is a complex surgical procedure which is increasingly performed for a number of indications, especially primary hyperoxaluria type 1 and autosomal recessive polycystic kidney disease. In CLKT, the early mortality is mostly related to infections and surgical complications of the liver graft. On the other hand, chronic complications with liver graft are fairly rare, and the liver protects the kidney allograft from rejection, which results in stable function and long term survival of the renal allograft. Long-term outcomes are promising in children who had CLKT with good overall long-term survival rates when performed in experienced centers with expertise.

Citation: Ranawaka R, Dayasiri K, Gamage M. Combined liver and kidney transplantation in children and long-term outcome. *World J Transplant* 2020; 10(10): 283-290
URL: https://www.wjgnet.com/2220-3230/full/v10/i10/283.htm
DOI: https://dx.doi.org/10.5500/wjt.v10.i10.283

INTRODUCTION

The first successful combined liver-kidney transplantation (CLKT) in an adult was reported in 1984. After that it has become more common in adults but remains a relatively infrequent procedure in children[1]. Between 1988 and 2007, there were 2829 CLKT procedures performed in the United States of which only 166 were carried out in children[2]. Combined liver-kidney transplantation is a challenging form of surgery in the paediatric age group[1] with only about thirty surgical procedures being performed worldwide over a given year[3]. CLKT is a procedure in which a liver (whole or in part) and kidney allografts, from the same deceased or living donor, are transplanted during a single surgical procedure. Sequential liver-kidney transplantation is isolated transplantation of the liver (or kidney) followed by the transplantation of the kidney (or liver) after a certain time interval.

Limited numbers of this surgical procedure are due to rarity of clear indications for surgery, long waiting times for the surgery and shortage of suitable donors[4]. With the advancement of medical practices and innovative surgery, it is crucial that clinicians are insightful about when would CLKT be the right choice for a child, as compared to alternative therapeutic and surgical interventions. In the paediatric age group, CLKT can be considered for: (1) Children with profound and irreversible liver and kidney disease *e.g.* autosomal recessive polycystic kidney disease; (2) Children with metabolic liver diseases causing end-stage renal disease *e.g.* primary hyperoxaluria and atypical haemolytic uremic syndrome. A minority of children undergo CLKT following combined liver and renal failure. CLKT has been shown to be associated with immunoprotection of the kidney allograft and reduced rejection rates as compared with sequential kidney and liver transplantation[5] or kidney transplantation alone[5-7]. However, the experience of this observation is limited in paediatric studies due to a lack of comparative paediatric studies[8].

This review focuses on clinical indications, procedures, and acute, short and long term outcomes of combined liver-kidney transplantation in the paediatric age group. The review also discusses the evidence that supports the immunoprotective effects of CLKT on renal graft survival.

Indications

Autosomal recessive polycystic kidney disease: Autosomal recessive polycystic kidney disease (ARPKD) is a rare renal cystic disease in children with an incidence of 1:20000[9]. It is also known as fibro-polycystic liver and kidney disease and the most common renal cystic/ciliopathy disease in children. In ARPKD there is a mutation in PKDHD1, a gene located on chromosome 6p12[10]. The defective gene encodes for fibrocystin and leads to the defective tubular formation in renal tubules and hepatic bile ducts, leading to the early development of cysts[10]. Most severe variants are associated with pulmonary hypoplasia and high neonatal mortality. Approximately 50% of children develop the end-stage renal disease (ESRD) during the first decade of life[11]. Hepatic fibrosis is also seen early in life leading to recurrent cholangitis and manifestations of chronic liver disease which includes portal hypertension, splenomegaly and variceal haemorrhage[8]. However, chronic liver failure has a variable age of onset as opposed to early-onset ESRD, making management of these

children quite a challenge. These children undergo early nephrectomy and renal transplantation followed by sequential liver transplantation[12] or combined liver-kidney transplantation.

Primary hyperoxaluria type 1: Primary hyperoxaluria type 1 (PH-1) is a rare disorder of oxalate metabolism which has an incidence of 1:120000[13]. It is an autosomal recessive disease and the most common indication for CLKT in children. Primary hyperoxaluria is characterized by elevated plasma and urinary oxalate levels due to the defective liver-specific perixisomal enzyme alanine/glyoxylate aminotransferase[14]. Increased accumulation of glyoxalate leads to increased oxalate and formation and deposition of insoluble calcium salts in the kidney[15]. Children with PH-1 develop early-onset nephrocalcinosis, nephrolithiasis and ESRD[16]. With the development of ESRD and impaired excretion, oxalate is deposited in other tissues such as the retina, blood vessels, nerves and heart[17]. PH-1 often has a variable age of onset for ESRD and oxaluria is responsive to pyridoxine in some children. Therefore, it is important that pyridoxine responsiveness is evaluated and DNA analysis is performed to confirm the diagnosis in all children before planning CLKT[14].

The definitive treatment is CKLT to prevent early recurrence of nephrocalcinosis in the transplanted kidney[18]. However, in developing countries, isolated kidney transplantation is considered initially unless a child is referred to a centre performing CLKT[19]. Hyperhydration is recommended in the immediate post-operative period to prevent the surge of plasma oxalate due to mobilization of oxalate from other tissues and subsequent damage to the transplanted kidney[14]. Hyperhydration should be supplemented by post-operative haemodialysis and use of crystallization inhibitors (*e.g.* citrate) for the same reason[14].

Atypical hemolytic uremic syndrome: Atypical hemolytic uremic syndrome (aHUS) is a rare disorder of the alternative complement pathway involving impaired synthesis or function of factor H, a complement control protein. This leads to a triad of microangiopathic haemolytic anaemia, thrombocytopenia and renal dysfunction[20]. For aHUS CLKT was previously the treatment of choice as it corrected both the renal failure and the underlying problem with factor H which is produced by the liver. However, this procedure is no longer recommended as the first choice of definitive treatment due to promising effects of Eculizumab (anti-C5 monoclonal antibody) as a medical treatment and significant incidence of long term postoperative complications of CLKT. Eculizumab has been shown to inhibit complement activation in an alternative pathway that leads to microangiopathy[21], thereby avoiding the need for liver transplantation. However, there are certain genetic variants such as DGKE (diacylglycerol kinase-epsilon) mutations for which Eculizumab is not effective[22]. AN international consensus statement recommends either liver transplant or CLKT as the only treatment of cure for severe aHUS or defective complement factors synthesized in the liver (CFH–Complement factor H, CFB–Complement factor B, C3–Complement 3) although Eculizumab is also given to reduce post-transplant recurrence in those who only had renal transplantation[23]. Use of Eculizumab is limited by lack of availability and very high cost.

Methylmalonic acidemia: Methylmalonic academia is a rare inherited autosomal recessive metabolic disorder mainly due to defective vitamin-B12-dependent enzyme, methylmalonyl-CoA mutase leading to increased formation of methylmalonic acid. Children with methylmalonic academia are at high risk of multi-organ complications including heart, kidney, eyes and nervous system[24]. These children can also present with acute metabolic crises with profound metabolic acidosis and seizures[25]. Methylmalonic academia leads to renal tubular interstitial injury and up to 60% of children develop ESRD during adolescence[26]. Since methylmalonyl-CoA mutase activity is present in both liver and kidney, transplantation of one organ will lead to only partial recovery with a risk of recurrence[27]. CLKT has been shown to improve methylmalonic academia, renal dysfunction[2] and overall quality of life[28].

However, even after the CLKT, some systemic disease manifestations (such as neurologic or muscle impairment) may persist despite normal liver and kidney graft function due to abnormal methylmalonic acid metabolism in other tissues, including the muscles and skin[27]. Therefore, it is crucial to provide lifelong specific high-calorie diet low in propiogenic amino acid precursors despite organ transplantation, due to on-going production of methylmalonic acid from skeletal muscles[29].

Combined liver and kidney failure: Combined liver and kidney failure occurs in certain metabolic diseases such as alpha-1 antitrypsin deficiency, glycogen storage disease type 1A, Boichis syndrome (nephronophthisis with congenital hepatic

fibrosis), and medical conditions such as hepatorenal syndrome and liver tumour with nephrotoxicity. CLKT had been variably successful in children with these conditions[12].

Hepatorenal syndrome (HRS) is one of the main complications of end-stage liver disease with high morbidity and mortality. It results from hypoperfusion of kidneys due to combined effects of intrarenal arteriolar vasoconstriction and peripheral vasodilatation, mainly in the splanchnic circulation. There are two types of HRS, type 1 (with the worst prognosis) is rapidly progressive with renal failure while type 2 has slowly developing renal dysfunction in patients with liver cirrhosis.

In most instances, HRS resolves with liver transplantation alone thus HRS is not being considered routinely for CLKT[30]. However, as prolonged HRS can progress to irreversible renal damage some patients with both the end-stage liver and kidney failure may be candidates for CLKT[3,31].

Procedure

In CLKT, both kidney and either whole or part of the liver from a donor (usually cadaveric) is transplanted to the same recipient during a single surgical procedure. Sequential liver-kidney transplantation is performed in two stages where the recipient initially undergoes isolated organ transplantation (either kidney or liver) followed by the other organ (liver or kidney) from two different cadaveric donors or a single living donor. It is of the paramount importance to keep the cold ischemic time shorter to avoid delayed graft function.

Whole cadaveric liver transplantation would help to reduce the post-transplant complications (*e.g.* bleeding, bile leak) by avoiding prolonged cold ischemic time for both liver and kidney, compared to partial liver graft transplantation. The liver graft is transplanted first to reduce the risk of cold ischaemia to liver and cold ischaemic time is usually kept to less than 8-10 h for the liver and 10–12 h for the kidney. After hepatic vascular anastomoses are performed, renal vessels are anastomosed to the common iliac vessels to achieve early re-perfusion. Uretero-vesical and biliary anastomoses are performed only after hepatic and renal vascular reperfusion is achieved.

Acute complications and short term outcomes

CLKT is a complex major surgical procedure and immediate post-operative complications are frequently reported. Analysis of the Scientific Registry of Transplant Recipients (https://www.srtr.org/) of 152 primary paediatric CLKTs performed from October 1987 to February 2011, revealed a total of 32 deaths (21.1%) during the first 30-mo postoperative period[32]. The main causes of death were: Infectious (18.7%), cardiovascular (18.7%), respiratory (6.2%), gastro-intestinal and haemorrhage (6.2%). However, with the advancement of surgical and medical interventions, the rate of complications has been progressively reducing over the last decade.

Post-operative hyperoxaluria and graft dysfunction is a major problem following CLKT for primary hyperoxaluria and ESRD and these patients should be managed with postoperative renal replacement therapy. Many studies reported that the acute post CLKT complications were higher in primary hyperoxaluria compared to other causes[33].

Further complications including, post-operative bleeding, bile leaks, hepatic artery thrombosis, and acute liver failure can lead to graft loss and even mortality. Due to bleeding and multiple vascular anastomoses, patients are at risk of hypovolaemia and shock or fluid overload due to multiple transfusions. Therefore, fluids and diuretics should be used carefully. A liver graft can suffer cold ischaemia with longer anastomosis times and the risk is higher with partial liver transplantations compared to whole liver transplantations[34].

Mortality during the initial six months following CLKT remains high. Septicaemia and multi-organ failure are common causes of mortality while on high doses of immunosuppressive medications[35]. Acute organ rejection was reported in 14% of CLKT patients during the first postoperative year in one study[36]. The combination of basiliximab and daclizumab reduces acute rejection in renal transplantation when used during the induction phase of immunosuppression[37]. Calinescu *et al*[32] examined 152 patients who had CLKT for short and long term outcomes. Overall, the one-year patient survival was 86.8% and the survival of the kidney and liver grafts was 83.4% and 81.9% respectively.

Immunoprotective effects of CLKT on renal allograft

In CLKT patients, the liver allograft confers immunoprotection of the kidney allograft. This was first demonstrated in animal model[38,39]. Later clinical studies of CLKT have

shown reductions in both acute cellular rejection and chronic rejection of kidney allograft in those who undergo CLKT when compared to cadaveric renal transplantation[36]. The molecular basis of immunoprotection is yet to be precisely defined but it is thought that the transplanted liver can modify the immune system of the recipient by neutralizing circulating autoantibodies[39]. Further, a liver graft provides HLA-G antigens that inhibit natural killer cells thought to be involved in acute rejection[40]. Improved renal outcomes from such immunoprotection in part explain the fact that CLKT has better outcomes as compared with sequential organ transplantation in patients with combined liver and renal impairment. Liver rejection rates were not different in those with CLKT when compared to isolated liver transplantations[41]. Rapamycin, a calcineurin inhibitor, is the mainstay of immunosuppression following CKLT. Use of Rapamycin has been associated with reduced rates of hepatic rejection in adult studies[42].

Long term outcome

The result of CLKT is in part dependent on the aetiology of hepatic and kidney dysfunction. The outcome is also dependent on the child's pre-transplant clinical condition. Diagnosis of metabolic disease and an early transplantation scenario are good prognostic indicators while multi-organ failure leading to CLKT is a poor prognostic indicator. The long term outcome of the transplanted liver is usually good without evidence of chronic rejection. However, chronic allograft nephropathy of the kidney is apparent in the long term.

Data regarding long term outcomes of CLKT are limited. Quintero Bernabeu *et al*[41] reported long term outcomes of 14 children who had CLKT. The majority of patients in that cohort had either ARPKD or PH-1. One child had renal re-transplantation following branch renal artery thrombosis of the kidney allograft after it was complicated by severe hypertension and renal dysfunction. One patient had chronic rejection 10 years after the transplant. Two children had BK viral infections which were treated with cidofovir whilst one child died following adenoviral infection 8 mo after CLKT. Several children developed progressive renal dysfunction and severe tubulopathy indicative of allograft nephropathy and needed renal re-transplantation.

Long term outcome was dependent on the primary disorder and patients with PH-1 have slower improvement of renal functions as compared with ARPKD. Five-year renal graft survival and overall survivals were 85.7% and 92.9% respectively. More recently, Ranawaka *et al*[6] reported long term renal outcomes in a cohort of 40 children who had CLKT with the majority being diagnosed with ARPKD. The investigators observed a statistically significant greater decline of estimated glomerular filtration rate in isolated kidney transplant patients compared to those who had CLKT whilst acute rejection was less in those with CLKT. The investigators observed better outcomes in those with ARPKD compared to PH-1 and comparative to observations made by Quintero Bernabeu *et al*[41] Although there are several studies which reported long term renal outcomes, only a few studies reported long term liver outcomes of which 5-year graft survival varied from 76.5%[32]-80%32[34].

In one large series, Calinescu *et al*[32] analyzed data using the Scientific Registry of Transplant Recipients to determine long term outcomes of 152 pediatric CLKT. The liver graft survival at five and ten years was 76.5%, and 72.6 % respectively, and kidney graft survival was 76.5% and 66.8 %, respectively. Patient survival was 82.1% at five years, and 78.9% at ten years, which was much similar to the isolated liver transplant at five and ten years (81.2% and 77.4%). But isolated kidney transplant showed much better results at those points (95.4% and 90%)[32].

The children with liver and kidney failure are shorter than their peers due to underlying chronic conditions but show improved growth after CLKT. Growth is an important determinant of better functional outcomes in employment, education and marital life[43,44]. North American Paediatric Renal Trials and Collaborative Studies data have shown that better catch-up growth is achieved when CLKT is performed at a younger age, especially below six years[45]. Human growth hormone has a place in this group of children and a recent Cochrane update demonstrated that children who were treated with growth hormone showed an increased height velocity of 3.88 cm/year[46].

Although life-saving, CLKT may not be curative in all children, and children who had CLKT may suffer from chronic health problems throughout their life. Therefore, the quality of life is an important aspect to assess in long term outcome of transplant recipients. The World Health Organization defines health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Thus, it is of the paramount importance to have a holistic approach from the multidisciplinary transplantation team with participation of primary care physicians, community nurse, psychologists, social workers and the school. Such an approach

should extend to address the common attentional, behavioural and peer relationship problems of these children to improve their overall school performance. Furthermore, they should be guided through a proper adolescent transition programme to achieve their ultimate goals in life as young adults.

CONCLUSION

CLKT is a complex surgical procedure which is increasingly performed for a number of indications, especially primary hyperoxaluria type 1 and autosomal recessive polycystic kidney disease. Given the risks of the procedure, selection of patients for this surgery needs to be done carefully taking into consideration, the clinical indication, the functional status of liver and kidney, the patient's general health, and the skills and expertise of the transplant centre. In CLKT, the early mortality is mostly related to infections and surgical complications of the liver graft. On the other hand, chronic complications with liver graft are fairly rare, and the liver protects the kidney allograft from rejection, which results in stable function and long term survival of the renal allograft.

However, liver survival rates are not different in CLKT compared to sequential liver and kidney transplantation or isolated liver transplantation. Acute complications are not uncommon given the complexity of the surgical procedure. However, these can be reduced by optimal precautions and early detection and management of problems. Long-term outcomes are promising in children who have had CLKT with good overall long-term survival rates when performed in experienced centres with expertise.

ACKNOWLEDGEMENTS

All authors sincerely thank Dr. Dominic Kelly of the University of Oxford for conducting English language editing of this manuscript.

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